Voretigene Neparvovec for Biallelic *RPE65*-Mediated Retinal Disease: Effectiveness and Value

Draft Evidence Report

November 14, 2017

Prepared for

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DATE OF PUBLICATION: November 14, 2017

We would also like to thank Erin Lawler and Maggie Webb for their contributions to this report.

About ICER

The Institute for Clinical and Economic Review (ICER) is an independent non-profit research organization that evaluates medical evidence and convenes public deliberative bodies to help stakeholders interpret and apply evidence to improve patient outcomes and control costs. ICER receives funding from government grants, non-profit foundations, health plans, provider groups, and health industry manufacturers. For a complete list of funders, visit http://www.icer-review.org/about/support/. Through all its work, ICER seeks to help create a future in which collaborative efforts to move evidence into action provide the foundation for a more effective, efficient, and just health care system. More information about ICER is available at http://www.icer-review.org.

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The Midwest Comparative Effectiveness Public Advisory Council (Midwest CEPAC) – a core program of ICER – provides a public venue in which the evidence on the effectiveness and value of health care services can be discussed with the input of all stakeholders. Midwest CEPAC seeks to help patients, clinicians, insurers, and policymakers interpret and use evidence to improve the quality and value of health care.

The Midwest CEPAC is an independent committee of medical evidence experts from across the Midwest, with a mix of practicing clinicians, methodologists, and leaders in patient engagement and advocacy. All Council members meet strict conflict of interest guidelines and are convened to discuss the evidence summarized in ICER reports and vote on the comparative clinical effectiveness and value of medical interventions. More information about Midwest CEPAC is available at https://icer-review.org/programs/midwest-cepac/.

The findings contained within this report are current as of the date of publication. Readers should be cognizant that new evidence may emerge following the publication of this report that could potentially influence the results. ICER may revisit its analyses in a formal update to this report in the future.

In the development of this report, ICER's researchers consulted with several clinical experts, patients, manufacturers, and other stakeholders. The following clinical experts provided input that helped guide the ICER team as we shaped our scope and report. None of these individuals is responsible for the final contents of this report or should be assumed to support any part of this report, which is solely the work of the ICER team and its affiliated researchers.

For a complete list of stakeholders from whom we requested input, please visit: https://icer-review.org/material/voretigene-stakeholder-list/.

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List of Acronyms Used in this Report

AAV2	Adeno-Associated Viral Serotype 2
AE	Adverse Event
CS	Contrast Sensitivity
CβA	Chicken Beta Actin
EOSRD	Early Onset Severe Retinal Dystrophy
FST	Full-Field Light Sensitivity Threshold
ICO	International Council of Ophthalmology
IRD	Inherited Retinal Dystrophy
ITT	Intent To Treat (includes all subjects enrolled and randomized)
LCA	Leber Congenital Amaurosis
LogMAR	LOGarithm of the Minimum Angle of Resolution
LUX	SI unit of illumination; one lumen per square meter
mITT	Modified Intent To Treat (includes all subjects exposed to investigational agent)
MLMT	Multi-Luminance Mobility Testing
OCT	Optical Coherence Tomography
PDUFA	Prescription Drug User Fee Act
PLR	Pupillary Light Reflex
PP	Per Protocol
RP	Retinitis Pigmentosa
RPE	Retinal Pigment Epithelium
SAE	Serious Adverse Event
SECORD	Severe Early Childhood Onset Retinal Dystrophy
TEAE	Treatment Emergent Adverse Event
VA	Visual Acuity
VF	Visual Field
VN	Voretigene Neparvovec
vg	Vector Genomes

1. Background

1.1 Introduction

Background

Inherited retinal diseases (IRDs) are an important cause of childhood blindness and affect approximately 1 in 2300 people worldwide.[1,2] A number of IRDs are caused by recessive mutations in the gene *RPE65* that codes for the protein RPE65. RPE65 (retinal pigment epithelium-specific 65 kDa protein; retinoid isomerohydrolase) is found in the retinal pigment epithelium where it plays a critical role in the regeneration of light-reacting proteins in the retina.[3]

Mutations that affect both copies of the gene *RPE65* (biallelic mutations) cause Leber Congenital Amaurosis, type 2 (LCA2), Early Onset Severe Retinal Dystrophy (EOSRD) and Severe Early Childhood-onset Retinal Dystrophy (SECORD), Retinitis Pigmentosa type 20 (RP20), and other phenotypes.[4-7] All of these different disorders are rare, and their exact prevalence is unknown. Distinctions among these disorders may reflect the amount of remaining RPE65 activity, but these may also reflect clinical difficulties in assigning correct phenotypic diagnoses.[8] Preliminary estimates from the manufacturer suggest that there are between 1,000 and 3,000 patients in the US with *RPE65*-mediated IRDs.[9]

Patients with these disorders have progressive vision loss, which varies depending on the type of mutation and other factors. Patients may become severely visually impaired during childhood, adolescence, or early adulthood.[3,4,7]

Effective treatments to reverse IRDs or slow their progression have generally been unavailable. Voretigene neparvovec (LUXTURNA™, Spark Therapeutics) is an investigational gene therapy. The FDA's Cellular, Tissue and Gene Therapies Advisory Committee unanimously recommended approval of voretigene neparvovec (VN) on October 12, 2017 for the treatment of vision loss due to confirmed biallelic *RPE65* mediated-IRD, and a decision by the FDA (Prescription Drug User Fee Act (PDUFA)) is expected as of January 12, 2018. [9]

If approved, VN would be the first therapy entering the market in the US that treats a disease using gene therapy. The first two gene therapies approved in Europe have price tags ranging from $650,000 to $1 million, and some analysts anticipate similar or higher prices for the cost of VN.[10,11] Key elements of an assessment of a gene therapy, therefore, must address how to capture all relevant aspects of the value of gene therapies; how to translate that understanding into considerations of value-based pricing; and how to evaluate the potential for innovative payment mechanisms to help balance long-term value with short-term affordability concerns (https://icer-review.org/wp-content/uploads/2017/03/ICER-Gene-Therapy-White-Paper-030317.pdf).

Scope of the Assessment

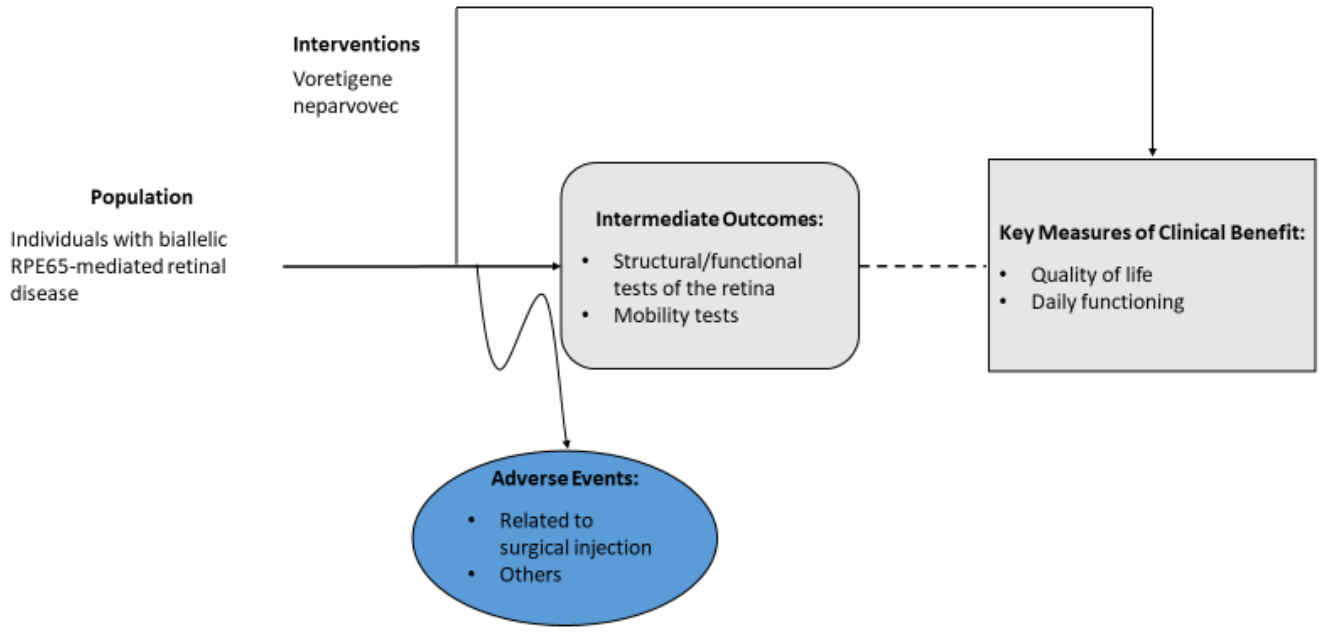
The scope for this assessment is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence was collected from available randomized controlled trials. Observational studies and case series were considered for inclusion as well, given the limited evidence base for VN.

Our evidence review included input from patients and patient advocacy organizations, data from regulatory documents, information submitted by manufacturers, and other grey literature when the evidence met ICER standards (for more information, see https://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/).

Analytic Framework

The analytic framework for this assessment is depicted in Figure 1.1.

Figure 1.1. Analytic Framework



Populations

The population of focus for this review was all persons with vision loss due to biallelic *RPE65*-mediated retinal disease.

Interventions

The intervention of interest was subretinal injections of VN.

Comparators

The comparator was best supportive treatment. This included correction of refractive error, low-vision aids, and optimal access to educational and work-related opportunities.

Outcomes

Outcome measures included tests of retinal function, such as visual acuity, full-field sensitivity testing (FST), and tests of functional vision, such as the multi-luminance mobility test (MLMT) used in the phase III trial of VN.[12] All outcomes are described in the clinical effectiveness section.

Discussions with patient groups highlighted certain outcomes that we assessed as the evidence allowed. These included improvements in visual acuity, improvements in night vision, and a halting or slowing of disease progression. The ability to navigate obstacles in lower light settings, for example, can translate into increased mobility and independence, which can have a significant impact on a visually-impaired individual's quality of life and productivity. We also looked for evidence on patient-reported quality of life.

Timing

Evidence on intervention effectiveness and harms were derived from studies of any duration.

Settings

All relevant settings were considered, including inpatient, clinic, and office settings.

Value Framework Considerations

ICER has modified its value assessment framework for treatments of certain ultra-rare conditions (http://icer-review.org/material/final-ultra-rare-adaptations/). Biallelic *RPE65*-mediated retinal disease meets ICER's criteria for an "ultra-rare" condition.

Although modifications to the framework were made after the initiation of this report, the present document takes into account the adaptations and accords VN all the appropriate advantages that

would have been expected had the framework been in place prior to the beginning of the assessment process.

2. The Topic in Context

Inherited Retinal Diseases

The advent of genetic testing over the last 20 years has revolutionized the diagnosis of IRDs. Clinical diagnosis is difficult and, when compared with genetic testing, has been found to incorrectly distinguish among individuals with the same mutation and categorize individuals with distinct mutations into similar phenotypes (Figure 2.1).[4,7,13] The American Academy of Ophthalmology recommends genetic testing and counselling as an important component of the assessment of patients with IRDs: "Methods for identifying the genetic cause of IRDs have advanced significantly in recent years, such that a causative mutation can be identified in up to 60-80% of patients with inherited retinal disorders. Genetic testing is appropriate for most patients with presumed genetically caused retinal degeneration."[14]

Leber Congenital Amaurosis (LCA), also known as congenital or early-infantile blindness, is one of the most severe IRDs. It accounts for around 5% of all inherited retinopathies and is present in approximately 20% of children attending schools for the blind.[13] The diagnosis is based on blindness or severe visual impairment presenting in infancy (frequently before age six months), the oculo-digital sign (poking, rubbing, and/or pressing of the eyes), nystagmus, and changes on the electroretinogram.[13,15] However, universally agreed-upon diagnostic criteria are lacking.[15] While some congenital retinal visual impairments are accompanied by other neurological features, LCA is limited to dystrophy of the retina.[13]

Mutations in many different genes result in LCA (Figure 2.2).[7,16] Each of these genes can exhibit a great number of mutations. LCA type 2 (LCA2), the LCA due to biallelic *RPE65* mutations, has been associated with about 125 different identified gene mutations to date.[9] Considering the number of genes and mutations involved, IRDs are one of the most genetically diverse groups of inherited disorders.[17]

The natural history of LCA varies with the genes and mutations involved. Overall, patients with *RPE65* mutations (LCA2), which account for about 6% of gene mutations causing LCA, tend to have better visual functions than typically seen in other LCA patients with visual acuity often of 20/50 or better early in life.[18,19] These patients may show temporary mild improvements in visual acuity, but inexorably decline after a time of stability, usually reaching a level of inability to see hand motion (20/20,000) in adulthood.[9,13,20] Even if visual acuity remains relatively preserved up to adolescence, declines in visual field are observed from infancy.[4] Regardless of different levels of decline in visual acuity or peripheral vision among patients with biallelic *RPE65*-mediated inherited retinal disease, all patients with this type of mutation are visually impaired at low levels of lighting.[21]

Conversely, while LCA comprises various gene mutations (including *RPE65*), a number of disorders due to *RPE65* mutations have different names. The diagnoses of Early Onset Severe Retinal Dystrophy (EOSRD), Severe Early Childhood-onset Retinal Dystrophy (SECORD), and early-onset RP are increasingly considered milder forms of LCA2.[7] In a retrospective chart review of 70 patients with biallelic mutations in *RPE65*, patients initially received 20 distinct clinical diagnoses, 44% had more than one diagnosis over the course of their care, and of those the average number of diagnoses was three. Clinical diagnoses of both RP and LCA were made in 13% of the patients (Figure 2.1).[4]

Figure 2.1. Initial Clinical Diagnosis in 70 patients with biallelic mutations in *RPE65*[4]

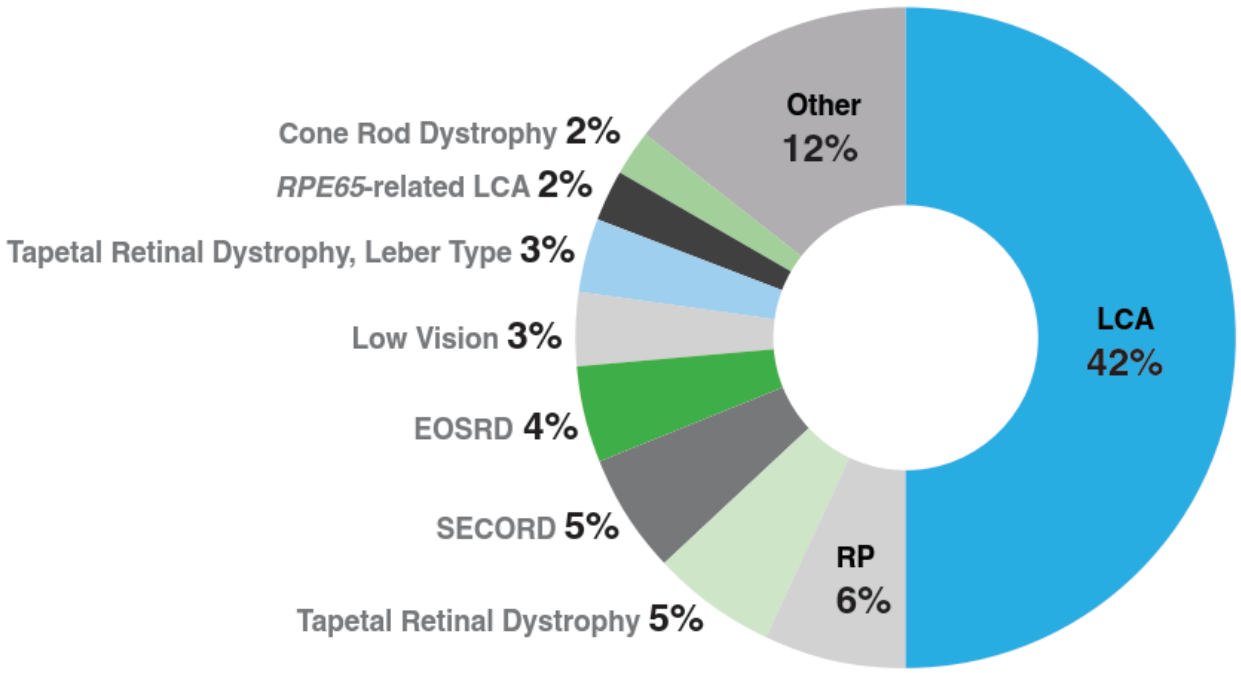
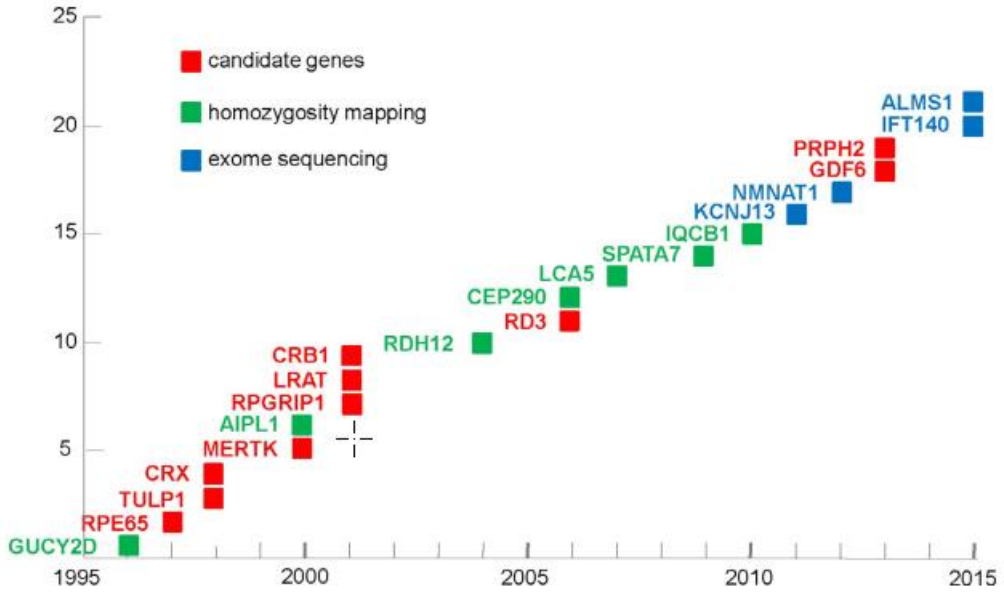


Figure 2.2. Cumulative Number of Identified LCA Genes[16]

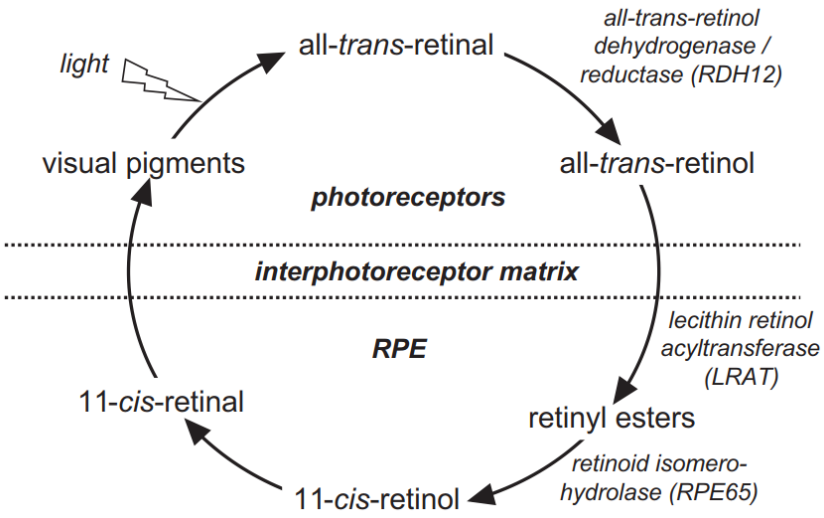


The disease process of RPE65-mediated IRD starts with the rod photoceptors, necessary for peripheral vision and night vision, and later progresses to the cone photoceptors in the macula that are necessary for visual acuity and color vision. The disease process involves two distinct processes: a biochemical blockade leading to malfunctioning rods and degenerative processes leading to the death of cells of the retinal pigment epithelium (RPE), a single layer of cells that form the blood-retina barrier and nourish photoreceptors.[9,21] The mechanisms responsible for the degenerative processes that lead to the absence of light perception are not well understood.[21]

The activity of the gene *RPE65* is essential for the chain of chemical reactions transforming light into electrical signals called the visual cycle (Figure 2.3). *RPE65* leads to the production of the protein RPE65, found in the retinal pigment epithelium (RPE) with a molecular weight of 65 kDa. RPE65 catalyzes a chemical reaction needed to produce 11-cis retinal, which is essential for the functioning of the rod photoceptors. Without 11-cis retinal peripheral and night vision would not be possible.

Depending on the *RPE65* mutation, the gene produces proteins which lack varying degrees of function. These proteins are often misfolded.[22] Abnormal proteins are believed to contribute to retinal degeneration via direct cytotoxic effects, increasing the absorption of photons and leading to cell death.[13,23,24] A lack of functioning RPE65 in the visual cycle also leads to the accumulation of cytotoxic retinal esters that contribute to cell death in the RPE.[9]

Figure 2.3. Visual Cycle[13]



Gene Therapy

Gene therapies modify the expression of genes to treat disease. These can involve strategies that repair genes or that introduce new genes into cells. The process of deliberately introducing functioning genes into cells is called transfection and is accomplished by using a vector, usually a virus.[25] The new gene can function either as an integral part of the genome, which means that the new properties will still be present when the cells divide, or it can function physically separated from the chromosomal DNA of the transfected cell and is usually not transmitted during the division of cells.[26] Delivering the gene to the right place and switching it on, avoiding immune responses that can either render the gene therapy ineffective or harm the patient, and making sure that the new gene doesn't disrupt the function of other genes, are some of central challenges of gene therapy.[25]

Therapy with VN involves using a viral vector (adeno-associated virus serotype 2 [AAV2]) to transfect cells in the RPE with a functioning copy of *RPE65*. This does not repair or eliminate the defective gene, but rather introduces a normal copy of the gene into the cell. Over the last decade, AAV has been used as a vector of choice in gene therapies, having been used in well over 100 clinical trials.[27] Adeno-associated virus vector is believed to be safe for many different types of gene therapy as it does not cause any disease, cannot reproduce without a helper virus, is less immunogenic than other viruses, and can be manufactured to only include the genetic information of the gene being transferred for therapy.[28-30] AAV2 has a specific affinity with retinal cells. The retina-brain barrier limits the distribution of the vector into other organs and creates an immune-privileged space limiting classical immune response, diminishing safety concerns about immune responses.[28,30]

The AAV2 vector must be delivered in close proximity to the retinal pigment epithelium (RPE), the region of the target cells for gene therapy. In order to access the retina during the procedure, it is necessary to completely remove the vitreous gel that fills the eye, a process called vitrectomy.[31] Vitrectomy involves an incision into the eyeball and is a standard procedure used for various interventions on the retina and eye. Cataracts are the most common complication, but infections and tears of the retina may also occur.[32]

After vitrectomy, the liquid containing the vector is injected into the space between the retina and the RPE, a "subretinal" injection. The subretinal injection is administered into or near the macula, the area of the retina needed for visual acuity, and can lead to macular holes and tears and to infection. Subretinal injection is not a common procedure, although it is performed for some other conditions, and the briefing document submitted by the manufacturer of VN mentions plans for intensive hands-on training of eye surgeons in the small number of centers that are expected to be authorized to administer VN.[9]

The recommended treatment regimen for VN is bilateral subretinal injections of 1.5E11 vg in 0.3 mL per eye. Each eye is treated separately but no more than 18 days apart. This spacing was designed to monitor for complications and reduce potential immune response from two administrations in a short timeframe.[9]

The therapeutic effects of gene therapy may not be permanent. Other AAV gene therapies have been studied, and treatment of *RPE65*-mediated IRD using AAV2 gene therapies other than VN showed limited duration of benefit.[33] In one study, the improvement in visual sensitivity peaked at 1 to 3 years after treatment and then declined with degeneration continuing at much the same rate as in the untreated retina.[34] In other studies, the treatment effect also declined a few years after injection.[35,36]

The decline in visual function in different gene therapies for biallelic *RPE65*-mediated retinal disease can be either due to a limited effect of the gene therapy being used or due to degenerative processes that continue despite an improvement in photoreceptor functioning.

The gene therapies used to date have differed. The AAV viruses themselves have different structures and there are potentially important differences in the genetic material accompanying the normal *RPE65* gene, such as promoters and enhancers.[28] Furthermore, the preparation of the solution used for administering the treatment may be different. For example, VN is administered in a solution containing surfactant to help prevent loss of vector on surfaces of the materials used in delivering the vector.[9] Due to these important differences, the efficacy and safety results of the different trials cannot be compared. As such, the systematic review on the comparative clinical effectiveness will be limited to the intervention VN.

With VN, the duration of effect is uncertain. It is important to consider the possibility of degenerative processes continuing despite an improvement in photoreceptor functioning. Indeed, the mechanisms responsible for these degenerative processes that are leading to the final stage of the disease, the absence of light perception, are not well understood. The mutated genes continue to produce mutant proteins in parallel to the functioning RPE65 produced by the normal gene delivered by transfection. As these mutant proteins are believed to contribute to retinal degeneration by different cytotoxic effects,[13,23,24] it is possible that degeneration continues, in spite of continuing therapeutic effect of the gene therapy. Until there is long-term follow-up of individuals treated with VN, the duration of benefit will remain uncertain.

Concurrent Innovations

- A series of phase I/II trials have examined the efficacy of the synthetic prodrug QLT091001, for replacing enzymatic activity in patients deficient in 11-cis-retinal both in patients with *RPE65* mutations and in those with *LRAT* mutations.[37] These trials have had promising results;[38-40] a phase III trial is due to commence in the near future.[7]
- As noted, retinal degeneration was seen to progress in some gene therapy trials. Neuroprotective therapies are currently being studied, and it has been proposed to eventually use them synergistically with gene therapy.[41]
- In animal models of gene therapy, new AAV vectors have been effective with intravitreal injections, potentially obviating the need for subretinal injections.[41] Intravitreal injections are easier and safer than subretinal injections.
- The Argus™ II retinal prosthesis system[42] received an FDA Humanitarian Device Exemption in 2013 for "use in patients with severe to profound retinitis pigmentosa who meet the following criteria: 1) adults, age 25 years or older; 2) bare light or no light perception in both eyes."[43] We did not find any reports on its use specifically in LCA or in biallelic *RPE65*-mediated retinal disease. A trial of stem cell treatments for various retinal degenerative diseases was started in 2016 and is expected to run until 2021.[44]

Definitions

Biallelic: Affecting both copies of a specific gene (on the paternal and maternal chromosomes)[45]

Cone cells: Photoreceptor cells in the central retina needed for color vision and visual acuity[46]

Fovea: Small central area in the macula with the highest concentration of cones providing sharp vision[46]

Intravitreal: Inside the vitreous humour, a transparent gel-like substance that fills the eye[46]

Macula: Area of the retina where the cones are located, used in seeing fine detail[46]

Rod cells: Photoreceptor cells in the outer regions of the retina used for peripheral and night vision[46]

Vector: Vehicle, often a virus, to carry the new DNA into the cells of a patient with a genetic disease[25]

Insights Gained from Discussions with Patients and Patient Groups

Educating a child with low vision takes significant amounts of time, energy, and money beyond that already required for any child. A treatment that delays the onset of visual impairment needs to be considered not simply in the number of years that visual loss is delayed, but also in terms of life stages. For example, being able to navigate on one's own in school can be very important, even if visual acuity is insufficient to learn without adaptive devices. Completing education and entering the work force is another important life stage where delaying visual loss can potentially have important affects on easing transitions that are required when first becoming employed.

Progressive vision loss can both create uncertainty for patients and require repeated re-adaptation of skills. We heard from patients that a therapy that stops decline in vision would be very important even if it did not improve vision. Such a therapy would provide greater certainty in decision making for the future base on stable skills and abilities.

Patients and patient advocacy organizations emphasized the challenges of growing up with low vision both for affected children and their parents/families. Individuals with *RPE65*-mediated retinal disease described the significant time and energy they have had to dedicate towards adapting to constantly deteriorating vision. Substantial adjustments are necessary for children to be able to perform at the same level as their peers in school, and their academic and career success may directly depend on the quality of assistive services and resources at their disposal. One mother who testified at the FDA's Cellular, Tissue, and Gene Therapies Advisory Committee meeting on VN, left her career to stay home and help "level the educational playing field" for her two visually-impaired sons.[47] This mother, along with other caregivers who participated in the meeting,

described the significant investments their families made in early intervention teachers, as well as the hundreds of hours spent learning braille, practicing how to navigate with a white cane, memorizing emergency escape routes, learning to cross the road safely, mapping out dark hallways at school, and completing homework assignments with assistance from special teachers and family members.[47]

While such adaptations require considerable investments of time and resources, they are not sufficient in and of themselves to 'level the playing field.' Certain career tracks may remain out of reach for the visually-impaired population. One individual publicly stated, "I knew I could adapt to being a blind person but that my passions for math and science may not be realized and that was devastating."[47] Insufficient access to disability services, as well as society's orientation around the need for sight, puts many individuals with visual impairment at a disadvantage. According to the 2015 American Community Survey, only 15% of individuals with a visual disability earn a bachelor's degree or higher and just 28% find full-time/full-year employment.[48] Nearly 30% of blind Americans live below the poverty line.[48]

Moreover, affected individuals often contend with feelings of social isolation. They may be perceived by others as "less intelligent" and may face bullying.[47] The inability of individuals with *RPE65*-mediated retinal disease to navigate independently in dimly-lit settings limits their ability to participate in social activities. Both patients and IRD clinical experts highlighted the inability to see in dark settings as among the most limiting features of conditions such as LCA. Several of the participants in the Phase III trial of VN noted that their condition did not permit them to participate in sports, go to the movies, leave the house without assistance on a cloudy day or after dusk, dine without special lighting accommodations, or even to see the facial features of friends and loved ones. One participant described her condition as follows: "it was like sunglasses over your eyes while looking through this little tunnel."[47] The potential for a therapy to increase light sensitivity and mobility in dim lighting, therefore raises great hope among the inherited retinal disease community. If VN receives FDA approval, patients and families are hoping the treatment will become rapidly available for all patients with biallelic *RPE65*-mediated retinal disease.

3. Summary of Coverage Policies and Clinical Guidelines

3.1 Coverage Policies

Besides supportive treatment, no other treatment is available to stop the progression or to improve vision for LCA and similar IRDs. Instead, individuals with IRD must turn to supportive services and rehabilitation services to address their needs as their vision wanes. Because these services are, many times, provided outside of the health care system, traditional coverage policies do not address the needs of visually impaired individuals. For example, while Medicare does cover some rehabilitative services, other supportive services, like white canes or guide dogs, are not covered by private or public payers. In 2002, the Centers for Medicare and Medicaid Services (CMS) issued a program memorandum indicating that individuals who are blind or visually impaired are eligible to receive rehabilitation services from covered providers as prescribed by a physician.[49] This includes therapeutic services relating to mobility, daily living activities, and other medically necessary rehabilitation goals.

In order to address these gaps in services, state-level agencies, national organizations, and local organizations have created different programming designed to support individuals with low vision or blindness, so as to provide services and supports not provided by the healthcare system. For example, the state of Missouri, through their Department of Social Services, provides rehabilitation services, such as job training, mobility, independent living training, children's services, and screening and treatment programs for the blind.[49] Other organizations, including American Council of the Blind, American Foundation for the Blind, Guide Dogs for the Blind, National Federation of the Blind, Foundation Fighting Blindness, and many others, provide services, resources, and funding to allow individuals to seek out the support they need.

3.2 Clinical Guidelines

The American Academy of Ophthalmology (AAO) has issued eye care guidelines for patients with inherited retinal disease. These guidelines focus on the diagnosis and screening of IRDs. Genetic testing and screening were particularly emphasized. These guidelines do not discuss treatment options as, until now, there have been few or no treatments available to individuals with IRDs.[50]

We found no guidelines that discussed gene therapy as a treatment for IRDs.

4. Clinical Effectiveness

4.1 Overview

To inform our analysis of the comparative clinical effectiveness of VN for confirmed biallelic *RPE65*-mediated inherited retinal diseases, we abstracted evidence from available clinical studies, whether in published or unpublished form (e.g., conference abstracts or presentations, FDA review documents).

Our population included individuals with *RPE65*-mediated inherited retinal diseases, particularly Leber Congenital Amaurosis type 2 (LCA2), Retinitis Pigmentosa type 20, Early Onset Severe Retinal Dystrophy (EOSRD), Rod Cone Dystrophy, and Severe Early Childhood Onset Retinal Dystrophy (SECORD).

Our primary intervention of interest was VN; studies of related *RPE65* gene therapies will be discussed in a contextual fashion. Because there is no current treatment for blindness caused by *RPE65*-mediated retinal diseases, we did not limit our search to any specific comparator, outcome, timing, or setting to capture the full universe of available data.

When reviewing clinical evidence in ultra-rare populations, ICER acknowledges the challenges of study design, recruitment, and availability of data on long-term outcomes. As such, we aim to add specific context to our findings, when possible.

4.2 Methods

Data Sources and Searches

Procedures for the systematic literature review on VN for *RPE65*-mediated retinal diseases followed established methods in systematic review research.[51] We conducted the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[52] The PRISMA guidelines include a checklist of 27 items, further detail of which is available in Appendix Table A1.

We searched MEDLINE, Cochrane Central Register of Controlled Trials, and EMBASE for relevant studies. We limited each search to English-language studies of human subjects and excluded articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news items. To supplement the above searches and ensure optimal and complete literature retrieval, we performed a manual check of the references of recent peer-reviewed publications and public

reports. Further details of the search algorithms, methods for study selection, and data extraction are available in Appendix A and Appendix D.

Study Selection

We included evidence from all relevant clinical studies, irrespective of whether they used a comparative study design. We did not include studies that used a product other than VN.

In recognition of the evolving science for gene therapy, we supplemented our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature that met ICER standards for review (for more information, see https://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/). We excluded abstracts that reported data also available in peer-reviewed publications. Where data was only available from a press release, we did not include the information in our review.

Data Extraction and Quality Assessment

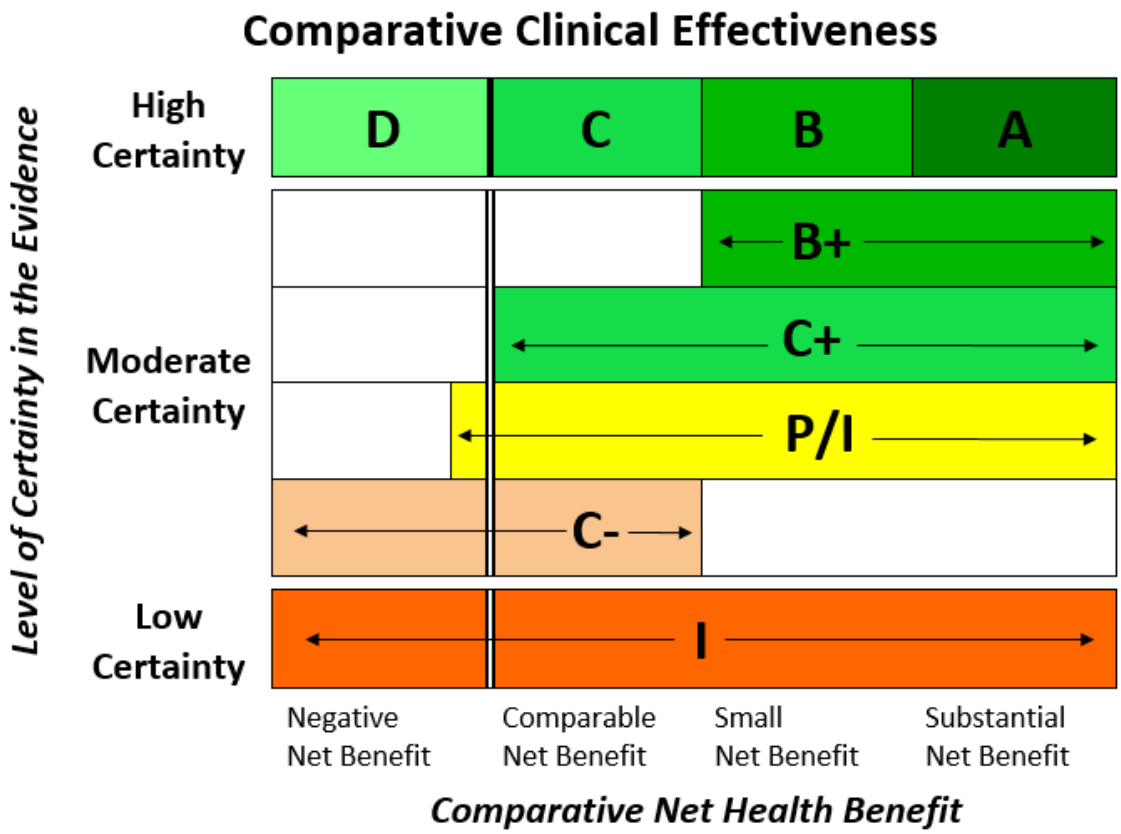
Data were extracted by one member of the research team and validated by two others. Because only one study was a randomized controlled trial, the overall quality of the supporting evidence was moderate. Attempts were made to negotiate with the sponsor to gain insight into endpoints that were missing or unclear. Where supplementary evidence was provided, it was incorporated into Section 4, as appropriate.

Assessment of Level of Certainty in Evidence

We used the ICER Evidence Rating Matrix (see Figure 4.1) to evaluate the evidence for a variety of outcomes. ICER does not change its approach to rating evidence for ultra-rare conditions. The evidence rating reflects a joint judgment of two critical components:

a) The **magnitude** of the difference between a therapeutic agent and its comparator in "net health benefit" – the balance between clinical benefits and risks and/or adverse effects AND
b) The level of **certainty** in the best point estimate of net health benefit.[53]

Figure 4.1. ICER Evidence Rating Matrix



A = "Superior" - High certainty of a substantial (moderate-large) net health benefit
B = "Incremental" - High certainty of a small net health benefit
C = "Comparable"- High certainty of a comparable net health benefit
D = "Negative"- High certainty of an inferior net health benefit
B+ = "Incremental or Better" - Moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit
C+ = "Comparable or Better" - Moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit
P/I = "Promising but Inconclusive" - Moderate certainty of a comparable, small, or substantial net health benefit, and a small (but nonzero) likelihood of a negative net health benefit
C- = "Comparable or Inferior" - Moderate certainty that the point estimate for comparative net health benefit is either comparable or inferior
I = "Insufficient" - Any situation in which the level of certainty in the evidence is low

Assessment of Bias

As part of our quality assessment, we evaluated the evidence base for the presence of potential publication bias. Given the emerging nature of the evidence base for newer treatments, we performed an assessment of publication bias using the clinicaltrials.gov database of trials. We scanned the site to identify studies completed more than two years ago that would have met our inclusion criteria and for which no findings have been published. Any such studies may have provided qualitative evidence for use in ascertaining whether there was a biased representation of

study results in the published literature. For this review, we did not find evidence of any completed studies that have not been published.

Data Synthesis and Statistical Analyses

Data on relevant outcomes were summarized in evidence tables (see Appendix F) and are synthesized qualitatively in the text of the report.

4.3 Results

Study Selection

Our literature search identified 359 potentially relevant references (see Appendix Figure A1), of which 13 met our inclusion criteria; these citations related to four individual studies. Primary reasons for study exclusion included being the wrong type of study (non-interventional) or the wrong intervention (different vector).

Details of all included studies are summarized in Appendix F and in the sections that follow.

Key Studies

Three of the four key studies had no control arm; however, two studies used the patient's untreated eye as a control. A safety and proof of concept study enrolled three individuals. The Phase I study (Study 101) was a dose escalation trial that treated 12 participants in their worse eye. Study 102, a Phase I follow-on to Study 101, treated the same participants in their contralateral eye.

The recently published Phase III randomized control trial (Study 301, n=31) provides the best quality evidence on the clinical effectiveness of VN.

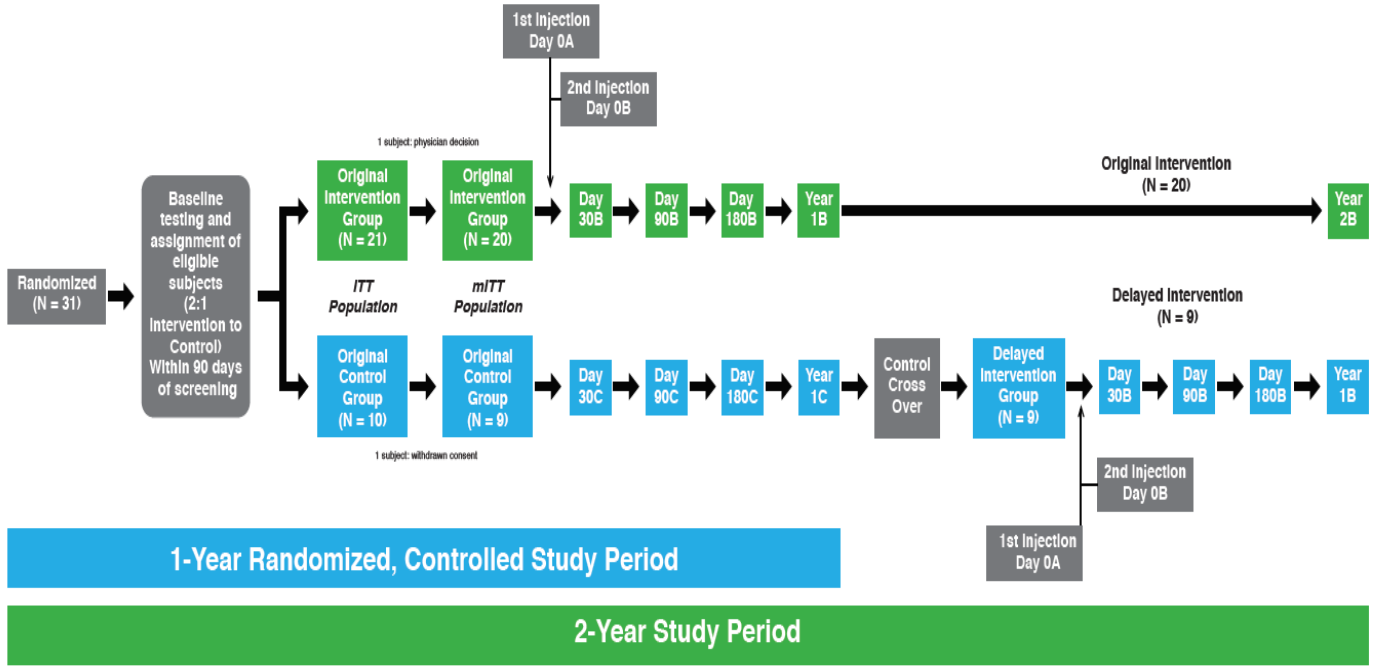
Long-term data from each study were included in our review, whether from publications or from conference proceedings. Data available only through a press release or annual report were not included in our evidence summary.

It is important to understand the challenges of completing large, randomized clinical trials in an ultra-rare disease population. ICER strives to consider feasibility constraints when reviewing evidence in these circumstances.

Phase III: Study 301

Study 301, the phase III trial of VN, enrolled 31 subjects randomized in a 2:1 fashion. Twenty-one subjects were randomized to treatment and 10 were randomized to treatment after one year (control cross-over). There was one dropout in each arm leaving 20 treated and nine control participants. Statistical analysis was performed on the intent-to-treat population and a modified intent-to-treat population (for a protocol deviation) (see Figure 4.2).

Figure 4.2. Study 301 Protocol Design[31,54]



ITT, intent-to-treat; mITT, modified intent-to-treat.

The average age of subjects enrolled in the study was 15.1 years (SD 10.9; range 4-44). Participants had a confirmed biallelic *RPE65* genetic mutation, visual acuity worse than or equal to 20/60, and/or visual field less than 20 degrees in any meridian. See Table 4.1 for study demographics.

Most characteristics were balanced between the two groups, although US vs non-US participants and passing levels on the multi-luminance mobility test (MLMT; described in detail below) were imbalanced. At baseline, 57% of the intervention group passed the test at the lux level of <125 (vs. 40% in the control arm) and 43% of the intervention group passed at ≥ 125 lux (vs. 60% in the control arm). It is unclear whether this imbalance affected the primary endpoint analysis, but imbalances like this are to be expected in trials with very few participants.

Table 4.1. Study 301 Demographics[31,55]

	Intervention (N=21)	Control (N=10)
Mean (SD) Age	14.7 (11.8)	15.9 (9.5)
Male	9 (43%)	4 (40%)
Race	-	-
White	14 (67%)	7 (70%)
Asian	3 (14%)	2 (20%)
American Indian or Alaska Native	2 (10%)	1 (10%)
Black or African American	2 (10%)	0
Ethnicity (Not Hispanic)	16 (76%)	9 (90%)
US Resident	17 (81%)	6 (60%)
Less than 10 years old	9 (43%)	4 (40%)
MLMT Passing Level at Baseline	-	-
< 125 lux	12 (57%)	4 (40%)
≥ 125 lux	9 (43%)	15 (60%)

Quality of Individual Studies

Using criteria published by the US Preventive Services Task Force (USPSTF; see Appendix D), we rated the phase III trial (Study 301) to be of fair quality. An imbalance in the randomized cohort's ability to pass the MLMT, the inability to fully blind investigators or participants, and changes in endpoints from the original study design led to the fair rating. Studies that lacked a control group or were only available in grey literature sources were not assigned a quality rating. The limitations, uncertainties, and gaps in evidence are discussed in the Controversies and Uncertainties section.

Clinical Benefits

As with many ultra-rare conditions, the endpoints used in the clinical trials of VN are novel. This was necessary to account for the unique pathophysiology and patient-centric needs of those with biallelic *RPE65*-mediated retinal disease, which may differ from other retinal diseases such as macular degeneration. An in-depth explanation of each endpoint is provided prior to data presentation.

Primary Endpoint

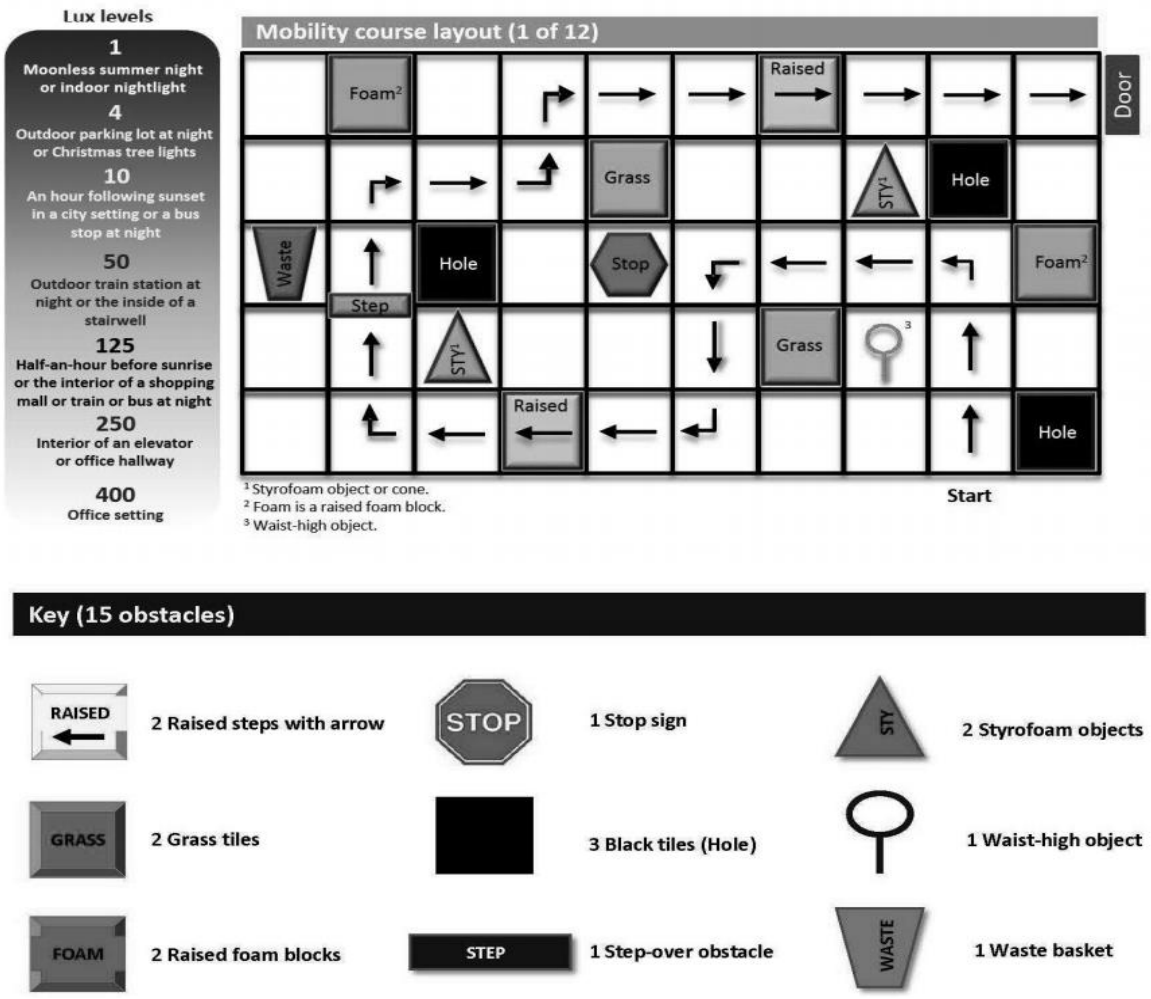
Change in Bilateral Multi-luminance mobility test (MLMT)

The primary efficacy endpoint for Study 301 was change in bilateral multi-luminance mobility test (MLMT) performance.[31] The MLMT was created by the study sponsor in conjunction with the FDA to define a quantifiable measure of functional vision that incorporates aspects of visual acuity, visual field, and light sensitivity.[56] The MLMT tests the ability to navigate an obstacle course at varying light levels and was designed to be a patient-centric endpoint for biallelic *RPE65*-mediated

retinal disease; however, the outcome could not directly assess real-world functional improvements.[57]

The MLMT is a 5ft by 10ft obstacle course with 12 unique but standardized layouts, each with the same number of arrows, turns, and hazards (designed for a visual acuity of 20/200 on the Snellen chart).[31,56] Participants are tested under seven different lighting conditions or lux levels.[57] Individuals without vision impairment pass this test at the lowest light level (1 lux) 100% of the time. Descriptions of each lux level and a visual model of the MLMT can be seen below in Figure 4.3.

Figure 4.3. Multi-luminance Mobility Test (MLMT) Example and Light Levels[57]



Passing is defined as completing the course in three minutes or less with fewer than four errors (total obstacles=15; <0.25 accuracy).[31] Each lux level is mapped to a number ranging from 0 to 6 with the lowest light level (1 lux) having the highest score (6). Passage at a 50-lux level corresponds to a score of 3 (see Table 4.2). Change in MLMT is calculated by taking the difference between the

baseline and 1-year score. Positive change numbers indicate passage at lower light levels (positive outcome).

Table 4.2. Scoring for Multi-Luminance Mobility Test to Calculate Change Score[31]

Mapping of Passing Lux Level to Score							
Lux	1 (lowest)	4	10	50	125	250	400 (highest)
Score	6	5	4	3	2	1	0

Per the Study 301 protocol, participants were dark adapted for 40 minutes, randomly assigned a patched eye and were started at the lowest light levels, moving higher until they passed.[56] Participants were randomized to a new configuration of the test each walk to reduce the chance of course memorization.[31] The walk was performed on each eye individually, as well as bilaterally (i.e., binocularly). The primary endpoint was reported as the bilateral change in MLMT score; however, change in scores for the first eye were reported as a secondary endpoint.[31] Walks were performed at baseline, 30, 90, 180 and 365 days after randomization.[31] A change of one light level in passing was considered clinically meaningful by the sponsor.[9]

All walks were audio and videotaped and scored by two masked, specially trained evaluators at a separate location from the testing site.[31]

The results show that participants treated with VN saw a difference of 1.6 (95% CI, 0.72 to 2.41) in their bilateral MLMT change score at 1 year compared to placebo (intervention arm score improvement of 1.8, control arm score improvement of 0.2).[9,31] This result indicates that participants treated with VN were able to see in lower light conditions.

Zero participants in the intervention group had worsening MLMT scores at one year while three participants in the control group were unable to pass at their baseline lux level one year later.[31] Additionally, 65% of the intent-to-treat intervention arm showed maximal improvement in MLMT (passing at 1 lux) as compared to zero participants in the control arm.[31]

As noted above, more patients in the intervention arm than the control arm were able to pass the test at low light levels (<125 lux) at baseline (57% vs 40%), suggesting that patients in the control arm had somewhat more advanced disease.[31]

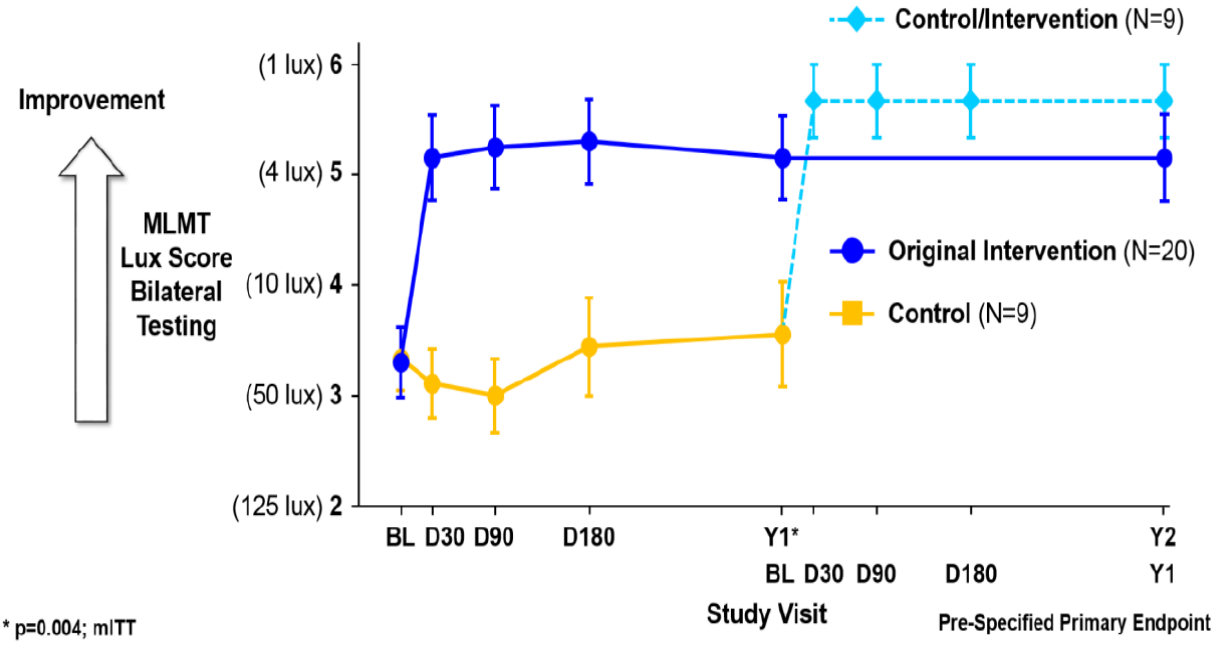
Table 4.3. Change in MLMT Score at 1 year[31]

MLMT Score Change from to 1 Year in Intent-To-Treat Population				
	Intervention (n=21)	**Control (n=10)**	**Difference (95% CI)**	**P-value (from permutation test)**
Both eyes				
Mean (SD)	1.8 (1.1)	0.2 (1.0)	1.6 (0.72 to 2.41)	0.0013
Range	0 to 4	−1 to 2	-	-
Median (IQR)	2 (1 to 3)	0 (-1 to 1)	-	-
First eye				
Mean (SD)	1.9 (1.2)	0.2 (0.6)	1.7 (0.89 to 2.52)	0.0005
Range	0 to 4	-1 to 1	-	-
Median (IQR)	2 (1 to 3)	0 (0 to 1)	-	-
Second eye				
Mean (SD)	2.1 (1.2)	0.1 (0.7)	2.0 (1.14 to 2.85)	0.0001
Range	0 to 5	-1 to 1	-	-
Median (IQR)	2 (1 to 3)	0 (0 to 1)	-	-

Permutation test p-value represents the proportion of p-values that are smaller than the value observed in the actual dataset using Wilcoxon rank-sum and exact method.

Two-year data were recently presented at the Association for Research in Vision and Ophthalmology (ARVO) 2017 Meeting. Mean bilateral MLMT score change in the intervention cohort (original intervention) was 1.9 (SD, 1.1) showing that benefits were sustained after the first year.[54] Results from the cross-over control group were also presented (delayed intervention arm). All nine subjects in the cross-over control arm went on to receive VN after completing the protocol-required control period. At one-year after treatment, these subjects showed a mean bilateral MLMT score change of 2.1 (SD, 1.6).[54] It is unclear why the delayed intervention cohort received greater benefit than the original intervention cohort; however, familiarity with the MLMT course and expectations may have played a role. See Figure 4.4 for lux score and change score data.

Figure 4.4. Observed Mean Bilateral MLMT Lux Score in Modified Intent-to-Treat Participants Out to 2-years in Phase III Study[9]



Secondary Endpoints

Three secondary endpoints were evaluated in a hierarchical order: full-field light sensitivity (FST) using white light averaged over both eyes, monocular MLMT score change for the first treated eye, and visual acuity averaged over both eyes.[9]

Full-Field Light Sensitivity Threshold (FST)

Full-field light sensitivity testing was performed using both white and chromatic stimuli and was reported as log10(cd.s/m^2). Light sensitivity testing is performed to assess photoreceptor response and a subject's perception of light sensitivity at different luminance levels.[9] White and blue lights target the rod photoreceptors while red light targets cone photoreceptors.[58]

In Study 301, participant's eyes were dilated, double patched and dark adapted for 40 minutes. Each eye was then tested (while the contralateral eye remained patched) using a Ganzfeld dome (a 40-cm dome shaped white screen).[9] Lights flashed inside the dome alongside a sound (beep or

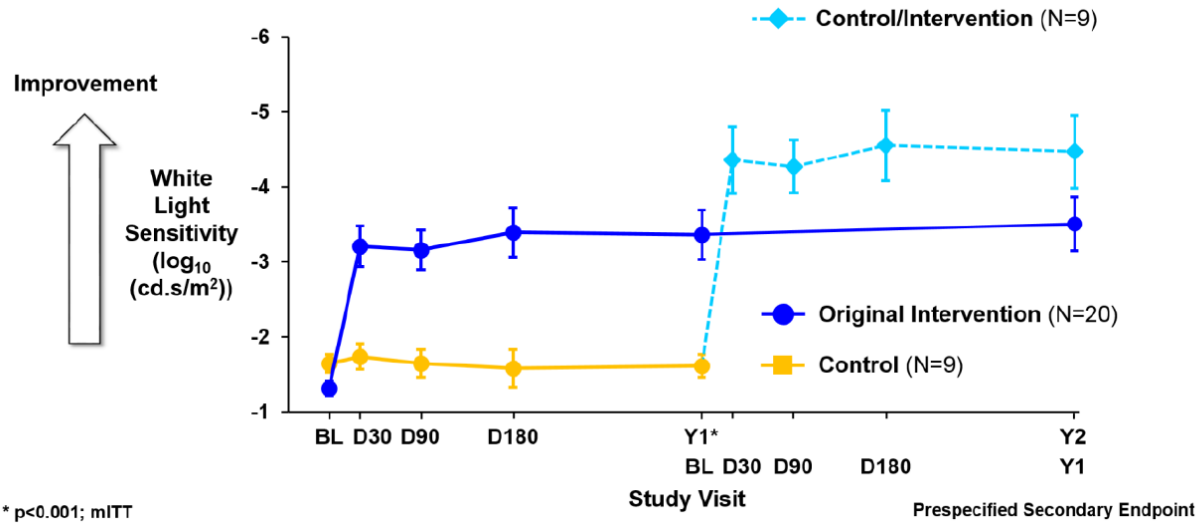
buzz) to notify the participant to indicate whether they see the light flash or not. Light flashes vary in intensity from bright to dim.

The study sponsor indicated that FST is a valuable outcome for the IRD population because it is not affected by nystagmus, allows for testing of those with high levels of visual disability, and does not incorporate sampling bias from tests where specific areas of vision are targeted.[9] As a disease predominantly defined by night blindness, full-field light sensitivity threshold testing was thought to be one of the most relevant measures to show benefit from VN therapy.[9]

For this measure, a negative result indicates improved light sensitivity.[9] Clinically meaningful improvement in FST was identified as a 1 log change (10 dB).[31]

In Study 301, participants in the intent-to-treat intervention group saw an improvement in white light FST of -2.08 log 10(cd.s/m^2) between baseline and 1-year with no improvement at 1-year in the control group (difference between groups: -2.11, 95% CI, -3.19 to -1.04) (Figure 4.5).[31] Results were seen immediately after treatment and continued out to one-year. Data qualify issues in FST measurements included missing data from unreliable testing (protocol-related deviations).[31] A quantitative description of missing data was not provided. The sponsor acknowledged that missing data was not imputed.[31] It is unclear how missing data may have affected the results.

Figure 4.5. Observed Mean FST White Light Averaged Over Both Eyes in the MITT Population in the Phase III Study[9]



The modeled treatment group difference between the intervention arm and control arm in Study 301 at 1-year was -2.11 (95% CI, -3.19 to -1.04) log10(cd.s/m^2).[9] Two year data showed a -2.27

log10(cd.s/m^2) in the original intervention arm indicating a durable response past the primary endpoint.[54] The cross-over control arm experienced a -2.86 log10(cd.s/m^2) difference at 1-year.[54]

An exploratory analysis modeled light sensitivity in red and blue light using a repeated measures model. The change in estimates of full-field light sensitivity with blue light averaged over both eyes was -1.96 log10(cd.s/m^2) (SD 0.37) in the intervention arm versus a change of 0.13 log10(cd.s/m^2) (SD 0.49) in the control arm (p-value=0.002).[31] The change in estimates for full-field light sensitivity with red light averaged over both eyes was similar (intervention arm mean change -1.29 log10[cd.s/m^2), SD 0.17; control arm mean change 0.16 log10[cd.s/m^2), SD 0.24; p-value=<0.001).[31]

It was noted that 90% of subjects with improvements on the MLMT also had clinically meaningful improvement in light sensitivity (FST).[31] A study to assess the relationship between found a strong correlation between these two measures (-0.74; p<0.001).[56]

Change in First Treated Eye Multi-Luminance Mobility Test (MLMT)

Change in monocular MLMT scores for the first treated eye also showed a difference in score of 1.7 from baseline to 1-year between the intervention and control arm (see Table 4.4).[31,55]

Table 4.4. Change in First Eye MLMT Score at 1 year in Study 301[31]

First Eye	Intervention N=21	Control N=10	Difference (95% CI)	Permutation p-value
Score Change				
Mean (SD)	1.9 (1.2)	0.2 (0.6)	1.7 (0.89 to 2.52)	0.001
Range (min, max)	0 to 4	-1 to 1		
Quartile				
25th	1	0		
Median	2	0		
75th	3	1		

Visual Acuity

Best corrected visual acuity (BCVA), or best vision an individual can achieve with the assistance of corrective lenses, averaged over both eyes, was evaluated as a secondary endpoint in Study 301. Using a scale adapted from Holladay,[59] which can calculate a visual acuity score for individuals who are unable to read conventional charts through the use of hand motion and counting fingers, investigators averaged together the BCVA of each individual eye. Over one year of follow-up, the mean treatment group difference (intervention – control) was -0.16 LogMAR (95% CI, -0.41 to 0.08; 0.029 decimals) which corresponded to a gain of 8.1 letters on the eye chart.[9] A post-hoc analysis using a different scale from Lange and colleagues[60] found comparable results, although differences

reached statistical significance (9.0 letters in the intervention group vs. 1.6 letters in the control group; difference of 7.4 letters; 95% CI 0.1 to 14.6; post-hoc p=0.0469).[31]

Study 301 investigators considered a meaningful change in visual acuity to be a gain of at least 15 letters (≤0.3 LogMAR) on the Early Treatment Diabetic Retinopathy Study eye chart. While no control participants achieved a meaningful change in visual acuity over the first year of the trial, six of 20 participants in the intervention group gained 15 or more letters in the first eye and four of 20 participants achieved such a change in the second eye.[31]

We heard from experts in the field that there are flaws with averaging visual acuity across both eyes, especially if one eye has extreme values. As part of our review, we assessed the individually-reported first and second eye visual acuity data published in the Study 301 supplement using a modified impairment method ((best eye*4+worst eye*1)/5 at baseline and 1-year) to calculate a "best eye visual acuity".[31,61] We found that individuals in the treatment arm saw an average improvement in visual acuity of -0.17 LogMAR at 1-year compared to a smaller improvement of -0.03 LogMAR in the control group. We did not perform statistical analysis.

Additionally, the FDA reviewed the data on monocular eye improvements in the first year and found no statistically significant differences between the treatment and control groups.[55]

Exploratory Endpoints

Visual Field

Visual field is an important outcome for biallelic *RPE65*-mediated retinal diseases. Unlike some other visual impairments, rods play a primary role in these diseases and degenerative loss of visual field is documented in the natural history.[8] Nearly 100% of participants with *RPE65*-mediated retinal diseases were found to have peripheral retinal abnormality.[4]

Multiple visual field measures were used in Study 301 as exploratory endpoints. The Goldmann visual field (GVF) perimetry test was used to measure kinetic fields, while the Humphrey computerized test was used to measure static fields in the macula and fovea. Within the GVF, both III4e and V4e stimuli were used; however, the smaller III4e was used whenever possible.[a]

Participants in Study 301 were tested in each eye individually. The Goldmann visual field test requires manual movement of a stimulus from non-seeing to seeing areas in the participant's visual field. Participants were instructed to press a button (or similar device) when the light became visible. Contour lines, also called isopters, were drawn to outline the visual fields. Scotomas, or areas of decreased light sensitivity, were mapped within these fields. Goldmann visual field (GVF) was reported as sum total degrees.[31]

[a] The "III" defines the stimulus size III while the"4e" identifies the intensity of the stimulus used.

The Humphrey visual field (HVF) test utilizes a machine (computer) to assess visual field and has become more common in clinical practice than Goldmann perimetry. In a Humphrey examination, the participant hits a button when a light is seen in the periphery while eyes are focused centrally. In Study 301, the Humphrey analyzer focused on the central areas of the retina, namely the macula and fovea. Humphrey visual field data are reported in decibels (dB). For Humphrey macular VF, a Fastpac strategy with size V test stimulus was used.[31]

Goldmann visual field measurement showed a statistically significant difference in total sum degrees in the intervention group compared with the control group following treatment with VN (Table 4.5).[31] However, differences in the median and mean baseline Goldmann visual field (sum total degrees) between the intervention and control arms were identified (median intervention = 153; median control = 372).[31] It is unclear how these differences may have influenced the statistically significant finding in this secondary endpoint.

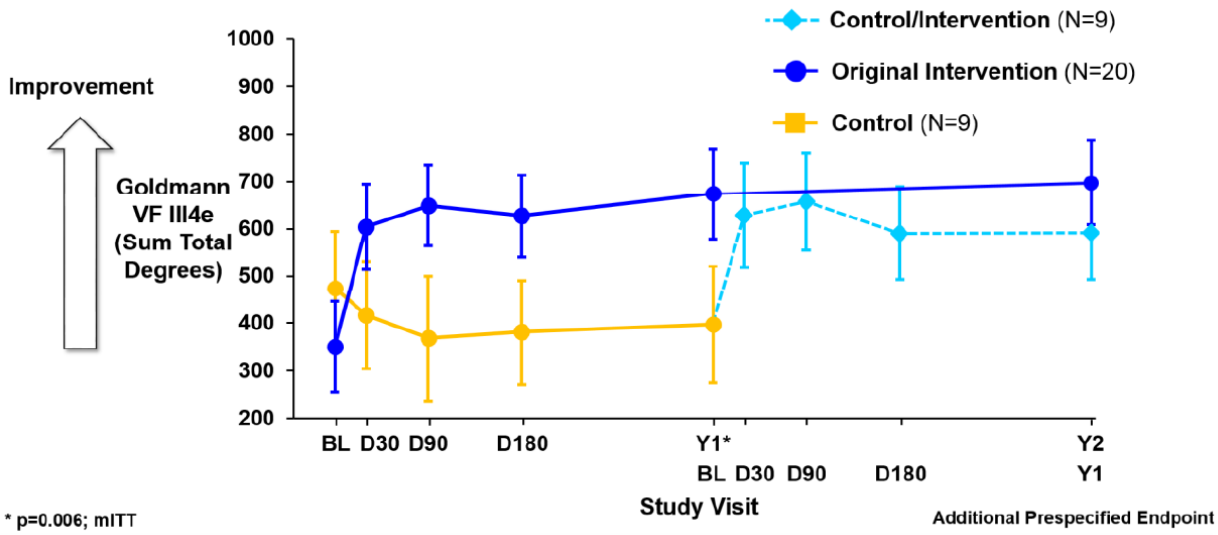
A statistically significant difference in macular threshold visual field was also reported; however, foveal sensitivity showed no differences between the arms (Table 4.5).[31] Authors of the phase III study indicated that participants in the intervention group had foveal sensitivities closer to normal levels at baseline compared with those in the control group and therefore hypothesize that lack of significant findings may be due to the limited potential for improvement.[31]

Table 4.5. Visual Field Outcomes[31]

Study 301 Visual Field Summary								
	Intervention (n=21)			Control (n=10)				1 year
	Baseline	1 year	Change	Baseline	1 year	Change	Difference in Arms (95% CI)	P-value (post-hoc)
N	20	20	19	10	9	9	-	-
Goldmann Visual Field III4e (Sum Total Degrees)								
Mean (SD)	332.9 (413.3)	673.9 (423.7)	302.1 (289.6)	427.7 (372.3)	397.8 (367.3)	-76.7 (258.7)	378.7 (145.5 to 612.0)	.0059
Median (IRQ)	153 (53 to 469)	592 (287 to 1045)	257 (19 to 520)	372 (109 to 686)	349 (105 to 474)	-4 (-186 to 31)	-	-
Humphrey Visual Field, Foveal Sensitivity (dB)								
Mean (SD)	22.4 (6.8)	25.8 (9.1)	2.4 (9.7)	17.6 (8.9)	21.5 (8.9)	2.3 (5.3)	0.04 (-7.1 to 7.2)	.18
Median (IRQ)	24 (19 to 27)	30 (21 to 32)	5 (-1 to 7)	17 (11 to 27)	26 (17 to 28)	2 (-1 to 3)	-	-
Humphrey Visual Field, Macula Threshold (mean dB)								
Mean (SD)	16.1 (5.5)	24.0 (8.0)	7.7 (6.2)	14.4 (8.0)	15.8 (7.4)	-0.2 (1.7)	7.9 (3.5 to 12.2)	0.0005
Median	15 (12 to 21)	28 (19 to 29)	8 (4 to 13)	16 (10 to 22)	16 (13 to 21)	-1 (-1 to 1)	-	-

Goldmann visual field and Humphrey macular threshold improvements were stable out to two-years in the original intervention group.[54] Cross-over controls (delayed intervention) showed a mean change in sum total degrees in Goldmann visual field of 194.3 (244.7) and mean change in Humphrey visual field macula threshold of 5.23 (SD, 9.92) at one year.[54]

Figure 4.6. Observed Mean Goldmann Visual Field Sum Total Degrees, Both Eyes, in Modified Intent-To-Treat Participants in Phase III Study[9]



Mean ± standard error. BL, baseline; GVF, Goldmann visual field; III4e, size and intensity of stimuli

Quality of Life

Study 301 included two patient-centric assessments, a modified visual function questionnaire (VFQ-25), and an in-home orientation and mobility assessment. Data presented to the FDA on the modified VFQ-25 can be seen in Table 4.6. Both subject-score and parent-score averages were significantly higher in the treated arm compared to the control arm at one year.[9] The sponsor communicated that the modified VFQ-25 tool is not validated, presenting a major limitation in our assessment of the effect of VN on quality of life.

The in-home mobility assessment included independent specialists watching subjects in their personal environment and documenting aspects of functional visual abilities.[31] A qualitative description of the findings provided to the FDA stated a correlation was found between improved MLMT scores and better in-home mobility testing outcomes; however, no data was available for this review.[9]

Table 4.6. Visual Function Questionnaire Average Scores (ITT)[9]

	Intervention N=21		Control N=10		Intervention N=21		Control N=10		Difference (Intervention-Control)	
	Observed				Change from Baseline					
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	Difference 95% CI	p- value
Subject Scores										
Baseline	21	4.4 (1.4)	9	4.9 (1.5)	-	-	-	-	-	-
Year 1	20	7.0 (1.9)	9	5.1 (1.8)	20	2.6 (1.8)	9	0.1 (1.4)	2.4 (1.0 to 3.8)	0.001
Parent Scores										
Baseline	15	3.6 (1.3)	5	3.3 (1.7)	-	-	-	-	-	-
Year 1	15	7.5 (1.5)	5	3.1 (1.8)	15	3.9 (1.9)	5	-0.2 (1.3)	4.0 (2.1 to 6.0)	0.002

Harms

In total, 41 participants and 81 eyes are part of ongoing safety monitoring.[9] At this time, more than ten individuals have been followed for safety issues for the past seven years.[9] The risks of VN are most frequently related to the surgical component of the procedure (see Table 4.7).[17] A full summary of treatment emergent adverse events on the full safety cohort can be found in Table 4.7.

Table 4.7. Summary of Treatment Emergent Adverse Events from Phase I and Phase III Studies[9]

	Phase I (N=12)	Phase III (N=29)	Total Population (N=41)
At least 1 TEAE	12 (100%)	29 (100%)	41 (100%)
Serious TEAE*	5 (42%)	4 (14%)	9 (22%)
TEAE Severity			
Mild	4 (33%)	10 (34%)	14 (34%)
Moderate	6 (50%)	15 (52%)	21 (51%)
Severe	2 (17%)	4 (14%)	6 (15%)
Vector-related TEAEs	0	3 (10%)	3 (7%)
Procedure-related TEAEs	10 (83%)	19 (66%)	29 (71%)
Ocular TEAEs	11 (92%)	19 (66%)	30 (73%)

*Phase I Serious TEAS: increased intraocular pressure, anal fistula, cryptorchidism, paresthesia, lower limb fracture; Phase III Serious TEAS: retinal disorder, convulsion, adverse drug reaction (2), menorrhagia, pneumonia; TEAES: Treatment Emergent Adverse Events

Secondary safety studies looked at the immune response to VN treatment and showed no cytotoxic responses to either the vector or the gene. Neutralizing antibodies remained near baseline after injection.[62] Vector was found in the tears and blood of some participants, but no systemic immune responses were reported.[31,63] One subject who underwent contralateral eye treatment in the phase I follow-on study had consistently increased antibody titers following their first treatment that did not materialize into clinical symptoms.[58] There are no data on whether reinjection in the same-eye

would cause an immune response, as same-eye retreatment has only been evaluated in animal studies.

Two treatment related serious adverse events following VN treatment occurred in the study population; one in the phase I follow-on trial and one in the phase III trial.[55]

One participant in the phase I follow-on study developed a bacterial (*Staphylococcus epidermidis)* endophthalmitis after surgery. This individual was treated with intravitreal antibiotics and periocular steroids; however, due to increased intraocular pressure from these treatments, experienced irreversible optic atrophy.[55,58] Data from this subject were not used in statistical analyses of efficacy.[58]

In the phase III study, a participant with an average (both eye) visual acuity of 1.95 LogMAR at baseline experienced decreased central vision and foveal thinning leading to worse visual acuity at 1 year (4.0 LogMAR).[31] Decreases in retinal thickness were also reported in *RPE65* gene therapy trials using a different vector following injection in the foveal area.[64]

Most of the adverse events reported in the safety population were ocular in nature (63% subjects).[55] A summary of ocular-specific adverse events is reported in Table 4.8.

Table 4.8. Summary of Ocular Adverse Events[55]

Ocular AEs	Subjects (N=41)	Treated Eyes (N=81)
Any ocular AE	30 (73%)	51 (63%)
Conjunctival Hyperemia	9 (22%)	9 (11%)
Increased Intraocular Pressure (IOP)	8 (20%)	10 (12%)
Cataract	7 (17%)	11 (14%)
Retinal Tear	4 (10%)	4 (5%)
Eye Pain	4 (10%)	4 (5%)
Corneal Dellen	3 (7%)	3 (4%)
Eye Inflammation	3 (7%)	5 (6%)
Subretinal Deposits	3 (7%)	3 (4%)
Endophthalmitis	1 (2%)	1 (1%)
Eye Irritation	3 (7%)	3 (4%)
Macular Hole	3 (7%)	3 (4%)
Maculopathy	2 (5%)	3 (4%)
Foveal Thinning	1 (2%)	2 (2%)
Retinal Hemorrhage	1 (2%)	1 (1%)
Fovea Dehiscence	1 (2%)	1 (1%)

Controversies and Uncertainties

There are limitations of the evidence base leading to many uncertainties. These include interpretation of the measured outcomes, duration of effect, variation of effect with age, and procedure technique.

Interpretation of Measured Outcomes

The endpoints used in the VN trials are novel. The primary endpoint, the multi-luminance mobility test (MLMT), was designed to capture a critical aspect of the disease process (i.e. being unable to navigate in low light); however, the test itself has not been correlated to outcomes measured in a real-world setting. As such, there remains uncertainty regarding what a one to two-unit improvement in MLMT score means for patients as they go about their day-to-day activities.

Duration of Effect

Long-term efficacy remains a question for this treatment. While four-year data are available in a select number of treated individuals, whether the benefits of VN last five years, 10 years, or a lifetime are unknown. A clinical expert involved in the phase I trial presented a testimonial to the FDA that the effects in navigating the MLMT did not diminish in two participants (single-eye treatment) after seven years. Even if treated retinal cells receive unlimited benefit, how that benefit may be offset by worsening vision from ongoing degeneration remains uncertain.

Individuals with an *RPE65* mutation have significant retinal degeneration leading to worse functional vision over time.[65] Whether VN has the potential to reduce or eliminate retinal degeneration is currently unknown; however, at least one researcher has published evidence that, in humans, *RPE65* gene therapy does not affect the progressive nature of retinal degeneration.[34] These studies used gene therapies other than VN, however. Multiple differences existed between these therapies and VN including the vector, manufacturing process, surgical procedure, and patients enrolled in the trials. This makes comparing outcomes across trials difficult. We are uncertain whether the deterioration seen in other therapies will occur in individuals who received VN. One challenge to assessing ongoing degeneration is the pace of deterioration in functional outcomes. It may take up to a decade to observe worsening in visual outcome measures in this population.[17]

Variability of Treatment Effect

Statements have been made by study investigators regarding improved efficacy in younger individuals with a healthier retinal structure.[17,63] Data to support this are scant, although the youngest participants in the phase I study did show substantial improvements in the multi-luminance mobility test (MLMT) while older participants did not show such a pronounced benefit.[63] The phase III study included a greater number of younger individuals in the treatment arm as

compared to the control arm.[9] Given the few candidates that have received treatment, an adequately-powered subgroup analysis of this question was not feasible. Testimonials provided to ICER and the FDA do point towards younger participants experiencing greater results after treatment.

The location of retinal injection plays a role in efficacy and safety of VN treatment. Whether efficacy improves when larger retinal areas are treated (at one time or over time with sequential treatment), has not yet been evaluated. The pathophysiology of rod versus cone contributions to visual function in this population and the effect of *RPE65* gene replacement on these types of photoreceptors is still unfolding.[64] When cells near the macula are targeted, there is a greater potential for improvements in visual acuity due to the larger number of cone photoreceptors in that region; however, due to the risk of macular holes, the phase III study avoided injection in this area.[31] Similarly, visual field improvements were reported to be correlated to the area of retina covered by the injected vector.[63] Functional MRI studies confirmed that cortical activation is related to the area of injection. Dose escalation studies determined that a single injection of 0.3 ml ($1.5x10^{11}$ vg) was optimal for the desired outcome although a clear dose response was not found.[63] The sponsor has indicated that increased dosages and volumes have the potential to increase risk without associated benefits.[9]

Summary

Voretigene neparvovec was shown to provide a significant improvement in mobility under dim light conditions in the treatment group as compared to the control group in the phase III trial. Harms, although present, were related to the surgical aspects of administration. No systemic immune responses from the vector or gene were seen following treatment. While visual improvement past five years was described by clinical experts, no published data exists. Even if improvements persist in treated cells, it remains unclear whether long-term retinal degeneration is impacted by gene therapy.

Table 4.9. ICER Evidence Ratings

ICER Evidence Rating	
Voretigene neparvovec	**B+**

The clinical studies of VN for the treatment of biallelic *RPE65*-mediated inherited retinal diseases show promise; however, fewer than 50 individuals have received treatment worldwide, and published follow-up data is less than five years in any participant. As a treatment for an ultra-rare disease, methodological limitations are anticipated. The manufacturer of VN has stated that they

will follow all subjects out to 15 years per regulatory requirements. Thus, long-term safety and efficacy data should be forthcoming.

The wide-ranging phenotypes and lack of clear improvement in some individuals lead to difficulty in identifying who will most benefit from treatment. Currently, signs point to highest efficacy in those individuals with healthy retinal cells (prior to degeneration or early degeneration) but no systematic subgroup analysis was reported using OCT evidence of retinal structure.

Voretigene neparvovec has a relatively good safety profile, although compared to not receiving treatment, there are harms that are not insignificant, including retinal damage and worsening vision. Similarly, no valid quality of life data has been reported, making it difficult to understand the value of this therapy to the individual. Participant testimonials provided at the FDA panel were overwhelmingly positive, however.

While many uncertainties remain, VN provided a small to substantial improvement over standard care. Thus, we consider the evidence on VN in biallelic *RPE65*-mediated inherited retinal diseases to be "incremental or better" (B+).

5. Comparative Value

5.1 Long-Term Cost Effectiveness

Overview

The primary aim of this analysis was to estimate the cost-effectiveness of VN for vision loss associated with biallelic *RPE65*-mediated inherited retinal disease compared to the standard of care. The model structure for this assessment is described below. The model was developed in Microsoft Excel. For this section of the report, any data inputs or sources that presented visual acuity in logMAR scale were converted to the decimal scale, using: $VA_{decimal} = 10^{(-VA_{logMAR})}$.

Cost-Effectiveness Model: Methods

Model Structure

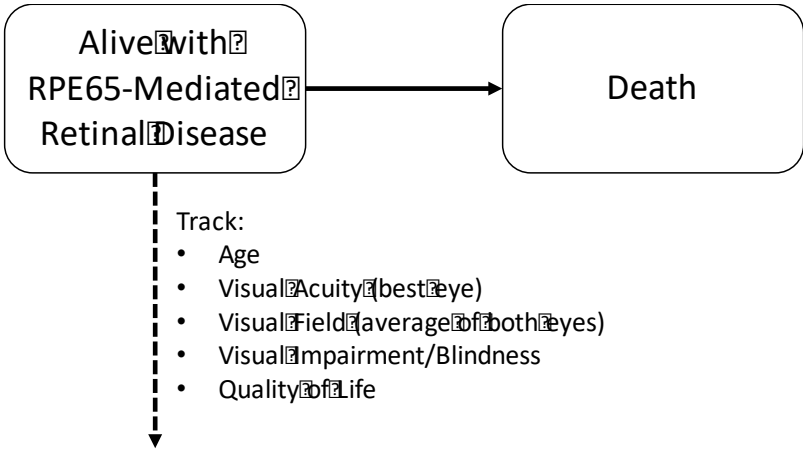
We developed a *de novo* Markov model with two general health states: "alive with biallelic *RPE65*-mediated retinal disease" and "dead". Within the alive individuals, we tracked vision-related clinical measures and quality of life. These measures were tracked over time for individuals who received VN and standard of care. This model structure was selected due to the limited availability of natural history data for biallelic *RPE65*-mediated inherited retinal disease, which precluded use of a more complex model structure.

Among those alive in the model, we tracked age, visual acuity, visual field, categorical visual impairment/blindness, and quality-of-life (Figure 5.1). Age was used to model life-expectancy.

Quality-of-life was modelled by applying an expected utility value by age group for the US population, then applying disutilities for visual impairment and blindness (see utilities methods section below for more detail). Visual acuity (best eye) and visual field (average of both eyes) was used to categorize individuals as not visually impaired, visually impaired, or blind (see clinical inputs methods section below for more detail). Ideally, we would use additional measures, such as the MLMT, to categorize individuals' visual impairment. However, data for these outcomes from VN trials were not available in metrics that could be linked and validated to these categories.

We used a US health care system perspective (i.e., focus on direct medical care costs only). However, *RPE65*-mediated inherited retinal disease is an ultra-rare condition where indirect and nonmedical costs comprise a substantial proportion of total costs, and these costs themselves are large. Therefore, we also included an analysis using a modified societal perspective which included direct medical costs as well as indirect costs for education, productivity loss, informal care, and nursing home care. For impact inventory see Appendix E. We used a 3% discount rate for costs and health outcomes. The model used one year cycles over a lifetime time horizon.

Figure 5.1 Model Framework



Target Population

The population for this analysis was individuals in the United States with biallelic *RPE65*-mediated inherited retinal disease. The modeled population reflected the VN clinical trial population, with an assumed mean age of 15 years and 43% male.[31] We also modeled a population with a mean age of three years.

Treatment Strategies

The interventions assessed in this model were:

- Voretigene neparvovec (Spark Therapeutics)
- Standard of care (SoC)

SoC treatment for individuals with vision loss associated with biallelic *RPE65*-mediated inherited retinal disease does not generally include major vision-related interventions aside from regular physician visits and supportive care.

The model estimated the average amount of time patients live and their quality of life over time with VN or SoC. Utility-adjusted time spent in each health state was summed to provide estimates of expected quality-adjusted life years (QALYs) for each treatment arm.

Model outcomes of interest included:

- By intervention:
  - Total health care costs (discounted)
  - Life-years (discounted)
  - QALYs (discounted)
- Pairwise comparisons:
  - Incremental cost-effectiveness ratio (ICER) of VN treatment versus SoC (cost per QALY)
  - Incremental cost per additional blindness-free year for VN treatment versus SoC

Key Model Characteristics and Assumptions

We made several assumptions for this model (Table 5.1).

Table 5.1. Key Model Assumptions

Assumption	Rationale
Biallelic *RPE65*-mediated inherited retinal disease and VN treatment do not affect mortality.	There is limited evidence that this disease or treatment affect mortality.
Treatment effect is maintained for 10 years, followed by a 10-year waning of effect, after which the rate of decline in vision is the same as with SoC.	Trial data for VN is limited to five years, and duration of treatment effect after that time is not known. As treatment effects do not appear to be changing at the five-year time point, we assumed a 10-year effect, as well as a waning period in which the rate of change is slower than SoC. We additionally modelled a lifetime treatment effect duration as a scenario analysis.
Impacted individuals receive two vision-related doctor visits per year.	Two doctor visits were assumed to be standard utilization for vision care.
Impacted individuals are considered visually impaired when VA<0.63 decimals or VF<1200 degrees, and blind when VA<0.015 decimals or VF<48 degrees based on the average of both eyes.	As defined in clinical categorizations.
Vision loss-related disutility is linearly proportional to visual acuity or visual field.	We created a function for disutility using two data points, for normal vision and blindness. We assume the relationship is linear between these points. See more detail in the utility methods section below.

VA=visual acuity; VF=visual field

Model Inputs

Clinical Inputs

Clinical Probabilities/Response to Treatment

We modeled categories of visual impairment and blindness based on visual acuity and visual field. We assumed that patients were considered visually impaired when they reached visual acuity <0.63 decimals or visual field <1200 degrees (as measured by Goldmann III4e). We assumed that patients were considered blind when they reached visual acuity <0.015 decimals or visual field <48 degrees (as measured by Goldmann III4e).[66]

We created a function for visual acuity by age based on the natural history of disease (data was digitized from figure 3), assuming an exponential functional form (based on visual fit) in the figure then converting to the decimal scale.[4] The resulting model form coefficients are shown in Table 5.2. To calculate the function for best eye visual acuity, we used the mean best eye visual acuity from the VN trial, 0.095 decimals, at mean age 15, to recalculate the intercept, and assumed the age coefficient and functional form were the same as for average visual acuity (Table 5.2).[54] For visual field, we used equivalent methods to create a function for the average visual field, using digitized natural history data. We assumed a linear functional form based on visual fit, and did not calculate best eye and worst eye separately.[4]

In order to model the effect of VN compared to SoC, we used the change in visual acuity between VN and SoC for average and best eye (Table 5.2).[54] We assumed this visual acuity would be maintained for the duration of the treatment effect, which was assumed to be 10 years. A 10-year treatment effect duration was selected because visual outcomes do not appear to be declining in five-year VN data, but effects in later years cannot be ensured. As discussed above, there are theoretical reasons to be concerned that the benefit may wane over time. After the treatment effect duration ends, patients entered a waning period, assumed to be 10 years. During the waning period, visual outcomes changed at a percentage of the SoC rate of change, based on the percentage of the waning period that has passed. For example, in year one of the waning period, the change in visual outcome would be 1/10 the SoC rate, and in year two would be 2/10 the SoC rate. After the waning period ends, we assumed that visual acuity for those treated with VN changed at the same rate at that of those treated with SoC.

Table 5.2. Visual Acuity (Decimal) Model and Visual Field (Sum Total Degrees from Goldmann III4e) Inputs

Clinical Category	Value	Source
Average Eye Visual Acuity Function		
Functional Form	10^-(function)	Assumed
Intercept	-0.55	Digitized data[4]
Age Coefficient	0.04360	Digitized data[4]
Best Eye Visual Acuity Function		
Functional Form	10^-(function)	Assumed
Intercept	-0.63	Calculated using the function above and Russell, 2017[31]
Age Coefficient	0.04360	Assumed same as average eye
Change in Visual Acuity with Voretigene Neparvovec		
Average	0.099	Russell, 2017[31]
Best Eye	0.103	Russell, 2017[31]
Average Eye Visual Field Function		
Functional Form	linear	Assumed
Baseline at Age 15	363.81	Russell, 2017[31]
Age Coefficient	-24.27	Digitized data[4]
Change in Visual Field with Voretigene Neparvovec, Average	281.56	Russell, 2017[31]
Duration of Treatment Effect	10 years	Assumed
Duration of Waning Period	10 years	Assumed

Mortality

We modeled mortality based on gender-specific United States life tables.[67] Biallelic *RPE65*-mediated inherited retinal disease and VN treatment were assumed to have no effect on mortality.

Utilities

To calculate health related quality of life impacts due to visual loss, we used standard utility values for the US population by age group and gender, as measured by a telephone-administered

standardized measure of health status (EQ-5D) in non-institutionalized adults greater than 35 years old.[68] We assumed that expected utility for a healthy individual under age 35 was one.

We then applied disutilities for vision-related impairment. We calculated disutility based on visual acuity in the best eye and visual field average of both eyes, and used whichever showed greater disutility at a given time. We used published values for average disutility for blindness (-0.38, average of included studies with values for levels corresponding to "counting fingers" to "no light perception") (Table 5.3).[69] This source was chosen as it is not disease specific and is an aggregated value from several studies. We created a linear function for disutility between normal sight and blindness. Specifically, anyone with visual acuity of 0.63 decimals or above and visual field of 1200 degrees or above was assumed to have normal sight and no disutility. The disutility threshold for blindness was assumed to be at visual acuity 0.015 decimals and visual field of 48 degrees; disutility continued linearly until visual acuity and visual field reached 0 (Table 5.3). This resulted in the following formulas: Disutility = 0.62*visual acuity - 0.39, and Disutility = 0.00033*visual field – 0.40. For a person with visual acuity above 0.63 decimals or visual field above 1200 degrees, the disutility would be 0. For a person with visual acuity at 0.015 decimals or visual field at 48 degrees, the disutility would be -0.38. Due to data limitations, we were not able to link MLMT with classifications of visual impairment.

Table 5.3. Utility Values for Health States

Clinical Category	Value	Source
Normal Sight		
Disutility	0	Assumed[70]
Lower Threshold, Visual Acuity	0.63 decimals	International Council of Ophthalmology, 2002[70]
Lower Threshold, Visual Field	1200 degrees	International Council of Ophthalmology, 2002[70]
Blind		
Disutility	-0.38	Average of included studies with values for levels corresponding to counting fingers to no light perception[71]
Blindness Threshold, Visual Acuity	0.015 decimals	International Council of Ophthalmology, 2002[70]
Blindness Threshold, Visual Field	48 degrees	International Council of Ophthalmology, 2002[70]

Adverse Events

We included three adverse events associated with VN use, based on adverse events categorized as moderate to severe in clinical trials, as shown in Table 5.4. Retinal tears were not included as they were assumed to be repaired during the surgery.

Table 5.4. Included Adverse Events

Adverse Event	Rate[31]	Cost	Disutility
Eye Irritation	5%	$80 *Source: CPT 99214*	0 *Assumed*
Eye Pruritus, Ongoing	5%	$80 *Source: CPT 99214*	0 *Assumed*
Macular Hole/ Degeneration	5%	$4,447 *Source: DRG 124*	0.13[72]

Economic Inputs

We assumed all affected individuals had two vision-related doctor visits per year. In addition, we assumed that those individuals categorized as blind (visual acuity of 0.015 decimals or below or visual field less than 150 degrees) had an additional annual cost of care for direct medical costs such as transportation, Braille equipment, and supplies (Table 5.5). We assumed a placeholder treatment cost of $1,000,000 for VN, plus a cost for the surgery (Table 5.5). Additionally, we completed a modified societal perspective analysis that included indirect costs for education, productivity losses, informal care, and nursing home care for visually impaired and blind people (Table 5.5).[69]

Table 5.5. Drug Cost Inputs

Cost Category	Value	Source
Direct Costs		
Voretigene Neparvovec	$1,000,000	Placeholder
Physician Visit	$80	CPT 99214
Surgery	$4,876	DRG 177, Intraocular procedures without CC/MCC
Direct Cost Of Blindness, Annual	$3,637	Examples include transportation, Braille equipment and supplies, and white canes.[73]
Indirect Costs*		
Education, Annual *Additional Costs of Education for Visually Impaired or Blind Child Compared to Normal Sighted Child*		
Visually Impaired		
Age 0-17	$11,984	Wittenborn 2013[69]
Blind		
Age 0-17	$11,984	Wittenborn 2013[69]
Productivity Loss, Annual		
Visually Impaired		
Age 18-39	$9,930	Wittenborn 2013[69]
Age 40-64	$21,074	Wittenborn 2013[69]
Age 65+	$7,316	Wittenborn 2013[69]
Blind		
Age 18-39	$18,068	Wittenborn 2013[69]
Age 40-64	$27,221	Wittenborn 2013[69]
Age 65+	$7,315	Wittenborn 2013[69]
Informal Care, Annual		
Visually Impaired		
Age 18-39	$723	Wittenborn 2013[69]
Age 40-64	$398	Wittenborn 2013[69]
Age 65+	$376	Wittenborn 2013[69]
Blind		
Age 18-39	$723	Wittenborn 2013[69]
Age 40-64	$398	Wittenborn 2013[69]
Age 65+	$376	Wittenborn 2013[69]
Nursing Home Care, Annual		
Visually Impaired		
Age 65+	$3,829	Wittenborn 2013[69]
Blind		
Age 65+	$7,988	Wittenborn 2013[69]

*Used in modified societal perspective only

Sensitivity Analyses

We ran one-way sensitivity analyses to identify the key drivers of model outcomes, using available measures of parameter uncertainty (i.e. standard errors) or plausible ranges for each input described in the model inputs section above. Probabilistic sensitivity analyses were also performed by jointly varying all model parameters over 5,000 simulations, then calculating 95% credible range estimates for each model outcome based on the results. We used normal distributions for age, gender, vision-related health outcomes and costs, and adverse event rates; beta distributions for utilities and disutilities. Additionally, we performed a threshold analysis by systematically altering the price of VN to estimate the maximum prices that would correspond to given willingness-to-pay (WTP) thresholds.

Scenario Analyses

We performed a scenario analysis in which we modelled a lifetime treatment effect duration for VN.

Model Validation

We used several approaches to validate the model. First, we provided preliminary methods and results to manufacturers, patient groups, and clinical experts. Based on feedback from these groups, we refined data inputs used in the model. Second, we varied model input parameters to evaluate face validity of changes in results. We performed model verification for model calculations using internal reviewers. Finally, we compared results to other cost-effectiveness models in other vision-related areas.

Cost-Effectiveness Model: Results

Base Case Results

We tracked best eye visual acuity and best eye visual field over time (Figure 5.2). Using these values, we tracked disutility over time, and calculated overall expected utility over time (Figure 5.3)

Figure 5.2. Best Eye Visual Acuity and Average Visual Field over Time for Patients at Age 15

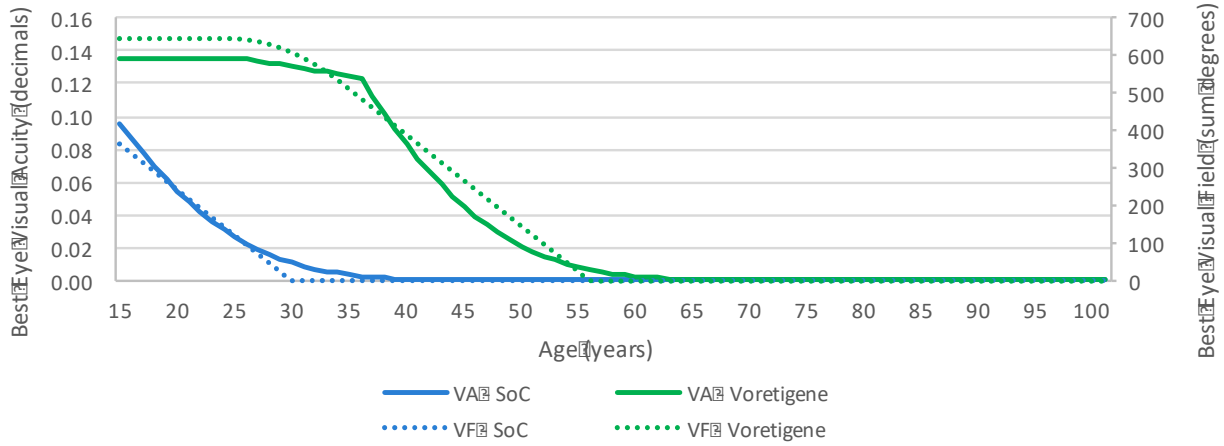
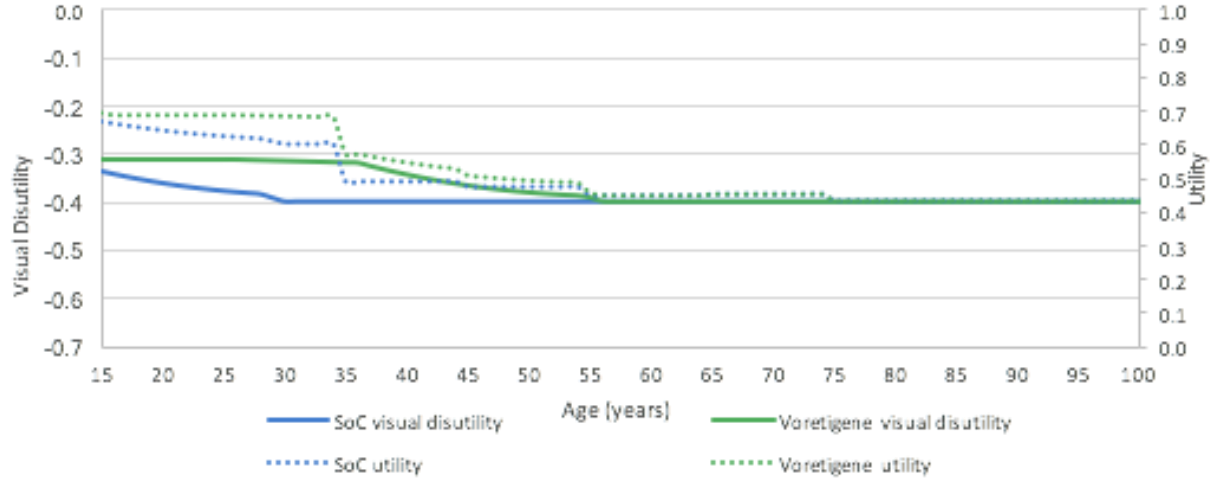


Figure 5.3. Visual Disutility and Overall Utility over Time for Patients at Age 15



In the population receiving VN at age 15, the average total lifetime cost for individuals treated with VN was approximately $1,032,600[b] from a US health care system perspective. This included VN costs of $1,004,900[b]. Patients treated with VN also accumulated a total of approximately $340 in adverse event costs, $4,600 in physician visit costs, and $22,800 in other blindness-related direct medical costs (Table 5.6). The average total lifetime cost for individuals treated with SoC was $68,600, including approximately $4,600 in physician visit costs and $64,000 in other blindness-related direct medical costs (Table 5.6). Indirect costs were approximately $420,600 for VN and $500,100 for SoC. Voretigene neparvovec provided an additional 1.3 QALYs over the remaining lifetime of an individual, leading to an incremental cost-effectiveness ratio of approximately $741,000[b] per additional QALY gained from the US health care system perspective, and $679,900[b]

[b] Includes $1,000,000 price placeholder for voretigene neparvovec.

per additional QALY gained from the modified societal perspective. Voretigene neparvovec provided an additional 10.9 blindness-free years over the remaining lifetime of an individual, leading to a cost of approximately $88,300[b] per additional blindness-free year from the US health care system perspective, and $81,000[b] per additional blindness-free year from the modified societal perspective.

In the population receiving VN at age 3, the average total lifetime cost for individuals treated with VN was approximately $1,023,600[b] from a US health care system perspective. This included VN costs of $1,004,900[b]. Patients treated with VN also accumulated a total of approximately $350 in adverse event costs, $4,800 in physician visit costs, and $13,600 in other blindness-related direct medical costs (Table 5.6). The average total lifetime cost for individuals treated with SoC was $49,700, including approximately $4,800 in physician visit costs and $44,800 in other blindness-related direct medical costs (difference from older age group due to discounting) (Table 5.6). Indirect costs were $420,800 for VN and $480,300 for SoC. Voretigene neparvovec provided an additional 3.25 QALYs over the remaining lifetime of an individual, leading to an incremental cost-effectiveness ratio of approximately $299,600[b] per additional QALY gained from the US health care system perspective, and $281,300[b] per additional QALY gained from the modified societal perspective. Voretigene neparvovec provided an additional 8.3 blindness-free years (difference from older age group due to discounting) over the remaining lifetime of an individual, leading to a cost of approximately $117,600[b] per additional blindness-free year from the US health care system perspective, and $110,400[b] per additional blindness-free year from the modified societal perspective.

Table 5.6. Base Case Results for Voretigene Neparvovec Compared to SoC

Treatment	SoC	Voretigene	Incremental
Treatment Age: 15			
Total Costs, US Health Care System Perspective	$68,571	$1,032,601 [b]	$964,030 [b]
Total Costs, Modified Societal Perspective	$568,626	$1,453,188 [b]	$884,561 [b]
Voretigene Costs	$0	$1,004,876 [b]	$1,004,876 [b]
AE Costs	$0	$341	$341
Vision-Related Physician Visit Costs	$4,570	$4,570	$0
Blindness Direct Costs	$64,001	$22,815	-$41,186
Indirect Costs	$500,055	$420,586	-$79,469
Total QALYs	15.85	17.15	1.30
Blindness-Free Years	11.59	22.51	10.92
ICER, US Health Care System Perspective	--	--	$740,937/QALY [b]
ICER, Modified Societal Perspective	--	--	$679,858/QALY [b]
$/Additional Blindness Free Year, US Health Care System Perspective	--	--	$88,285/QALY [b]
$/Additional Blindness Free Year, Modified Societal Perspective	--	--	$81,007/QALY [b]
Treatment Age: 3			
Total Costs, US Health Care System Perspective	$49,653	$1,023,625 [b]	$973,972 [b]
Total Costs, Modified Societal Perspective	$529,993	$1,444,389 [b]	$914,396 [b]
Voretigene Costs	$0	$1,004,876 [b]	$1,004,876 [b]
AE Costs	$0	$347	$347
Vision-Related Physician Visit Costs	$4,839	$4,839	$0
Blindness Direct Costs	$44,814	$13,563	-$31,251
Indirect Costs	$480,340	$420,763	-$59,576
Total QALYs	18.45	21.70	3.25
Blindness-Free Years	18.36	26.65	8.29
ICER, US Health Care System Perspective	--	--	$299,625/QALY [b]
ICER, Modified Societal Perspective	--	--	$281,297/QALY [b]
$/Additional Blindness Free Year, US Health Care System Perspective	--	--	$117,551/year [b]
$/Additional Blindness Free Year, Modified Societal Perspective	--	--	$110,361/year [b]

Sensitivity Analysis Results

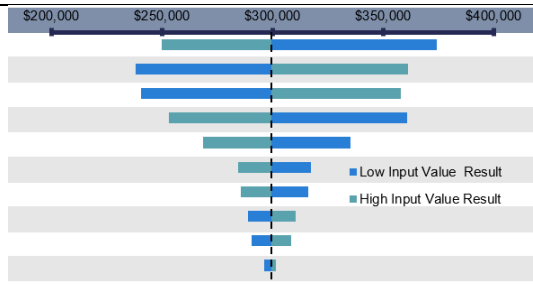
To demonstrate effects of uncertainty on both costs and health outcomes, we varied input parameters using available measures of parameter uncertainty (i.e. standard errors) or plausible ranges to evaluate changes in cost per additional QALY for all model input parameters. We found that key drivers of the model were annual change in visual acuity, baseline visual acuity, and age for the older population; and disutility for blindness, cost of VN, and average visual acuity for the younger population (Figure 5.4). Results were similar for the modified societal perspective.

Figure 5.4. Tornado Diagram(s) for One-Way Sensitivity Analyses of Incremental Cost-Effectiveness Ratio for Voretigene Neparvovec versus Standard of Care for Individuals Who Receive Voretigene Neparvovec at Age 15 (top) and Age 3 (bottom) from the US Health Care System Perspective

Age 15

Parameter	Low Input Value	High Input Value
Annual change in BEVA (SoC)	0.03	0.05
Baseline Best VA	-0.51	-0.76
Age at intervention	12.00	18.00
Cost of voretigene	800000.00	1200000.00
Blindness disutility	-0.31	-0.46
Normal average VA	0.50	0.76
Best VA effectiveness	-0.12	-0.18
Change in best eye VF with Voretigene	8.00	12.00
Duration if waning effect	8.00	12.00
Blindness, average VF	38.40	57.60

Age 3



Parameter	Low Input Value	High Input Value
Blindness disutility	-0.31	-0.46
Cost of voretigene	800000.00	1200000.00
Normal average VA	0.50	0.76
Baseline Best VA	-0.51	-0.76
Best VA effectiveness	-0.12	-0.18
Change in best eye VF with Voretigene	8.00	12.00
Duration if waning effect	8.00	12.00
Age at intervention	2.40	3.60
Annual change in BEVA (SoC)	0.03	0.05
Normal, average VF	960.00	1440.00

We ran 5,000 Monte Carlo simulations for a probabilistic sensitivity analysis. We assumed a normal distribution with a standard error of $102,000 around a placeholder price of $1,000,000 for VN. We found that for the older population, VN had a nearly 0% probability of being cost-effective compared to SoC at any threshold $150,000/QALY or lower, from both the US health care system and modified societal perspective. For the younger population, VN had a nearly 0% probability of being cost-effective compared to SoC at any threshold $150,000/QALY or lower from the US health care system perspective, and had 0.1% probability of being cost-effective at a $150,000/QALY threshold from a modified societal perspective.

Table 5.7. Probabilistic Sensitivity Analysis Results: Voretigene Neparvovec versus Standard of Care

	Cost-Effective at $50,000 per QALY[b]	Cost-Effective at $100,000 per QALY[b]	Cost-Effective at $150,000 per QALY[b]
Age 15, US Health Care Perspective	0.0%	0.0%	0.0%
Age 3, US Health Care Perspective	0.0%	0.0%	0.0%
Age 15, Modified Societal Perspective	0.0%	0.0%	0.0%
Age 3, Modified Societal Perspective	0.0%	0.0%	0.1%

Scenario Analysis Results

We modelled a scenario in which the duration of benefit is maintained over the lifetime of the patient. In this scenario, we found higher health gains and lower costs for VN patients relative to the base case. This led to lower ICERs of $438,900/QALY for the older age group and $180,800/QALY for the younger age group from the US health care system perspective, and $387,000/QALY for the older age group and $166,100/QALY for the younger age group from the modified societal perspective.

Table 5.8. Scenario Results for Voretigene Compared to SoC When Duration of Treatment Benefit is Lifetime*

Treatment	SoC	Voretigene	Incremental
Treatment Age: 15			
Total Costs, Us Health Care System Perspective	$68,571	$1,009,786	$941,216
Total Costs, Modified Societal Perspective	$568,626	$1,398,613	$829,986
Voretigene Costs	$0	$1,004,876	$1,004,876
AE Costs	$0	$341	$341
Vision-Related Physician Visit Costs	$4,570	$4,570	$0
Blindness Direct Costs	$64,001	$0	-$64,001
Indirect Costs	$500,055	$388,826	-$111,229
Total QALYs	15.85	18.00	2.14
Blindness-Free Years	11.59	28.56	16.97
ICER, US Health Care System Perspective	--	--	$438,839/QALY
ICER, Modified Societal Perspective	--	--	$386,978/QALY
$/Additional Blindness Free Year, US Health Care System Perspective	--	--	$55,469/QALY
$/Additional Blindness Free Year, Modified Societal Perspective	--	--	$48,914/QALY
Start Age: 3			
Total Costs, US Health Care System Perspective	$49,653	$1,010,063	$960,409
Total Costs, Modified Societal Perspective	$529,993	$1,412,519	$882,526
Voretigene Costs	$0	$1,004,876	$1,004,876
AE Costs	$0	$347	$347
Vision-Related Physician Visit Costs	$4,839	$4,839	$0
Blindness Direct Costs	$44,814	$0	-$44,814
Indirect Costs			
Total QALYs	18.45	23.77	5.31
Blindness-Free Years	18.36	30.24	11.88
ICER, US Health Care System Perspective	--	--	$180,789/QALY
ICER, Modified Societal Perspective	--	--	$166,128/QALY
$/Additional Blindness Free Year, US Health Care System Perspective	--	--	$80,833/year
$/Additional Blindness Free Year, Modified Societal Perspective	--	--	$74,278/year

*Assuming a placeholder WAC of $1,000,000

Threshold Analysis Results

Prices necessary to reach cost-effectiveness thresholds of $50,000, $100,000, $150,000, $250,000, and $500,000 per QALY are listed in Table 5.9, for both age groups and both perspectives. Threshold prices were higher for the younger age group, and higher from the modified societal perspective. With a placeholder WAC of $1,000,000, a discount of at least 43%, and up to 77%, would be necessary to reach a cost-effectiveness threshold of $150,000/QALY. Smaller discounts would be needed to achieve cost-effectiveness thresholds of $250,000 and $500,000 per QALY, with no discount required at the $500,000/QALY threshold for the younger age group.

Table 5.9. Threshold Analysis Results

	WAC Per Unit[b]	Unit Price to Achieve $50,000 /QALY	Unit Price to Achieve $100,000 /QALY	Unit Price to Achieve $150,000 /QALY	Unit Price to Achieve $250,000 /QALY	Unit Price to Achieve $500,000 /QALY	Discount from WAC To Reach Thresholds[b]
Age 15, US Health Care Perspective	$1,000,000	$101,024	$166,079	$231,134	$361,244	$686,518	31% - 90%
Age 3, US Health Care Perspective	$1,000,000	$188,560	$351,091	$513,623	$838,687	$1,651,346	0% - 81%
Age 15, Modified Societal Perspective	$1,000,000	$180,494	$245,548	$310,603	$440,713	$765,987	23% - 82%
Age 3, Modified Societal Perspective	$1,000,000	$248,136	$410,668	$573,200	$898,263	$1,710,922	0% - 75%

[b] Assuming a placeholder WAC of $1,000,000

Model Validation

Model validation followed standard practices in the field. We tested all mathematical functions in the model to ensure they were consistent with the report (and supplemental Appendix materials). We also conducted sensitivity analyses with null input values to ensure the model was producing findings consistent with expectations. Further, independent modelers tested the mathematical functions in the model as well as the specific inputs and corresponding outputs.

Model validation was also conducted in terms of comparisons to other model findings. We searched the literature to identify models that were similar to our analysis, with comparable populations, settings, perspective, and treatments.

We also compared the ICER model to previously published models. We searched the literature to identify models that were similar to our own, with comparable populations, settings, perspective,

and treatments. While there are no economic evaluations assessing the cost-effectiveness of VN, we reviewed other relevant models in vision-related diseases, with comparisons focusing primarily on modeling approach, and less on the results of these economic evaluations. The incremental cost-effectiveness results whenever stated are intended to serve only as illustrative of what different treatments offer for treating severe visual impairment stemming from different disorders, and not as a direct comparison to the ICER analysis on VN.

Bennison et al. evaluated the cost-effectiveness of ocriplasmin relative to standard-of-care for the treatment of vitreomacular traction (VMT) and macular hole.[74] This model comprised two parts, a short-term decision tree to simulate whether patients had a successful anatomic outcome, and a long-term Markov model simulating long-term clinical and cost outcomes. While blindness in the ICER model was defined as visual acuity <0.015 decimals, Bennison et al. defined it as 6/60, or 0.1 decimals. Visual acuity decline over time was also modeled differently, with Bennison et al. treating visual acuity decline in the non-study eye the same as that of those in the general population. In the ICER model, disutilities for vision-related impairment were linked to visual acuity in the best eye and visual field average of both eyes, whereas Bennison et al. awarded disutilities based on adverse events related to underlying cause of vision impairment. The ICERs of ocriplasmin relative to standard-of-care ranged from £18,056 for treating VMT without epiretinal membrane (ERM) or full thickness macular hole (FTMH), to £61,059 for treating VMT with ERM but no FTMH.

Dunbar et al. evaluated the cost-utility of screening and laser treatment relative to no screening and treatment for retinopathy of prematurity (ROP), in infants with birthweight <1500g or gestational ages of 28 weeks or less, in a neonatal intensive care unit.[75] Treatment effect with laser therapy was assumed to be permanent. Visual acuity was measured at the time of screening and at the 10-year post-therapy time point. Utilities were derived from visual acuity estimates in the better-seeing eye. Utility for non-treated eye was 0.59 and treated eye was 0.69, with treatment effect lasting 77.5 years. This study estimated a cost per QALY ratio of $1,565 for screening and laser therapy. Another economic evaluation by Rothschild et al. comparing screening and laser treatment relative to no screening and treatment for retinopathy of prematurity (ROP) in infants with birthweight <1500g found screening and treatment to be cost-saving from a US societal perspective.[76]

Mitchell et al. evaluated the cost-effectiveness of ranibizumab monotherapy or in combination with laser therapy relative to laser monotherapy for the treatment of diabetic macular edema (DME) in a UK population.[77] The study used clinical efficacy estimates from the RESTORE trial. Health state utilities for the target patient population were derived from the EQ-5D, and then linked to the best corrected visual acuity (BCVA), with a BCVA score of 0-25 associated with a mean utility of 0.547 and a health state with BCVA score of 86-100 associated with a mean utility value of 0.860. At the end of 15 years, the mean cost per QALY gained with ranibizumab monotherapy was £24,028 and with ranibizumab combination therapy was £36,106. Another economic evaluation conducted from a Canadian health system perspective by Haig et al., using the same clinical efficacy estimates from the RESTORE trial as Mitchell et al. found cost per QALY results of CA$24,494 using ranibizumab

monotherapy and CA$36,414 of ranibizumab combination therapy relative to laser monotherapy over a three-year time horizon.[78]

In the treatment of age-related macular degeneration (AMD), a leading cause of severe visual impairment in older adults, we found three economic evaluations conducted in different regional settings.[79-81] Utility estimates in these models for severe visual impairment ranged between 0.534 to 0.55 across the three studies, while those for full vision (in at least the better-seeing eye) ranged from 0.653 to 0.89. Incremental cost-effectiveness results from these three studies are listed below.

Table 5.10: Key Prior Economic Models Assessing Cost-Effectiveness of Age-Related Macular Degeneration (AMD) Treatments

Study	Setting (Perspective)	Intervention	Comparator	Time Horizon	Incremental Cost-effectiveness ratio (cost per QALY gained)
Yanagi et al., 2017[79]	Japan (Societal)	Intravitreal aflibercept injection (IAI)	Ranibizumab/ Pegaptanib sodium/ Photodynamic therapy/ Best Supportive Care	12 years	IAI dominates (more effective at lower cost)
Hopley et al., 2004[80]*	United Kingdom (Third Party Payer)	Screening + treatment with high dose zinc & antioxidants in 65+ year-olds	No screening or treatment	5 years	£22,722
Vottonen & Kankaanpaa[81]*	Finland (Hospital)	Aflibercept	Bevacizumab/Ranibizumab	8 years	€1,801,228/Dominates

*These studies assessed cost-effectiveness of treatments for wet AMD

5.2 Value-Based Price Benchmarks

Value-based benchmark prices will be released in the revised Evidence Report, which will be released on or about January 11, 2018.

5.3 Potential Budget Impact

We used the cost-effectiveness model to estimate the potential total budgetary impact of VN for the population with biallelic *RPE65*-mediated inherited retinal disease. We used the assumed placeholder price and the three threshold prices for each drug in our estimates of budget impact.

Potential Budget Impact Model: Methods

We used results from the same model employed for the cost-effectiveness analyses to estimate total potential budget impact. Potential budget impact was defined as the total differential cost of using the new therapy rather than relevant existing therapy for the treated population, calculated as differential health care costs (including drug costs) minus any offsets in these costs from averted health care events. All costs were undiscounted and estimated over one- and five-year time horizons. The five-year timeframe was of primary interest, given the potential for cost offsets to accrue over time and to allow a more realistic impact on the number of participants treated with the new therapy.

The potential budget impact analysis included the candidate population eligible for treatment: individuals in the US with biallelic *RPE65*-mediated inherited retinal disease. To estimate the size of the potential candidate population for treatment, we used inputs from a US Securities and Exchange Commission Form 10-K Annual Report by Spark Therapeutics, Inc., which estimated "that there are approximately 3,500 individuals with *RPE65*-mediated inherited retinal diseases in the United States and the five major European markets."[82] The US population represents approximately 50.06% of the total population in the US and the five major European markets (Germany, France, Italy, Spain and the United Kingdom). Applying that proportion to the total of 3,500 patients results in an estimate of approximately 1,750 eligible individuals in the US. Assuming equal distribution over five years, this resulted in an estimate of 350 patients eligible for VN in the US per year.

ICER's methods for estimating potential budget impact are described in detail at this link: https://icer-review.org/final-vaf-2017-2019/ and have recently been updated. The intent of our revised approach to budgetary impact is to document the percentage of participants that could be treated at selected prices without crossing a budget impact threshold that is aligned with overall growth in the US economy.

Briefly, we evaluate a new drug that would take market share from one or more drugs, and calculate the blended budget impact associated with displacing use of existing therapies with the new intervention. In this analysis, we assumed that VN would not displace an active treatment for biallelic *RPE65*-mediated inherited retinal disease, as none were available for these patients.

Using this approach to estimate potential budget impact, we then compared our estimates to an updated budget impact threshold that represents a potential trigger for policy mechanisms to improve affordability, such as changes to pricing, payment, or patient eligibility. As described in ICER's methods presentation (http://icer-review.org/wp-content/uploads/2016/02/ICER-Value-Assessment-Proposed-Updates-Webinar-021317.pdf), this threshold is based on an underlying assumption that health care costs should not grow much faster than growth in the overall national economy. From this foundational assumption, our potential budget impact threshold is derived using an estimate of growth in US gross domestic product (GDP) +1%, the average number of new drug approvals by the FDA over the most recent two-year period, and the contribution of spending on retail and facility-based drugs to total health care spending. Calculations are performed as shown in Table 5.11.

For 2017-18, therefore, the five-year annualized potential budget impact threshold that should trigger policy actions to manage access and affordability is calculated to total approximately $915 million per year for new drugs.

Table 5.11. Calculation of Potential Budget Impact Threshold

Item	Parameter	Estimate	Source
1	Growth in US GDP, 2017 (est.) +1%	3.20%	World Bank, 2016
2	Total health care spending, 2016 ($)	$2.71 trillion	CMS NHE, 2014
3	Contribution of drug spending to total health care spending (%)	17.7%	CMS National Health Expenditures (NHE), 2016; Altarum Institute, 2014
4	Contribution of drug spending to total health care spending ($) (Row 2 x Row 3)	$479 billion	Calculation
5	Annual threshold for net health care cost growth for ALL new drugs (Row 1 x Row 4)	$15.3 billion	Calculation
6	Average annual number of new molecular entity approvals, 2013-2014	33.5	FDA, 2016
7	Annual threshold for average cost growth per individual new molecular entity (Row 5 ÷ Row 6)	$457.5 million	Calculation
8	Annual threshold for estimated potential budget impact for each individual new molecular entity (doubling of Row 7)	$915 million	Calculation

Potential Budget Impact Model: Results

Table 5.12 illustrates the per-patient budget impact calculations, based on the assumed placeholder price for VN ($1,000,000), and the prices for VN to reach $150,000, $100,000, and $50,000 per QALY ($231,134, $166,079, and $101,024, respectively) compared to standard of care. Note that we used the threshold prices assuming treatment at age 15 rather than age three as we assumed

that the prevalent population would be treated initially. Treatment at age three would result in higher threshold prices (due to greater QALY gains) but would apply to the much smaller incident population.

Table 5.12. Per-Patient Budget Impact Calculations Over a Five-year Time Horizon

Average Annual Per Patient Budget Impact				
	Placeholder*	**$150,000/QALY**	**$100,000/QALY**	**$50,000/QALY**
Voretigene Neparvovec	$459,161	$108,045	$78,337	$48,629
Standard of Care	$160			
Difference	$459,001	$107,885	$78,177	$48,469

QALY: quality-adjusted life year

*Assumed placeholder price of $1,000,000.

The average annual potential budgetary impact when using the assumed placeholder price ($1,000,000) was an additional per-patient cost of approximately $459,000. Average annual potential budgetary impact at the three cost-effectiveness threshold prices for the drug ranged from approximately $107,900 per patient using the price ($231,134) to achieve $150,000 per QALY to approximately $48,500 using the price ($101,024) to achieve a $50,000 per QALY cost-effectiveness threshold.

For VN treatment of individuals with biallelic *RPE65*-mediated inherited retinal disease, the annual potential budgetary impact of treating the entire eligible population across all prices (the assumed placeholder price and the three cost-effectiveness threshold prices for $50,000, $100,000, and $150,000 per QALY) did not exceed the $915 million threshold. The greatest potential annual budget impact of treating the described population with VN was at the assumed placeholder price of $1,000,000, reaching 38% of the $915 million threshold. This was largely due to the relatively small number of patients assumed to be treated per year (350) and the relatively low health care costs incurred following initial treatment with VN.

5.4 Summary and Comment

Limitations

This study had several limitations. First, the natural history of *RPE65*-mediated inherited retinal disease has not been thoroughly studied, therefore our underlying disease models have limited data. Second, we were limited in measures of effectiveness for VN to those measures that were captured in the clinical trials as outcomes, as well as in what measures could be linked to quality of life. Because the majority of existing quality-of-life literature for blindness has used visual acuity, we were unable to thoroughly utilize all meaningful outcome measures from the clinical trials.

Additionally, costs and quality of life measures have not, to our knowledge, been studied for this specific patient population; therefore we assumed similarities between this population and people with other types of blindness or visual impairment.

Conclusions

We found that VN improves patient health outcomes compared to standard of care. However, at a placeholder price of $1,000,000, the high cost makes this unlikely to be a cost-effective intervention at commonly used cost-effectiveness thresholds. However, for ultra-rare diseases, decision-makers in the US and in international settings often give special weighting to other benefits and to contextual considerations that lead to coverage and funding decisions at higher prices, and thus higher cost-effectiveness ratios, than applied to decisions about other treatments.

We found that VN provided more health benefits when given to a younger population, and was therefore more likely to be cost-effective for younger patients. We also found that inclusion of indirect and non-medical costs slightly decreased the total incremental costs for VN, and therefore slightly decreased cost-effectiveness ratios. However, in all base case scenarios, VN would require large discounts to reach commonly used thresholds of cost-effectiveness.

6. Additional Considerations

6.1 Other Benefits and Contextual Considerations

Our reviews seek to provide information on other benefits offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. These elements are listed in the table below.

Table 6.1. Potential Other Benefits or Contextual Considerations

Potential Other Benefits
This intervention provides significant direct patient health benefits that are not adequately captured by the QALY.
This intervention offers reduced complexity that will significantly improve patient outcomes.
This intervention will reduce important health disparities across racial, ethnic, gender, socio-economic, or regional categories.
This intervention will significantly reduce caregiver or broader family burden.
This intervention offers a novel mechanism of action or approach that will allow successful treatment of many patients who have failed other available treatments.
This intervention will have a significant impact on improving the patient's ability to return to work or school and/or their overall productivity.
This intervention will have a significant positive impact outside the family, including on schools and/or communities.
This intervention will have a significant impact on the entire "infrastructure" of care, including effects on screening for affected patients, on the sensitization of clinicians, and on the dissemination of understanding about the condition, that may revolutionize how patients are cared for in many ways that extend beyond the treatment itself.
Other important benefits or disadvantages that should have an important role in judgments of the value of this intervention.
Potential Other Contextual Considerations
This intervention is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.
This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.
This intervention is the first to offer any improvement for patients with this condition.
Compared to best supportive treatment, there is significant uncertainty about the long-term risk of serious side effects of this intervention.
Compared to best supportive treatment, there is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.
There are additional contextual considerations that should have an important role in judgments of the value of this intervention.

Individuals born with biallelic *RPE65*-mediated retinal diseases currently have no therapies that alter the progression of vision loss. As such, VN represents the first therapy that may stabilize, delay, halt, or reverse loss of vision. Additionally, the availability of treatment may change the paradigm of care by fostering improved screening processes, including genetic testing.

Although biallelic *RPE65*-mediated inherited retinal disease represents a lifelong condition, its perceived severity is highly individual.[83] Several individuals who received VN appreciated the improvements in self-confidence, mobility, and independence that they felt following treatment. These benefits may not be adequately captured in the QALY.

A qualitative study of research priorities for people with visual impairments in the Netherlands showed that improving mobility in a visually-oriented society has the potential to improve quality of life through increased independence, decreased social isolation, and improved overall enjoyment.[84] Although the overall impact of VN on productivity has not yet been studied, it can be postulated that improvements in independence, mobility, and overall visual function may expand the range of employment options open to individuals with biallelic *RPE65*-mediated inherited retinal disease and increase their ability to participate in social activities. One phase III participant provided insight into how treatment with VN directly allowed her to perform work that she would not be able perform had she not received treatment.

Improvements in independence also have the potential to add value to the lives of parents, caregivers and other friends or family members who often make special accommodations to their homes, routines, and employment to ensure that the needs of with visual impairment met. In our discussion with patients and parents, some patients expressed the improved ability to navigate their school settings without assistance and shared stories of successful transitions between education and the workforce.

As discussed in the Controversies and Uncertainties section, the degree to which VN may alter disease progression over the long term is unknown. Likewise, while the adverse events surrounding administration of the therapy appear mild to moderate in severity, the long-term risk of serious side effects remains unclear.

Finally, as with many new therapies entering the market, the potential for VN to exacerbate health disparities cannot be ignored. Spark Therapeutics has publicly stated that VN will only be available in a limited number of Centers of Excellence that specialize in inherited retinal diseases.[9] Individuals who do not live in close proximity to one of these centers may have difficulty accessing the treatment. Similarly, the high price tag that is likely to be attached to VN, compounded by the deductibles and copayments associated with the treatment's surgical component, may make this therapy out of reach for those without adequate insurance coverage.

6.2. Identification of Low-Value Services

As described in its Final Value Assessment Framework for 2017-2019, ICER will now include in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create headroom in health care budgets for higher-value innovative services (for more information, see https://icer-review.org/final-vaf-2017-2019/). ICER encourages all stakeholders to suggest services (including treatments and mechanisms of care) currently used for people with visual disorders that could be reduced, eliminated, or made more efficient. We are looking for information on low-value services used in the management of visual disorders beyond the potential offsets that arise from a new intervention.

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This is the first ICER review of voretigene neparvovec.

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Appendix A. Search Strategies and Results

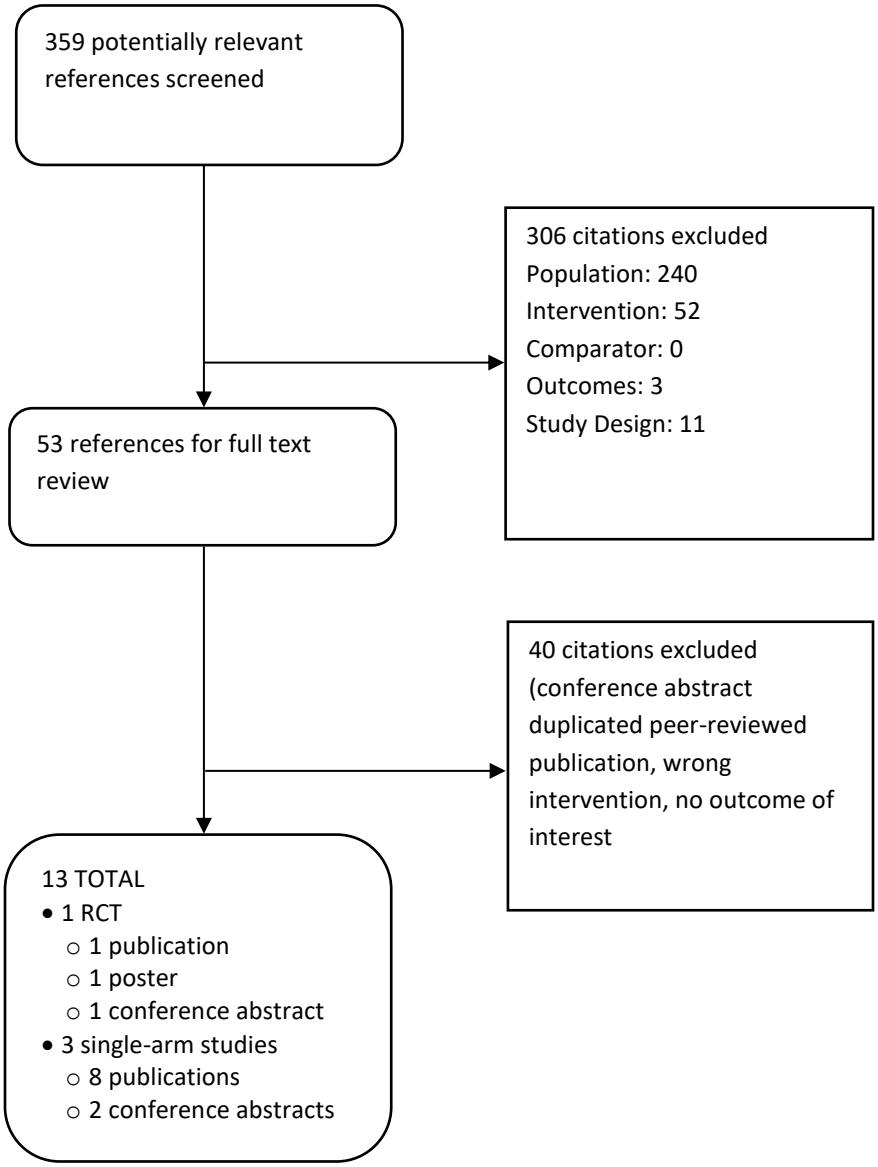
Table A1. PRISMA 2009 Checklist

	#	Checklist Item
TITLE		
Title	1	Identify the report as a systematic review, meta-analysis, or both.
ABSTRACT		
Structured Summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.
INTRODUCTION		
Rationale	3	Describe the rationale for the review in the context of what is already known.
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).
METHODS		
Protocol and Registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.
Eligibility Criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.
Information Sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.
Study Selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).
Data Collection Process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.
Data Items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.
Risk of Bias in Individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.
Summary Measures	13	State the principal summary measures (e.g., risk ratio, difference in means).
Synthesis of Results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.
Risk of Bias Across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).
Additional Analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.
RESULTS		

Study Selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.
Study Characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.
Risk of Bias within Studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).
Results of Individual Studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.
Synthesis of Results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.
Risk of Bias Across Studies	22	Present results of any assessment of risk of bias across studies (see Item 15).
Additional Analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).
DISCUSSION		
Summary of Evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.
FUNDING		
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.

From: Moher D, Liberati A, Tetzlaff J, Altman DG. The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

Figure A1. PRISMA Flow Chart Showing Results of Literature Search for Voretigene Neparvovec



Appendix B. Previous Systematic Reviews and Technology Assessments

We did not identify any completed technology assessments or peer-reviewed systematic reviews of voretigene neparvovec for Biallelic *RPE65*-Mediated Retinal Disease, however the National Institute for Health and Care Excellence (NICE) in the UK has published a draft scope for an appraisal of the clinical and cost effectiveness of voretigene. The appraisal's completion date is yet to be confirmed.

NICE: Voretigene neparvovec for treating inherited retinal dystrophies caused by RPE65 gene mutations

https://www.nice.org.uk/guidance/indevelopment/gid-ta10200/documents

NICE has proposed to appraise the clinical and cost effectiveness of voretigene neparvovec within its marketing authorization for treating inherited retinal dystrophies caused by RPE65 gene mutations.

Appendix C. Ongoing Studies

Title, Trial Sponsor, ClinicalTrials.gov Identifier	Study Design	Treatment Arms	Patient Population	Key Outcomes	Estimated Completion Date
Clinical Trial of Gene Therapy for the Treatment of Leber Congenital Amaurosis (LCA) (OPTIRPE65) MeiraGTx UK II Ltd NCT02781480	Phase I/II Non-randomized Single group assignment Estimated Enrollment: 27	1. Low dose AAV-RPE65 subretinal administration 2. Intermediate dose AAV-RPE65 subretinal administration 3. High dose AAV-RPE65 subretinal administration	Inclusion Criteria • Age ≥3 • Early-onset severe retinal dystrophy consistent with RPE65 deficiency Exclusion Criteria • Females who are pregnant or breastfeeding • Participation in another research study involving investigational therapy for ocular disease within last 6 months	Primary Outcome Measures • Adverse events related to treatment Secondary Outcome Measures • Visual function • Retinal function • Quality of life	October 2018 Long-term follow-up until April 2023

Appendix D. Clinical Effectiveness Supplemental Information

Additional Endpoints from Clinical Trials

Pupillary light reflex (PLR)

Pupillary light reflex (PLR) was measured in early voretigene neparvovec studies as a secondary endpoint. However, in the phase III study, a decision was made by the study sponsor (with FDA approval) to make PLR an exploratory instead of secondary endpoint due to issues with control (no untreated eye), measurement (nystagmus) and maintenance of the pupillometer. Exploratory data on PLR are not reported in the phase III manuscript, supplement, or 2-year poster.

Prior trials stated improved pupillary response after treatment and cite individual study participant data (no aggregate results).[58,63]

Ocular motility testing

The original pilot study of three participants who underwent low dose voretigene neparvovec treatment in the worst-seeing eye used digital eye-movement video to assess ocular motility including nystagmus. Each of the three enrolled individuals had frequent ocular movements of varying degrees at baseline. Following treatment, all three participants had reduced monocular and binocular nystagmus frequency and amplitude which lasted out to 1.5 years.[85] It has been hypothesized that improvements in visual acuity may stem from reduced nystagmus.[86] The phase III study did not provide baseline or follow-up nystagmus data.

Functional magnetic resonance imaging (fMRI)

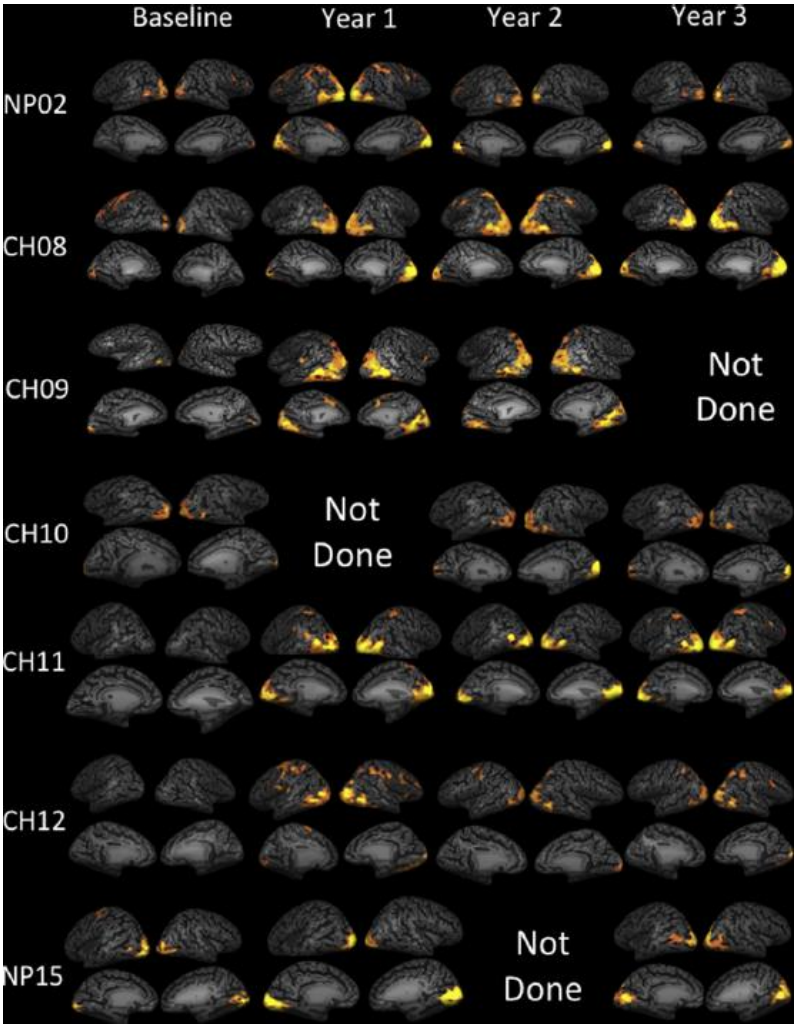
To assess whether treatment with voretigene neparvovec altered the visual cortex responsiveness to light, a longitudinal functional MRI study was performed on a subset of participants enrolled in the Phase I and II studies.[87,88]

Participants scheduled to receive contralateral treatment in the Phase I follow-on study underwent baseline magnetic resonance imaging (MRI) to identify baseline cortical response. Images were looked at both in the areas of the brain associated with the untreated and originally treated eye and provided a baseline with which to assess changes after contralateral eye treatment (Phase I follow-on study).

Follow-up data out to three years shows that in the seven participants imaged, all but one had increased cortical activation following treatment.[89] Levels of activation varied widely depending on

the subject's age, disease progression and location of voretigene neparvovec injection (see Appendix Figure D1).[89] A longitudinal regression using mixed effects showed associations between visual cortex activation and clinical measures of visual function. Full-field light sensitivity and pupillary light response were positively correlated with improvement while visual acuity and visual field were not.[89]

Figure D1. Longitudinal Functional Magnetic Resonance Imaging (MRI) in subset of Phase I follow-on study subjects[89]



Appendix E. Comparative Value Supplemental Information

Figure E1. Impact Inventory[90]

Sector	Type of Impact (list category within each sector with unit of measure if relevant)[a]	Included in This Reference Case Analysis From...Perspective?		Notes on Sources of Evidence
		Health Care Sector	Societal	
Formal Health Care Sector				
Health	Health outcomes (effects)			
	Longevity effects	☒	☒	
	Health-related quality-of-life effects	☒	☒	
	Other health effects (eg, adverse events and secondary transmissions of infections)	☒	☒	
	Medical costs			
	Paid for by third-party payers	☒	☒	
	Paid for by patients out-of-pocket	☒	☒	
	Future related medical costs (payers and patients)	☒	☒	
	Future unrelated medical costs (payers and patients)	☐	☐	
Informal Health Care Sector				
Health	Patient-time costs	NA	☒	
	Unpaid caregiver-time costs	NA	☒	
	Transportation costs	NA	☐	
Non–Health Care Sectors (with examples of possible items)				
Productivity	Labor market earnings lost	NA	☒	
	Cost of unpaid lost productivity due to illness	NA	☒	
	Cost of uncompensated household production[b]	NA	☐	
Consumption	Future consumption unrelated to health	NA	☐	
Social Services	Cost of social services as part of intervention	NA	☒	
Legal or Criminal Justice	Number of crimes related to intervention	NA	☐	
	Cost of crimes related to intervention	NA	☐	
Education	Impact of intervention on educational achievement of population	NA	☒	
Housing	Cost of intervention on home improvements (eg, removing lead paint)	NA	☐	
Environment	Production of toxic waste pollution by intervention	NA	☐	
Other (specify)	Other impacts	NA	☐	

Appendix F. Data Extraction Summary Table

Author & Year of Publication (Trial Name) Quality rating	Study Design and Duration of Follow-up	Interventions (n) & Dosing Schedule	Major Inclusion & Exclusion Criteria	Patient Characteristics	Key Outcomes	Harms
Russell, Lancet (2017)[31] **manuscript** **Study 301** **Fair**	Phase III, open-label, randomized control trial 1-year primary endpoint Performed by 5 surgeons at 2 hospitals: CHOP/U of Iowa	1) Voretigene neparvovec (VN) [AAV2-hRPE65v2 or *LUXTURNA™*] (n=21) $1.5x10^{11}$ vector genomes (vg) per eye in 0.3ml subretinal injection 2) Control group, eligible to receive VN after 1 year (n=10)	Inclusion ≥ 3 years old; biallelic *RPE65* gene mutation; both eyes 20/60 or worse or visual field < 20° in any meridian; sufficient viable retinal cells; able to perform mobility test (MLMT) but unable to pass at 1 LUX Exclusion Participation in gene therapy or investigational drug study; used high dose retinal compounds in past 18 months; intraocular surgery in past 6 months; contraindications to operative meds; conditions that preclude outcome interpretation	*Age, yrs* Mean (SD) 1) 14.7(11.8) 2) 15.9(9.5) *Sex, N(%)* Female 1) 12(57) 2) 6(60) *Age group, N(%)* <10 yrs/ ≥10 yrs 1) 9(43)/12(57) 2) 4(40)/6(60) MLMT passing level, N(%) <125 lux/≥125 lux 1) 12(57)/9(43) 2) 4(40)/6(60)	*1 year Mean MLMT (SD)* *Both eyes* 1) 1.8(1.1) 2) 0.2(1.0) P=0.0013 *First eye/ Second eye* 1) 1.9(1.2)/ 2.1(1.2) 2) 0.2(0.6)/ 0.1(0.7) P=0.0005/ P=0.0001 *Goldmann visual field, sum total degrees* *Mean (SD)* 1) 673.9(423.7) 2) 397.8(367.3) P=0.0059 *Humphrey visual field, foveal sensitivity/macula threshold (dB)* *Mean (SD)* 1) 25.8(9.1)/ 24.0(8.0) 2) 21.5(8.9)/ 15.8(7.4) P=0.18/ P=0.0005	1 year TEAEs (mITT) in intervention group (n=20) # events, # patients (% pts) Increased intraocular pressure: 5, 4(20) Cataract 4, 3(15) Retinal tear 2, 2(10) Eye inflammation 6, 2(10) Macular hole 2, 1 (5%) - same eye, full-thickness macular hole spontaneously resolved

Author & Year of Publication (Trial Name) Quality rating	Study Design and Duration of Follow-up	Interventions (n) & Dosing Schedule	Major Inclusion & Exclusion Criteria	Patient Characteristics	Key Outcomes	Harms
Russell, ARVO poster, 2017[54] **Study 302**	See Russell 2017 2 years for original intervention group 1 year from crossover controls "delayed intervention"	See Russell 2017 1) Original intervention at 2 years 2) Delayed intervention at 1 year	See Russell 2017	See Russell 2017	*MLMT- Mean bilateral change score (SD)* 1) 1.9 (1.1) 2) 2.1 (1.6) <u>Averaged over both eyes</u> *White light FST Mean change (cd.s/m2) (SD)* 1) 2.27 −log10 (1.65) 2) 2.86 (1.49) *Visual Acuity LogMAR mean (SD) change* 1) −0.16 (0.36) (+8 letters) 2) −0.09 (0.22) (+4.5 letters) *Visual Field mean (SD) change* Goldmann sum total degrees on GVF III4e 1) 311.6 (295.3) 2) 194.3 (244.7) Humphrey macula threshold 1) 6.45 (7.35) dB 2) 5.23 (9.92) dB	Total adverse events: 32 in 19 subjects (66%) Cataract: 7 events in 4 subjects (14%) Retinal tear: 3 events in 3 subjects (10%) Retinal deposits: 3 events in 3 subjects (10%) Macular hole: 2 events in 2 subjects (7%) Eye inflammation: 4 events in 2 subjects (7%)

Author & Year of Publication (Trial Name) Quality rating	Study Design and Duration of Follow-up	Interventions (n) & Dosing Schedule	Major Inclusion & Exclusion Criteria	Patient Characteristics	Key Outcomes	Harms
Hui, Molecular Therapy (2016)[91] **abstract**	See Russell 2017 Safety study	See Russell 2017 Immunological assays designed to monitor cellular immune responses.	Russell 2017	See Russell 2017	18/21 intervention subjects tested negative for T cell responses against AAV2 and RPE65 across all timepoints. One subject was positive against AAV2 capsid at baseline (55.0 SFU) and positive against RPE65 at the 1 year timepoint (171.7 SFU). Another subject was positive at 1 year for RPE65 only (170.0 SFU). Positive responses were considered very weak with respect to threshold cutoff values. One subject displayed a moderate response (518.3 SFU) against RPE65 at baseline only. Positive T cell responses prior to vector administration are unlikely to be related to gene transfer.	None

Author & Year of Publication (Trial Name) Quality rating	Study Design and Duration of Follow-up	Interventions (n) & Dosing Schedule	Major Inclusion & Exclusion Criteria	Patient Characteristics	Key Outcomes	Harms
Maguire, Lancet (2009)[63] **Manuscript** **Study 101**	Single arm comparative study to contralateral eye with some normal age-matched individuals for pupillary light reflexes Dose escalation Performed by 2 physicians at 2 centers: CHOP Seconda Universitá degli Studi de Napoli 2 year follow-up	Voretigene neparvovec (VN) or AAV2-hRPE65v2 1) Low dose: $1.5x10^{10}$ vector genomes (vg) per eye in 0.3ml subretinal injection (n=3) 2) Medium dose: $4.8x10^{10}$ vector genomes (vg) per eye in 0.3ml subretinal injection (n=6) 3) High dose: $1.5x10^{11}$ vector genomes (vg) per eye in 0.3ml subretinal injection (n=3)	<u>Inclusion</u> LCA diagnosis; molecular diagnosis of RPE65 mutations; age 8-44 yrs; visual acuity < 20/200 or visual field less than 20° <u>Exclusion</u> Participation in trial of investigational drug in past 6 months; condition that precludes accurate measure of endpoints; lack of sufficient retinal cells; ocular surgery in past 6 months; sensitivity to surgical meds; neutralizing antibodies AAV2 of 1:1000	Age Range: 8-44 Female, N(%) Total: 5/12 (41.7) Nystagmus frequency at baseline Range 0.3-4.2:	*Nystagmus frequency (Hz)* 90 days Range 0-3.0 *Visual acuity* improved in 9 patients, although not significantly; 2 unchanged, 1 worsened. Not correlated with dose or age. *Visual field* improvements in 12 patients but with substantial variability. Younger subjects saw more improvement; correlated with amount of viable retina *Pupillary reflex* improved in treated eye of all subjects compared to untreated eye *Mobility test* 4 children increased accuracy and speed after tx	No serious adverse events reported Macular hole (1 subject) @ day 14 post treatment Vector detected in tears of 6 subjects ranging from 1-4 days after procedure. Vector in blood or serum detected in 2/3 high dose subjects

Author & Year of Publication (Trial Name) Quality rating	Study Design and Duration of Follow-up	Interventions (n) & Dosing Schedule	Major Inclusion & Exclusion Criteria	Patient Characteristics	Key Outcomes	Harms
Testa, Ophthalmology Manuscript (2013) [86]	Three-year follow up of 5 Italian patients from Maguire 2009 NP01, NP02, NP03, NP04 and NP15	See Maguire 2009	See Maguire 2009	Age: 11-26 Gender: F 2/5; M: 3/5 Eye injected: R 4/5; L 1/5 Vector volume: 150-300 µL Concentration: 1.0-5.0 (10 per µL)	*Best Corrected Visual Acuity* NP01: Baseline RE: 2.0 Year 3 RE: 1.52 NP02: Baseline RE: 2.0 Year 3 RE: 1.49 NP03: Baseline RE: 1.48 Year 3 RE: 0.96 NP04: Baseline LE: 1.02 Year 3 LE: 0.57 NP15 Baseline RE 0.85 Year 3 RE: 0.56	None in third yr

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Bennett, Lancet (2016)[58] Manuscript **Study 102**	Phase I follow-on (Study 101) Treatment of contralateral eye See McGuire 2009 3 years	Voretigene neparvovec (VN) or AAV2-hRPE65v2 Dose: $1.5x10^{11}$ vector genomes (vg) to contralateral eye in 0.3ml subretinal injection N= 11 although final data provided on 10 patients (one patient had post-op eye infection)	See McGuire 2009 *Descriptive stats, N(%) calculated by ICER; 3 years*	See McGuire 2009 Age at re-administration Range 11-46 1 patient from first injection not eligible for follow-on because of glaucoma in contralateral eye Time between first and second injection (years) Range: 1.71-4.58	*Goldman visual field, N(%)* Increase ≥20 sum total degrees: 6(60) Decrease ≥20 sum total degrees: 3(30) No change: 1(10) *Change in full-field light sensitivity threshold (dB) (>10dB):* 8(80) *Visual acuity* No change: 8(80) Improved: 1(10) Worsened: 1(10) *Mobility-at lower light levels* No change: 2(20) 1 level: 1(10) 2 levels: 3(30) 3 levels: 3(30) 5 levels: 1 (10) *Pupillary light reflex* improvement in all patients	No AEs related to AAV vector Dellen formation (uneven surface of cornea) - 3 patients Cataracts – 2 pts SAEs: Post-op bacterial endophthalmitis with intraocular pressure and optic atrophy – 1 pt Myopia requiring correction of >10 diptres and retinal thinning – 1 pt Humoral and cell-mediated response to AAV2 at 4 weeks – 1 pt

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Ashtari, Opthalmology (2017)[89] **Manuscript**	Single arm N=7 (from 11 that had contralateral eye tx in 102) 3 yrs	See Bennett 2016	See Bennett 2016	See Bennett 2016	fMRI baseline (after 1st gt, before contralateral eye) and after tx of contralateral eye. Increases in right, left and total hemisphere cortical activation after gene therapy was associated with improved clinical outcomes of white red and blue light full field stimulus threshold and pupillary reflex	None described
Astari, Molecular Therapy (2016)[92] **abstract**	See Bennett 2016 Pre-tx for contralateral eye compared to treated eye in Maguire (post-tx reported above in Ashtari Opthamology 2017)	See Bennett 2016 10 GT 11 matched controls For fMRI	See Bennett 2016	See Bennett 2016	Tractography results showed higher RT tract density for LCA2 patients in the hemisphere ipsilateral to their untreated eye and a higher GS tract density ipsilateral to their treated eyes. Control subjects showed symmetrical tracts for both RT and GS pathways.	NA

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Ashtari, Science Translational Medicine (2016)[92] Manuscript	See Bennett 2016 10 LCA2 patients and 11 demographically matched sighted controls matched for age, gender, ethnicity, and handedness.	See Bennett 2016 Diffusion tensor imaging (DTI) to examine the effect of deprivation and subsequent unilateral retinal gene therapy on the organization and/or reorganization of white matter microstructure in V1.	See Bennett 2016	See Bennett 2016	Results from DTI, diffusion tractography, and fMRI along with correlation of these data with nystagmus measures, age, and length of time after treatment in LCA2 patients suggested that retinal gene therapy may promote remyelination of geniculostriate fiber axons as well as local changes within the V1 favoring the treated eye. These observations suggest that the functional plasticity for patients receiving retinal gene therapy may be related to structural changes in the brain.	NA

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Ashtari, Molecular Therapy (2012)[87] **abstract**	5 pts from Bennet 2016 after contralateral injection	See Bennett 2016	See Bennett 2016	See Bennett 2016	All subjects showed significant increased cortical activations after re-administration. While younger subjects showed considerable activations, there were no significant cortical responses for the baseline of the older subjects. fMRI results revealed significant improvement in visual function of 5 LCA patients who received re-administration of AAV2-hRPE65v2 to their contralateral eye with no adverse effect to the functionality of their previously treated eye. Younger subjects' cortical activations at baseline may be due to less advanced retinal degeneration as compared to older patients.	NA

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Bennett, Science Translational Medicine (2012)[62] Manuscript **Subset 102 for safety**	Single arm safety report on first 3 patients to receive contralateral treatment as part of Phase 1 Follow-on (see Bennett 102 for full results) 2/3 pts F/U until day 180 1 pt final data is average 180 & 365	Voretigene neparvovec (VN) or AAV2-hRPE65v2 See Bennet 2016	See Bennett 2016	Age: CH12: 46 CH11: 27 NP01: 29 Sex: all Female Years after first treatment: CH12: 2.1 CH11: 2.3 NP01: 3.7 Visual acuity in logMAR (higher=worse) pre-contral inject: CH12: 2.6 CH11: 0.64 NP01: 1.83	*Visual acuity, logMAR* (higher=worse) post-contralateral injection CH12: 2.0 CH11: 0.58 NP01: 1.6 *Full-field light sensitivity* CH12: no improv CH11: increased NP01: increased *fMRI total visual cortex changes* with high contract at 30/60 days post injection (mm^2) CH12: 1729/8110 CH11: 9658/13366 NP01: 241/784 *Pupillary light reflex* improved after treatment of contralateral eye *Mobility test*: CH12 no data reported CH11 10 lux (p=0.015) NP01 5 lux (p=0.005)	No surgical complications No serious AEs AE: Surface irritation Sprained ankle Headache Vector present in tears and blood after injection up to day 3 Some transient immune response, one pt with high background forming units

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Simonelli, Molecular Therapy (2010)[85] **Manuscript** **Follow-up to Maguire 2008**	See Maguire 2008 Follow-up out to 1.5 yrs	See Maguire 2008	See Maguire 2008	See Maguire 2008	<u>Objective measures</u> *Pupillary light reflex* at 1.5 years showed sustained improvement in velocity and amplitude in treated vs untreated eye *Reductions in ocular motility* maintained (and lowered) at 1.5 yrs compared to baseline in both eyes *Electroretinography*: no change from baseline to 1.5 years (response flash) <u>Subjective measures</u> *Visual acuity* same at 1.5 years (see Maguire, 2008) Pts 1&3 flipped best eye after treatment *Mobility testing* showed slight continuous improvement between day 30 and 1.5 years.	No serious adverse event through 1.5 years Mild increase in short run serum neutralizing antibodies to AAV2 in 2 patients –normal at 1 year Prior macular hole (subject 2) not expanded

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Maguire, JAMA 2008[93] **Manuscript** **Pilot/Safety**	Safety N=3 LCA2	Voretigene neparvovec (VN) or AAV2-hRPE65v2 1) Subject 1 2) Subject 2 3) Subject 3 Single injection-subretinal Dose: $1.5x10^{10}$ vg in 150 µl of phosphate-buffered saline supplemented with Pluronic F-68 NF Prill Poloxamer 188 and chicken β actin (CBA) promoter	<u>Inclusion</u> LCA diagnosis; *RPE65* mut; age 8-27; visual acuity ≤ 20/200 or visual field less than 20 degrees <u>Exclusion</u> Participation in study of investigational drug or ocular surgery in past 6 months; conditions that preclude endpoint interpretation; lack of sufficient viable retinal cells by OCT; complicating systemic diseases or abnormal baseline labs; sensitivity to meds for surg; presence of neutralizing antibodies to AAV2 above 1:1000	Ages: 19, 26, 26 All pts: right eye treated Female, N (%): 2 (66.7) Nystagmus Freq before injection (Hz), right/left eye 1) 2.0/2.0 2) 1.0/1.0 3) 1.5/1.37 *Visual Acuity (logMAR), right/left eye* 1) 2.0/1.72 2) 2.0/1.04 3) 1.5/1.05 *Visual Field (degrees), right/left eye* 1) 41/36 2) 62/55 3) 147/203	*Reductions in Nystagmus Freq after injection (Hz), right/left eye* 1) 1.2/1.2 (difference -0.8/-0.8) 2) 0.9/0.9 (difference -0.1/-0.1) 3) 1.4/1.1 (difference -0.1/-0.27) *Pupillary Light Reflex* All pts had greater response to light stimulus; each eye ~3x as sensitive to light *Visual Acuity, logMAR right/left eye (difference in treated eye)* 1) 1.72/1.74 (0.28) 2) 1.55/1.04 (0.45) 3) 1.16/1.03 (0.34) *Visual Field, degrees (difference in treated eye)* 1) 177/26 (136/-10) 2) 213/75 (151/20) 3) 210/160 (63/-43)	Patient 2: Outer lamellar cyst in fovea noted on day 5 after injection; Macular hole 2 weeks post-surgery Patient 1: Tear showed AAV2 on Day 1 post surgery, no evidence of dissemination, no humoral immune response Patient 2: neutralizing antibody titers increased post-surgery but diminished over time