# Sonpiretigene Isteparvovec for Advanced Retinitis Pigmentosa: Effectiveness and Value

**Final Report**

**May 15, 2025**

**Prepared for**

NEW ENGLAND CEPAC
COMPARATIVE EFFECTIVENESS PUBLIC ADVISORY COUNCIL

**June 10, 2026:** New evidence regarding treatments and therapies gets published on an ongoing basis. ICER reached out to key stakeholders included in this review 12 months after the publication of this report giving them an opportunity to submit public comments regarding new relevant evidence or information on coverage that they wish to highlight. Their statements can be found here. ICER has launched ICER Analytics to provide stakeholders an opportunity to work directly with ICER models and examine how changes in parameters would affect results. You can learn more about ICER Analytics here.

Per ICER's guidelines on the acceptance and use of "In-Confidence" data from manufacturers of pharmaceuticals, academic in-confidence data that was redacted in the report has been unmasked 12 months following the date of the public ICER meeting.

Additionally, some data elements in Table 3.5 and Supplement Tables D3.2 and D3.3 were incorrectly listed as "NR" when they had actually been redacted; these elements have also been unredacted.

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**DATE OF PUBLICATION:** May 15, 2025

**How to cite this document:** Makam AN, Richardson M, McKenna A, Lee W, Herce-Hagiwara B, Phillips M, Rind DM. Sonpiretigene Isteparvovec for Advanced Retinitis Pigmentosa: Effectiveness and Value; Final Report. Institute for Clinical and Economic Review, May 15, 2025. https://icer.org/assessment/retinitis-pigmentosa-2025/

Anil Makam served as the lead author on the report. Avery McKenna and Belén Herce-Hagiwara led the systemic review and authorship of the comparative clinical effectiveness section of this report with assistance from Sol Sanchez. Marina Richardson developed the cost-effectiveness model and authored the corresponding sections of the report in collaboration with Woojung Lee. Marie Phillips and Woojung Lee conducted the analysis for the budget impact model. David Rind provided methodologic guidance on the clinical and economic sections. We would also like to thank Madeline Booth, Anna Geiger, Kelsey Gosselin, and Grace Ham for their contributions to this report.

## About ICER

The Institute for Clinical and Economic Review (ICER) is an independent, non-profit research institute that conducts evidence-based reviews of health care interventions, including prescription drugs, other treatments, and diagnostic tests. In collaboration with patients, clinical experts, and other key stakeholders, ICER analyzes the available evidence on the benefits and risks of these interventions to measure their value and suggest fair prices. ICER also regularly reports on the barriers to care for patients and recommends solutions to ensure fair access to prescription drugs. For more information about ICER, please visit ICER's website.

The funding for this report comes from non-profit foundations, with the largest single funder being the Arnold Ventures. No funding for this work comes from health insurers, pharmacy benefit managers (PBMs), or life science companies. ICER receives approximately 21% of its overall revenue from these health industry organizations to run a separate Policy Summit program, with funding approximately equally split between insurers/PBMs and life science companies. A complete list of funders and more information on ICER's support, is available on the funding page of the ICER website.

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The findings contained within this report are current as of the date of publication. Readers should be aware 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.

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*In the development of this report, ICER's researchers consulted with clinical experts, patients, manufacturers, and other stakeholders. The following individuals served as external reviewers of the draft evidence report:*

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*None of the external reviewers or other experts we spoke to are responsible for the final contents of this report, nor should it be assumed that they support any part of it. Furthermore, it is possible that external reviewers may not have had the opportunity to review all portions of the draft report. The report should be viewed as attributable solely to the ICER team and its affiliated researchers.*
*To protect patient confidentiality, ICER does not routinely name individual patients or care partners who provided us with input and feedback.*

*For a list of stakeholders from who we requested input from, or who have submitted public comments so far, please visit our Key Stakeholders List.*

# Table of Contents

## List of Acronyms and Abbreviations Used in this Report

| | |
|---|---|
| % | Percent |
| AAV2 | Adeno-associated virus serotype 2 |
| AE | Adverse event |
| AHRQ | Agency for Healthcare Research and Quality |
| AUC | Area under the curve |
| BCVA | Best corrected visual acuity |
| BLA | Biologics license application |
| CDR | Clinical Trial Diversity Rating |
| CE | Cost-effectiveness |
| CI | Confidence interval |
| evLYs | Equal value of life years |
| FDA | Food and Drug Administration |
| FrACT | Freiburg Visual Acuity Test |
| Gc | Genome copies |
| Gc/eye | Genome copies per eye |
| GDP | Gross domestic product |
| HD | High-dose |
| HIDI | Health Distribution Index |
| IRD | Inherited retinal disease |
| IVT | Intravitreal treatment |
| LD | Low-dose |
| LogMAR | Logarithmic minimum angle of resolution |
| LSM | Least-squares mean |
| LYs | Life years |
| MCO-010 | Multi-characteristic opsin |
| mITT | Modified intention-to-treat population |
| MLSDT | Multi-luminance shape discrimination test |
| MLYMT | Multi-luminance Y-mobility test |
| n | Number |
| N | Total number |
| N/A | Not applicable |
| NA | Not available |
| NR | Not reported |
| OCT | Optical coherence tomography |
| PRISMA | Preferred Reporting Items for Systematic Reviews and Meta-Analyses |
| QALY | Quality-adjusted life year |
| RCT | Randomized controlled trial |
| RP | Retinitis Pigmentosa |
| SD | Standard deviation |
| SE | Standard error |
| SEM | Standard error of the mean |
| TBD | To be determined |
| TEAE | Treatment-emergent adverse event |
| UC | Usual care |
| US | United States |

# Executive Summary

Retinitis pigmentosa (RP) is a group of inherited retinal diseases characterized by progressive degeneration of photoreceptor cells in the retina. RP affects about one in 4,000 individuals worldwide with an estimated 80,000-110,000 people affected in the United States (US).[1,2] About 12% develop advanced RP with severe vision loss such that they can only count fingers or detect hand motion, and more rarely, experience total blindness without any light perception.[3-5] RP by itself is not a lethal disease. Overall annual health care costs per person are estimated to be only $7,000 more in people with retinitis pigmentosa than the general population, but vision loss can also lead to substantial individual productivity losses, including unemployment, as well as harms to wellbeing.[6-10]

There are currently no known cures for RP. Across all forms of RP, photoreceptor degeneration can progress such that some people develop severe vision loss, although the percentage who develop such severe loss varies based on the specific mutation involved. While some gene therapies target a specific mutation, another therapeutic approach involves optogenetic therapy.[11] Optogenetic therapy involves inserting light-sensitive proteins, known as opsins, into the eye which can allow non-photoreceptor cells in the retina to act as photoreceptors and potentially restore vision.[12] This approach may work across a wide range of RP mutations since the therapy does not directly target any particular genetic cause.

Sonpiretigene isteparvovec (Nanoscope Therapeutics), referred to as "sonpiretigene" hereafter, is an adeno-associated virus serotype 2 (AAV2) gene therapy for individuals with advanced RP with severe vision loss that is administered by a one-time intravitreal injection into a single eye with the lower visual acuity and delivers a multi-characteristic opsin (MCO-010).[13] MCO-010 photosensitizes bipolar cells, which are neurons that connect the outer retina to the inner retina.[14] A rolling submission of a Biologics License Application (BLA) to the US FDA is anticipated to begin in the first quarter of 2025.[15]

The RESTORE trial randomized 27 participants to one of two doses of sonpiretigene or to a sham protocol. At 52 weeks, treated participants on average had clinically meaningful improvements (e.g., ≥0.3 LogMAR improvement) in best corrected visual acuity (BCVA) in both the low-dose and high-dose sonpiretigene arms compared to the sham-control group. These treatment effects appeared to persist up to 100 weeks. The sonpiretigene-treated group also had numerically greater improvements on mobility and shape discrimination tests that were not statistically significant. In responder analyses, sonpiretigene-treated participants had greater response rates than the sham-control participants across all combinations of BCVA, mobility, and shape discrimination.

RP affects different aspects of vision (peripheral vision, light perception, color perception, acuity) over time and, as such, any single measure of benefit may be inadequate for assessing a given patient. The data in RESTORE, with only 27 participants, are sometimes difficult to interpret given the variability in treatment response across different outcomes measures. Patients may respond differently to the treatment. Although, floor and ceiling effects in the various outcome measure ranges contribute to this issue, and some of the outcomes in single patients appear internally inconsistent (see Uncertainties and Controversies in Section 3.2 for details). There were secondary outcomes described in RESTORE that have not been publicly reported. Some were not fully collected, and others were noted to have challenges with interpretation. The mismatch between the protocol and data available raises some concerns about reporting bias. We necessarily have concerns about the durability of benefits and unknown short-term and long-term harms. Additionally, some experts we spoke to expressed skepticism about the biologic plausibility of the treatment. Given these considerations, for adults with advanced RP and severe vision loss, we rate treatment with sonpiretigene as promising but inconclusive ("**P/I**").

**Table ES1. Evidence Rating**

| Treatment | Comparator | Evidence Rating |
|---|---|---|
| **Adults with Advanced Retinitis Pigmentosa** | | |
| **Sonpiretigene Isteparvovec** | Usual Care | P/I: Promising, but Inconclusive |

We conducted an economic analysis that modeled the long-term cost-effectiveness of sonpiretigene using a placeholder price of $437,500 assuming that treatment is only given in one eye. Short-term treatment effect (improvement at Year One) was modeled using individual patient-level data submitted by the manufacturer under ICER's academic-in-confidence policy. Patients treated with sonpiretigene had improved health outcomes (0.72 discounted incremental evLYs and QALYs) and higher costs ($464,000 incremental costs) compared to usual care. At the placeholder price, assuming that only one eye is treated, our analysis suggests that treatment with sonpiretigene would exceed commonly used cost-effectiveness thresholds. Results were primarily driven by health state utilities, durability of treatment effect, and the starting age of patients receiving treatment, and were robust to numerous sensitivity and scenario analyses. Assuming a five-year durability of treatment effect, sonpiretigene would meet commonly used cost-effectiveness thresholds if priced between $67,400 and $101,300 for treatment in one eye. The potential benefit of treating both eyes is unknown, and as such, there is no evidence to support an additional cost for treating a second eye beyond the cost of manufacturing. If sonpiretigene is shown to have a longer durability of effect, cost-effectiveness would improve. However, even when assuming a lifetime durability of treatment effect, sonpiretigene remained above commonly used cost-effectiveness thresholds.

ICER is not issuing an access and affordability alert for sonpiretigene. At the placeholder price of $437,500, assuming that treatment is only given in one eye, 91% of patients expected to be eligible for treatment over five years can be treated without crossing the ICER potential budget impact threshold of $880 million per year, and at the $150,000 threshold price of $101,300, 100% of patients could be treated without crossing this threshold.

Key policy recommendations include:

- Researchers and regulators should partner with patients, clinical specialty societies, and manufacturers to validate and standardize patient-centered outcome measures for use in registries and future trials that capture the full range of perceived visual function in individuals with advanced RP with severe vision loss.

- Given that response to sonpiretigene appears to be widely variable across patients and that the durability of response is uncertain, payers that consider implementing outcomes-based contracts using BCVA should have a mechanism for judging meaningful responses that cannot be captured from BCVA. An outcomes-based contract that allows for patient and clinician reported outcomes and allows for refunds or rebates for treatment effects that are not maintained may be appropriate for a gene therapy that is expected to have a high price.

- The manufacturer should moderate launch pricing decisions to reflect the substantial uncertainty regarding treatment response, durability of treatment effect, and longer-term safety.

- While some payers may consider a requirement that sonpiretigene be administered by retinal specialists or at a center of excellence for retinal care, clinical experts agreed that most ophthalmologists could administer this treatment in their office given the intravitreal route of injection. Payers may consider requiring consultation with a retinal specialist to attest the diagnosis and eligibility for treatment.

Appraisal committee votes on questions of comparative effectiveness and value, along with key policy recommendations regarding pricing, access, and future research are included in the main report in Section 8 and Supplement G.

# 1. Background

Retinitis pigmentosa (RP) is a group of inherited retinal diseases characterized by progressive degeneration of photoreceptor cells in the retina. This loss of photoreceptor cells results in decreased night vision, loss of peripheral vision and, in advanced stages, near total blindness. RP affects about one in 4,000 individuals worldwide with an estimated 80,000-110,000 people affected in the United States (US).[1,2] About 12% develop advanced RP with severe vision loss such that they can only count fingers or detect hand motion, and more rarely, experience total blindness without any light perception.[3-5] RP is not a lethal disease, although visual impairment is generally associated with greater mortality.[16-18] Overall annual health care costs per person are estimated to be only $7,000 more in people with RP than the general population, but vision loss can also lead to substantial individual productivity losses, including unemployment, as well as harms to wellbeing.[6-10]

RP is diagnosed by a combination of eye examinations, genetic testing, and family history.[19] Genetic testing has become increasingly important because the rate of progression and visual prognosis depends on the inheritance pattern and underlying genetic mutation.[20] Around 80 causative genes have been identified.[21] Approximately 65% of RP cases are non-syndromic, meaning only the eyes are affected.[22] Among non-syndromic cases, inheritance patterns include autosomal dominant (30%), autosomal recessive (20%), X-linked (15%), and sporadic cases (35%). The other 35% of RP cases are syndromic, meaning other organs beyond the eye are also affected.[22] Known risk factors for RP pertain to its hereditary pattern, including a family history and male sex (for X-linked RP).[23] The age of onset and rate of progression vary depending on the genetic mutation; some individuals develop significant vision loss in childhood, while others are asymptomatic until adulthood.[1]

There are currently no known cures for RP. Few therapies, if any, are effective in modifying the disease and restoring vision. Historically, treatment for advanced RP includes managing ophthalmic complications of RP, such as cataracts and macular edema, and providing supportive care such as the use of low-vision aids.[24] In 2017, the Food and Drug Administration (FDA) approved voretigene neparvovec (Luxturna®), a gene therapy for *RPE65* mutation-associated retinal dystrophy.[11,25] This mutation most commonly causes a retinal disorder related to RP, but rarely causes a form of RP. Evidence from observational studies suggest sustained efficacy with longer follow-up, however has noted an elevated risk of retinal atrophy at the subretinal injection site of uncertain clinical significance.[26,27] A number of gene therapies for RP are in various phases of development and evaluation.[28]

Across all forms of RP, photoreceptor degeneration can progress such that some people develop severe vision loss, although the percentage who develop such severe loss varies based on the specific mutation involved. While some gene therapies target a specific mutation, another therapeutic approach involves optogenetic therapy.[11] Optogenetic therapy involves inserting light-sensitive proteins, known as opsins, into the eye to allow non-photoreceptor cells in the retina to act as photoreceptors and potentially restore vision.[12] This approach may work across a wide range of RP mutations since the therapy does not directly target any particular genetic cause.

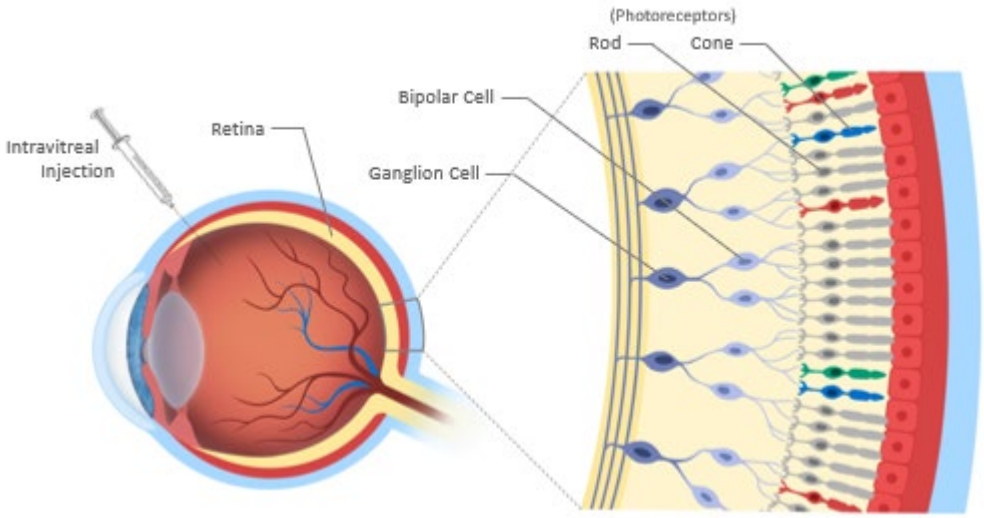
Sonpiretigene isteparvovec (Nanoscope Therapeutics) is an adeno-associated virus serotype 2 (AAV2) gene therapy for individuals with advanced RP with severe vision loss that is administered by intravitreal injection into an eye and delivers a multi-characteristic opsin (MCO-010).[13] MCO-010 photosensitizes bipolar cells, which are neurons that connect the outer retina to the inner retina (see Figure 1.1).[14] Unlike other opsins, MCO-010 is activated by ambient light without the use of external devices. A rolling submission of a Biologics License Application (BLA) to the United States (US) FDA is anticipated to begin in the first half of 2025.[15]

**Table 1.1. Intervention of Interest**

| Intervention | Mechanism of Action | Delivery Route | Prescribing Information |
|---|---|---|---|
| **Sonpiretigene Isteparvovec** | Mutation-agnostic AAV2 gene therapy which expresses light-sensitizing MCO-010 in bipolar cells of the retina | One-time intravitreal injection into the eye | TBD |

Table 1.1 Abbreviations - AAV2: adeno-associated virus serotype 2, MCO: multi-characteristic opsin, TBD: to be determined

**Figure 1.1 Cross-Section of the Retina**



# 2. Patient Community Insights

ICER engaged with patients, representatives from the Foundation Fighting Blindness and from Prevent Blindness, and clinical experts to understand the perspectives of those living with RP, their specific challenges and unmet needs, contextual considerations, and outcomes most relevant to patients and the retinitis pigmentosa community (See Supplement Section B for details). ICER also conducted focused sessions with four patients from the retinitis pigmentosa community to discuss ICER's early thinking on the approach to the cost-effectiveness analysis and to discuss draft findings. Details of these discussions and the impact on our model development are reported in the Supplement Section E1.

People living with RP experience many visual symptoms, including night blindness, loss of peripheral vision, difficulty in discriminating colors, poor dark or light adaptation, and progressive central visual loss. These visual symptoms can limit important day-to-day activities, such as reading, driving, and a range of activities from playing sports to performing household chores.[29,30] They also may have difficulty with relationships and participating in social events. According to national survey data, Americans with visual impairment, like people with advanced RP, were less likely to obtain higher education degrees and employment opportunities.[31] Nearly one-third (31%) of Americans with visual impairment had incomes below the federal poverty limit.[32]

We heard that vision loss from RP progresses gradually for many years until the later stages when it becomes more rapid such that affected individuals require re-adaptation of skills to continually overcome the "series of losses" in vision. Patients with advanced RP discussed how contrast in light was essential and that sudden changes from dark to brightly lit settings, or vice versa, were extremely challenging. Another common theme was the day-to-day variation in their vision which patients attributed in part to differences in their sleep, diet, exercise, and psychosocial stress. In the most advanced stages of RP, near or total loss of light perception was described as "devastating" such that even a slight improvement in vision may "connect them back to the world." People with advanced RP expressed considerable concerns about progressing to complete blindness, and the impact of complete blindness on personal safety. They also described considerable psychosocial and emotional distress, including frustration and worry.[29] People with RP have higher rates of anxiety and depression symptoms than sighted individuals.[33] More awareness of the progression of vision loss and adaptive tools and training could help individuals better cope with living with RP.

With continual adaptation, many patients with advanced RP with severe vision loss expressed that they still lead meaningful lives as active members of society. They would need to carefully consider the potential harms, costs, and durability of a new therapy, particularly if the gains in vision were more modest, such as going from some light perception to being able to count fingers. Patients with advanced RP were more eager for treatments that would enable greater vision restoration, such as recognizing faces and to being able to read again. However, if completely blind, gaining some light perception could help people regain the most basic functions such as recognizing the "red glow of an exit sign" to navigate to the door or the direction of a speaker to properly position themselves to avoid "social embarrassment." Others who were earlier in their disease course expressed more willingness to try new therapies with less severe vision loss, even if the benefits were more modest. Despite the commonality of developing coping strategies and the resilience of individuals living with RP, there is an unmet need to improve light sensitivity and restore vision in advanced RP.

Research shows that there are also considerable emotional, physical and financial impacts on caregivers, particularly for individuals who are less able to cope and adapt to severe vision loss.[34] Dependence on caregiving can strain caregivers' interpersonal relationships and cause psychological stress, as well as financial burden due to reduced work hours and out-of-pocket health expenses for adaptive aids and visual rehabilitation.

### *Health Equity Considerations*

All stakeholders recognized that the ability of individuals with RP to meaningfully adapt to severe vision loss is variable and often contingent on socioeconomic status given the need for visual aids, assistive technologies, vision rehabilitation, skills training, and home modifications. These resources are largely accessed outside of the health care system with added out-of-pocket costs. A new treatment that is accessible and preserves or restores vision would have potential health equity gains, particularly for individuals from lower socioeconomic backgrounds. This includes those with limited financial means, digital literacy, workplace flexibility, and social support networks to help them cope with and successfully adapt to progressive vision loss, including historically marginalized racial and ethnic minorities and rural populations. An effective therapy may also improve caregiver outcomes for these individuals, since caregivers may need to reduce working hours to care for their loved one, drive them to appointments, or contribute financially to their treatments.[34]

# 3. Comparative Clinical Effectiveness

## 3.1. Methods Overview

### Scope of Review

We evaluated the clinical effectiveness of sonpiretigene isteparvovec (MCO-010), referred to as "sonpiretigene" hereafter, versus usual care, which includes low vision aids, vision-related rehabilitation, and managing ophthalmic complications (i.e., cataracts), for adults with advanced retinitis pigmentosa (RP) with severe vision loss. We sought and reviewed evidence on patient-important outcomes, including improvements in vision, slowing of disease progression, independence in daily life, quality of life, and harms, such as intraocular inflammation and ocular hypertension. The full protocol of the review is available in Section D1 of the Supplement.

### Evidence Base

Evidence informing our review of sonpiretigene for the treatment of advanced RP was derived from the Phase IIb/III RESTORE randomized controlled trial (RCT).[35] This was supplemented by data on harms from the Phase I/II SAD dose-escalation trial (see Supplement Section D2).[36-38] Data sources include both publicly available conferences presentations and data submitted by the manufacturer of sonpiretigene.[35,39-47]

#### *Study Design*

The Phase IIb/III RESTORE trial evaluated the efficacy and safety of sonpiretigene in adults with advanced RP with severe vision loss. Participants were randomized 1:1:1 to low-dose sonpiretigene, high-dose sonpiretigene, or a sham procedure in a single eye.[48] Participants were eligible to enroll in the trial if they were 18 years of age or older, had a confirmed diagnosis of advanced RP based on clinical examination and genetic testing, and had a best corrected visual acuity (BCVA) worse than 1.9 LogMAR in the study eye and no better than 1.6 LogMAR in the non-study eye. (LogMAR is explained further in the next section of the report.) Participants were ineligible to enroll if they participated in a prior gene therapy program, had pre-existing glaucoma or other diseases affecting the optic nerve, active ocular inflammation, or recurrent history of idiopathic or autoimmune associated uveitis.[48]

Of the 27 participants enrolled, nine received low-dose sonpiretigene ($0.9x10^{11}$ genome copies/eye), nine received high-dose sonpiretigene ($1.2x10^{11}$ genome copies/eye), and nine received a sham procedure to imitate an intravitreal injection in the study eye. All treated participants received prophylactic oral steroids with a tapering regimen of 21 days beginning three days prior to the injection to limit inflammation at the injection site. Sham participants received matching placebo. Participants were followed for up to week 100 and those who were treated with sonpiretigene were eligible to enroll in an open-label follow-up study for three additional years (REMAIN).[49]

The primary analysis was conducted at week 52 in the modified intention-to-treat population (mITT), which included all 27 enrolled participants. As the trial was small and findings were similar, we opted to also report the pooled data from the two sonpiretigene doses where available. There were two protocol deviations: one sham participant had an incorrect measurement of BCVA (the timing of the measurement is not reported publicly), and one sonpiretigene participant's treatment was stored outside of the specified temperature range.[46]

### *Key Outcomes*

The primary endpoint of the trial was the change from baseline in BCVA of the study eye at week 52 measured by the Freiburg Visual Acuity Test (FrACT). Secondary endpoints included change from baseline in BCVA at week 76 and both the change from baseline and proportion of individuals with a greater than 2-level light improvement in the multi-luminance Y-mobility test (MLYMT) and multi-luminance shape discrimination test (MLSDT) at week 52 in the study eye.[48] Descriptions of these outcomes are detailed in Table 3.1. Additional outcomes (e.g., pupillary response, full field stimulus threshold test) described in the trial protocol were not available or provided to ICER at the time of our review.

**Table 3.1. Minimal Clinically Importance Differences for Patient-Reported Outcomes**

| Outcome | Score Range | MCID |
|---|---|---|
| **Best Corrected Visual Acuity (BCVA)** | 2.25 (floor of FrACT) to 0 (20/20 vision) | >0.3 LogMAR improvement |
| **Multi-Luminance Y-Mobility Test (MLYMT)** | -1 (fail at 100 lux) to 5 (pass at 0.3 lux) | ≥2 light level improvement |
| **Multi-Luminance Shape Discrimination Test (MLSDT)** | 0 (fail at 21 lux) to 5 (pass at 0.2 lux) | ≥2 light level improvement |

Table 3.1 Abbreviations – FrACT: Freiberg Visual Acuity Test, LogMAR: logarithmic minimum angle of resolution

**Best Corrected Visual Acuity:** BCVA was measured using the FrACT and was reported using the logarithmic minimum angle of resolution (LogMAR). The FrACT scores visual acuity on a chart beginning at 0 LogMAR (20/20 vision) with a greater LogMAR score indicating worse vision. While the FrACT is a validated tool to measure visual acuity in people with low vision, it is unable to capture LogMAR scores worse than 2.25 which is the floor measurement for this outcome. For

interpretability, LogMAR scores have been approximately mapped to key visual stages including: better than counting fingers (~1.4-1.8 LogMAR), counting fingers (~1.8-2.1 LogMAR), hand movement (~2.1-2.25 LogMAR), light perception (below the floor), and no light perception (below the floor) (See Table 3.2).[50] However, there is limited literature on translating LogMAR scores to each vision stage, especially for the stages of light perception and no light perception since these are below the floor of measuring BCVA.[45,50-52]

**Table 3.2. LogMAR and Visual Stage Mapping**[50]

| Visual Stage | Better than Counting Fingers | Counting Fingers | Hand Movement | Light Perception | No Light Perception |
|---|---|---|---|---|---|
| **LogMAR** | ~1.4 to 1.8 | ~1.8 to 2.1 | ~2.1 to 2.25 | Not measurable | Not measurable |

**Multi-Luminance Y-Mobility Test (MLYMT)**: This manufacturer-developed measure evaluates a person's ability to navigate a Y-shaped course with three obstacles (to the left, right, and in front of the participant) to locate a lighted panel. It was adapted from a previously validated multi-luminance mobility test and simplified to account for people with lower vision.[53] The MLYMT utilizes six levels of illumination for the lighted panel ranging from 100 lux (similar to an overcast day) to 0.3 lux (dark night sky). Successful completion of the test at each illumination level was defined as correct identification of the lighted panel three different times (see Table 3.3 for scoring).[46]

**Table 3.3. Multi-Luminance Y-Mobility Test Scoring**[46]

| Score | -1 | 0 | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|---|---|
| **Interpretation** | Failing at 100 lux (brightest) | Passing at 100 lux | Passing at 32 lux | Passing at 10 lux | Passing at 3 lux | Passing at 1 lux | Passing at 0.3 lux (dimmest) |

**Multi-Luminance Shape Discrimination Test (MLSDT):** The MLSDT is a novel manufacturer-developed measure that evaluates a person's ability to identify three different shapes at five different illumination levels ranging from 21 lux (dimly lit room) to 0.2 lux (dark night sky). Successful completion of the test at each illumination level was defined as correct identification of the shapes three different times (see Table 3.4 for scoring).[46]

**Table 3.4. Multi-Luminance Shape Discrimination Test Scoring**[46]

| Score | 0 | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|---|
| **Interpretation** | Failing at 21 lux (brightest) | Passing at 21 lux | Passing at 7 lux | Passing at 2.1 lux | Passing at 0.7 lux | Passing at 0.2 lux (dimmest) |

### *Baseline Characteristics*

Baseline characteristics of the RESTORE trial are reported in Table 3.5. Participants were predominantly white (93%), male (63%), and had a mean age of 56 years (range: 23 to 84).[46] Overall, the mean visual acuity in the study eye at baseline was 2.2 LogMAR (ability to see hand movement). At baseline, the mean MLYMT score was 1.1, meaning that on average, participants could navigate to the light source in the Y-mobility test when illuminated at the second brightest of six luminance levels (32 lux). The mean MLSDT score was 1.1, meaning that on average, participants correctly identified shapes when illuminated at the second brightest of five luminance levels (21 lux).[35,41]

**Table 3.5. Baseline Characteristics of RESTORE Study Participants[40,46]**

| | Low-Dose Sonpiretigene (N=9) | High-Dose Sonpiretigene (N=9) | Combined Sonpiretigene (N=18) | Sham Control (N=9) |
|---|---|---|---|---|
| **Baseline Demographic Characteristics** | | | | |
| **Age, Years, Mean (SD)** | 52.2 (16.2) | 60.4 (13.3) | 56.3 (15.0) | 56.7 (10.9) |
| **Female Sex, n (%)** | 3 (33.3) | 3 (33.3) | 6 (33.3) | 4 (44.4) |
| **Race - White, n (%)** | 7 (77.8) | 9 (100) | 16 (88.9) | 9 (100) |
| **Race - Asian, n (%)** | 1 (11.1) | 0 | 1 (5.6) | 0 |
| **Race - Other, n (%)** | 1 (11.1) | 0 | 1 (5.6) | 0 |
| **Hispanic/Latino, n (%)** | 4 (44.4) | 3 (33.3) | 7 (38.9) | 4 (44.4) |
| **Baseline Vision Measures** | | | | |
| **BCVA, Mean LogMAR (SE)** | 2.21 (NR) | 2.3 (NR) | 2.2 (0.02) | 2.2 (0.05) |
| **MLYMT, Mean Score (SE)** | 0.77 (NR) | 1.55 (NR) | 1.2 (0.6) | 1.0 (1.0) |
| **MLSDT, Mean Score (SE)** | 1.44 (NR) | 0.22 (NR) | 0.8 (0.4) | 1.7 (0.6) |

Table 3.5 Abbreviations - %: percent, n: number, N: total number, NR: not reported, SD: standard deviation, SE: standard error

### *Evaluation of Clinical Trial Diversity*

We did not rate the demographic diversity (race/ethnicity, sex, age) of the participants in the RESTORE trial using the ICER-developed Clinical trial Diversity Rating (CDR) Tool due to a lack of prevalence estimates stratified by demographic categories for RP.[54] Instead, the demographic diversity of the RESTORE trial is described qualitatively in Supplement D1.

## 3.2. Results

### Clinical Benefits

#### *Best-Corrected Visual Acuity (BCVA)*

*BCVA: Change from Baseline*

At week 52, the low- and high-dose sonpiretigene groups on average showed clinically meaningful (≥0.3 LogMAR) and statistically significant improvement in LogMAR of -0.38 and -0.34 respectively compared to the sham group (see Table 3.6).[40] An area under the curve (AUC) analysis was also conducted for this outcome and is reported in Supplement Section D2.

**Table 3.6. Mean Changes in Visual Acuity[35,40]**

| BCVA Score | Low-Dose Sonpiretigene (N=9) | High-Dose Sonpiretigene (N=9) | Sham Control (N=9) |
|---|---|---|---|
| **Mean Change from Baseline (SEM);* p-value vs. Sham** | -0.38 (0.12); p=0.029 | -0.34 (0.08); p=0.021 | -0.05 (0.07) |

Table 3.6 Abbreviations - BCVA: best corrected visual acuity, N: total number, SEM: standard error of the mean
Table 3.6 Footnote - *Calculated using a linear mixed effects model for repeated measures (MMRM).
Negative values represent an improvement in BCVA.

At week 76, the 18 sonpiretigene-treated participants continued to have higher mean LogMAR improvements compared to the nine sham participants. (Low-Dose: -0.37, High-Dose: -0.54, Sham: -0.078). The change from baseline in BCVA at week 76 was statistically significant for the high-dose group versus sham (p=0.0014) but not for the low-dose group versus sham (p=0.065). The effect persisted up to week 126 but was more attenuated (Figure 3.1).[44] The denominator of participants at 126 weeks in each group was not specified at the time of this report.

**Figure 3.1. Changes in Visual Acuity over Time, LogMAR**

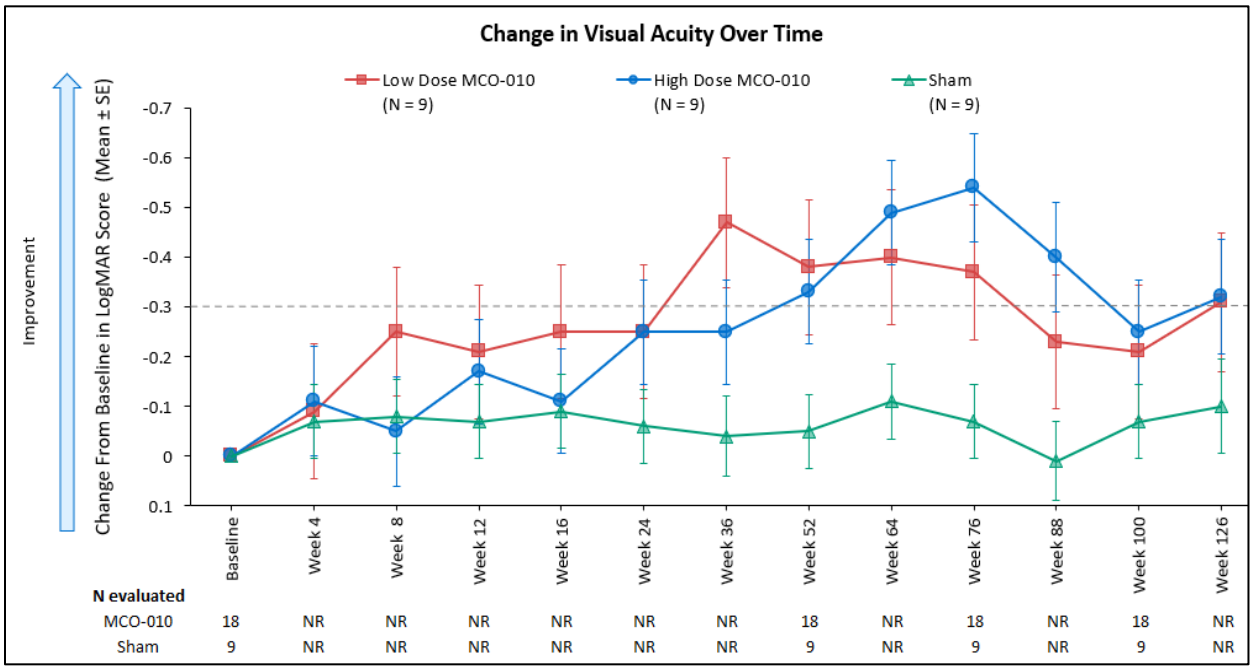



Figure 3.1 Abbreviations – LogMAR: logarithmic minimum angle of resolution, MCO-010: sonpiretigene isteparvovec, N: total number, NR: not reported, SE: standard error

Figure 3.1 Source: Data from a presentation by Monés 2024.[44] Adapted with permission.

*BCVA: Responders*

At week 52, seven (39%) sonpiretigene-treated participants were considered responders (≥0.3 LogMAR improvement from baseline) compared to the one (11%) sham participant who experienced a protocol deviation. The number of sonpiretigene responders increased at week 76 (56%) but subsequently decreased at week 100 (28%). Responder data for the sham cohort were not reported at weeks 76 and 100.[43]

*BCVA: Individual Patient Data*

From publicly available individual participant data shown in Figure 3.2, most participants were at the floor LogMAR value (2.25) at baseline (15 of 18 sonpiretigene-treated participants and six of nine sham participants). At week 52, eight sonpiretigene-treated participants (seven of whom were at the floor at baseline) and six sham-control participants (all at the floor) had no detectable changes in BCVA.[43] Ten of eighteen sonpiretigene-treated participants had a detectable change in BCVA at week 52, with a wide range of improvement (-0.04 to -1.83). One sham-treated participant appeared to have clinically meaningful change (-0.8 LogMAR improvement) but had a protocol deviation due to incorrectly measured BCVA. Another sham-treated participant had a small improvement in BCVA but was well below the meaningful clinically important difference. Lastly, one

sham-treated participant had a negligible worsening in BCVA (+0.01 change).[43] Individual participant data for Week 76 showed a similar pattern (Supplement Figure D2.1)

**Figure 3.2 Individual Participant Data for Changes in Visual Acuity at Week 52**

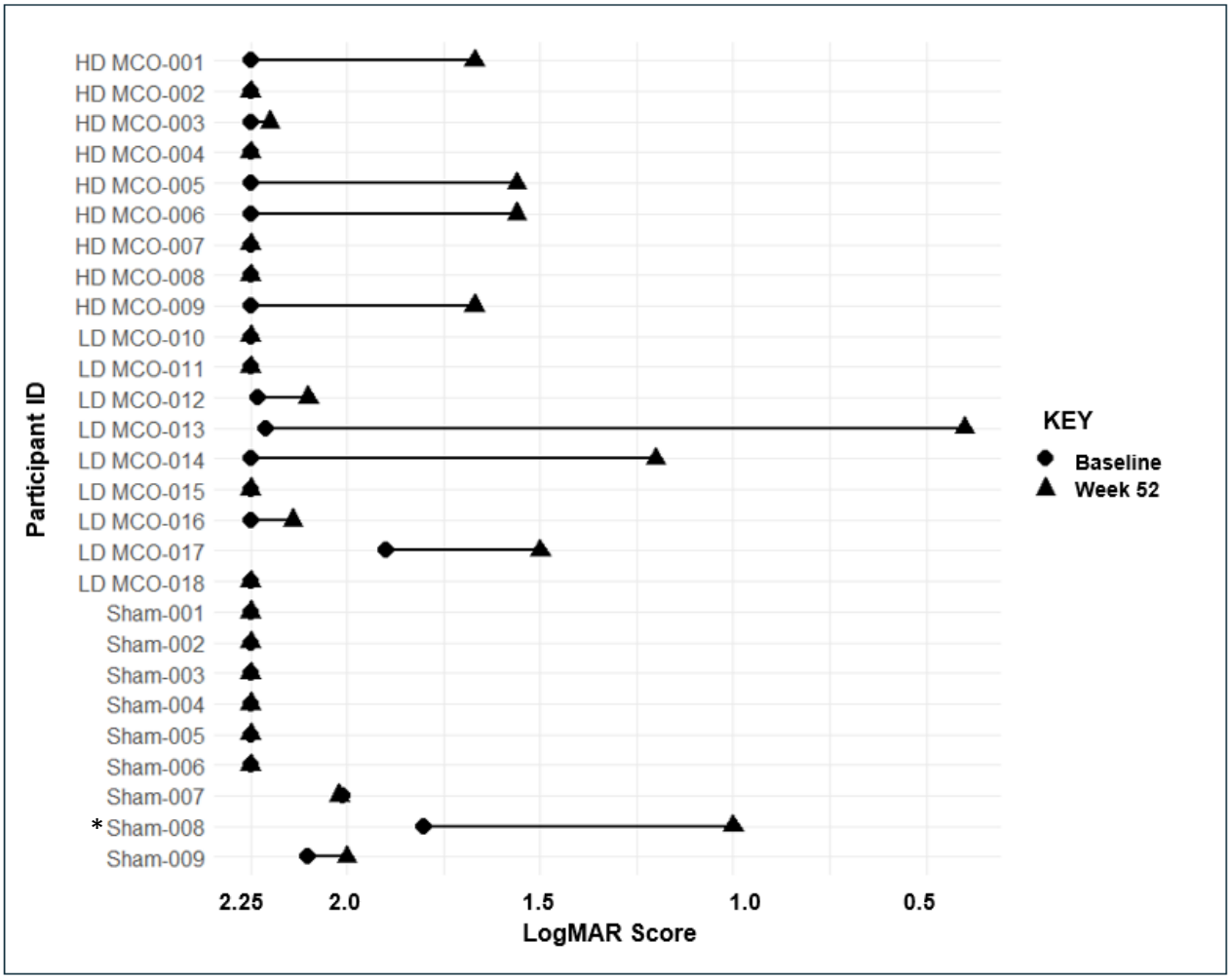



Figure 3.2 Abbreviations - HD: high-dose, LD: low-dose, LogMAR: logarithmic minimum angle of resolution, MCO: sonpiretigene isteparvovec

Figure 3.2 Footnote - * Major protocol deviation related to incorrect recording of BCVA.

Source: Data from a presentation by Loewenstein 2024.[43]

### *Multi-Luminance Y-Mobility Test (MLYMT)*

*MLYMT: Change from Baseline*

After 52 weeks, the combined sonpiretigene-treated group improved by an average of 3.0 illumination levels (p<0.001) from a mean baseline score of 1.2 (passing at the second brightest illumination of 32 lux) to 4.2 (passing at the second dimmest luminance level of 1 lux). This improvement was numerically greater than the improvement observed in the sham-control group (2.0 levels), but was not statistically significant (p=0.20).[41] See Table 3.7. below.

**Table 3.7. Mean Changes in Y-Mobility Test Scores[41]**

| MLYMT Score* | Combined Sonpiretigene (N=18) | Sham Control (N=9) |
|---|---|---|
| **Mean Score (SEM) – Baseline** | 1.17 (0.61) | 1.0 (1.0) |
| **Mean Score (SEM) – Week 52; p-value vs. baseline** | 4.17 (0.43); p<0.001 | 3.0 (1.0); p=0.08 |
| **Mean Change from Baseline (SEM);† p-value vs. sham** | +3.00 (0.59); p=0.20 | +2.00 (1.0) |

Table 3.7 Abbreviations - MLYMT: multi-luminance Y-mobility test, N: total number, SEM: standard error of the mean

Table 3.7 Footnotes - * Scores range from -1 (failing at brightest luminance) to 5 (passing at dimmest luminance). † Method used to derive change from baseline values is unknown.

*MLYMT: Responders*

Twelve participants (67%) in the combined sonpiretigene group achieved a clinically meaningful improvement of at least two light levels in the MLYMT assessment compared to three participants (33%) in the sham group. Five sonpiretigene-treated participants (28%) and three sham-treated participants (33%) performed at or near the ceiling of the Y-mobility test at baseline (e.g., inability to detect further improvement).[35] A third of participants in each arm achieved the maximum of six light level improvement (Table 3.8). No improvement was observed in four sonpiretigene-treated participants and six in the sham group.[35] No participants had a worsened MYLMT score.

**Table 3.8. MLYMT: Participants with Light Level Improvement Ranging from 0-6 Levels[35]**

| Arm | N | Number of Light Levels Improved* from Baseline to 52 weeks, n (%) | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
| **Low-Dose Sonpiretigene** | 9 | 3 (33) | 0 | 2 (22) | 0 | 0 | 1 (11) | 3 (33) |
| **High-Dose Sonpiretigene** | 9 | 1 (11) | 2 (22) | 2 (22) | 1 (11) | 0 | 0 | 3 (33) |
| **Sham Control** | 9 | 6 (67) | 0 | 0 | 0 | 0 | 0 | 3 (33) |

Table 3.8 Abbreviations - %: percent, MLYMT: multi-luminance y-mobility test, n: number, N: total number

Table 3.8 Footnote - * Each number of light levels improved is mutually exclusive.

### *Multi-Luminance Shape Discrimination Test (MLSDT)*

*MLSDT: Change from Baseline*

At 52 weeks, sonpiretigene-treated participants improved by 1.9 illumination levels to a score of 2.4 on the shape discrimination test, correctly identifying shapes when illuminated between 2.1 and 0.7 lux. However, this improvement was not a statistically significant difference (p=0.17) compared to the smaller sham group change from baseline of +0.22 points (Table 3.9).[41]

**Table 3.9. Mean Changes in Shape Discrimination Test Scores[41]**

| MLSDT Score* | Combined Sonpiretigene (N=18) | Sham Control (N=9) |
|---|---|---|
| **Mean Score (SEM) – Baseline** | 0.83 (0.36) | 1.67 (0.62) |
| **Mean Score (SEM) – Week 52; p-value vs. baseline** | 2.44 (0.50); p=0.02 | 1.89 (0.77); p=0.86 |
| **Mean Change from Baseline (SEM);† p-value vs. sham** | +1.94 (0.59); p=0.17 | +0.22 (0.86) |

Table 3.9 Abbreviations - MLSDT: multi-luminance shape discrimination test, N: total number, SEM: standard error of the mean

Table 3.9 Footnotes - * Scores range from 0 (failing at brightest luminance) to 5 (passing at dimmest luminance).
† Method used to derive change from baseline values is unknown.

*MLSDT: Responders*

A clinically meaningful improvement of at least two light levels was observed in ten sonpiretigene-treated participants versus two sham-treated participants (56% versus 22%). It is not publicly known how many participants performed at the ceiling of the shape discrimination test at baseline. At 52 weeks, two sonpiretigene-treated participants (both in the high-dose arm) and one in the sham group had a maximum five light level improvement (22% versus 11%; see Table 3.10). Seven sonpiretigene-treated participants (39%) and six sham-treated participants (67%) did not have any detectable improvement.[41]

**Table 3.10. MLSDT: Participants with Light Level Improvement Ranging from 0-5 Levels[41]**

| Arm | N | Number of Light Levels Improved* from Baseline to 52 weeks, n (%) | | | | | |
|---|---|---|---|---|---|---|---|
| | | 0 | 1 | 2 | 3 | 4 | 5 |
| **Low-Dose Sonpiretigene** | 9 | 3 (33) | 1 (11) | 0 | 1 (11) | 4 (44) | 0 |
| **High-Dose Sonpiretigene** | 9 | 4 (44) | 0 | 1 (11) | 1 (11) | 1 (11) | 2 (22) |
| **Sham Control** | 9 | 6 (67) | 1 (11) | 0 | 1 (11) | 0 | 1 (11) |

Table 3.10 Abbreviations - MLSDT: multi-luminance shape discrimination test, n: number, N: total number
Table 3.10 Footnote - * Each number of light levels improved is mutually exclusive.

### *Composite Responder Analysis*

Composite responder analyses across the three main efficacy outcomes (BCVA, MLYMT, and MLSDT), which were predominantly post hoc, were reported at week 52 using the same minimal clinically important differences defined in Table 3.1 above.[40] Across all combinations of outcomes, sonpiretigene-treated participants had higher response rates than the sham participants (Table 3.11). All sonpiretigene-treated participants (100%) improved on at least one of the outcomes compared to 56% of sham participants. Ten sonpiretigene-treated participants (56%) were responders in at least two outcomes compared to one (11%) in the sham group.[40] Only one sonpiretigene-treated participant was a responder in all three outcomes.

**Table 3.11. Composite Outcomes: Responder Analysis at Week 52**[40]

| Outcome(s) | Combined Sonpiretigene (N=18) | Sham Control (N=9) |
|---|---|---|
| **Responders in One Outcome, n (%)*** | | |
| **BCVA** | 7 (39) | 1 (11) |
| **MLYMT** | 12 (67) | 3 (33) |
| **MLSDT** | 10 (56) | 2 (22) |
| **BCVA or MLYMT or MLSDT** | 18 (100) | 5 (56) |
| **Responders in Two Outcomes, n (%)*** | | |
| **MLYMT and MLSDT** | 6 (33) | 1 (11) |
| **MLSDT and BCVA** | 4 (22) | 0 (0) |
| **MLYMT and BCVA** | 2 (11) | 0 (0) |
| **Responders in Three Outcomes, n (%)** | | |
| **MLYMT and MLSDT and BCVA** | 1 (6) | 0 (0) |

Table 3.11 Abbreviations - %: percent, BCVA: best corrected visual acuity, MLSDT: multi-luminance shape discrimination test, MLYMT: multi-luminance Y-mobility test, n: number, N: total number

Table 3.11 Footnote - * Responders are not mutually exclusive within the one and two outcome groups.

## Quality of Life

At the time of this review, complete data on quality of life outcomes were not reported.

## Harms

At 52 weeks of follow-up, almost all participants treated with sonpiretigene experienced at least one mild to moderate ocular adverse event (94.4%) compared to two-thirds of the sham-control group (66.7%).[46] No participants treated with sonpiretigene experienced a serious adverse event.[46] Ocular adverse events were most commonly intraocular inflammation (primarily presence of anterior chamber cells), increased intraocular pressure (ocular hypertension), and damaged ocular blood vessels (conjunctival hemorrhage). Two sonpiretigene-treated participants (11.1%) and two sham-treated participants (22.2%) with intraocular inflammation required treatment with oral or topical steroids at week 52.[41] No participants experienced inflammation of the retina, choroid, or

blood vessels of the eye, ischemic neuropathy (sudden vision loss due to interrupted blood flow to the optic nerve), hypopyon (accumulation of white blood cells in the anterior chamber), or hypotony (low intraocular pressure).[44] No deaths were observed in this trial. These findings were consistent at 100 weeks of follow-up with only one additional case of ocular hypertension and anterior chamber cells in the high-dose sonpiretigene arm.[45] See Supplement Table D3.4 for the full reporting of adverse events.

No serious adverse events were observed in the open-label, dose-escalation Phase I/II SAD trial. Mild to moderate intraocular inflammation occurred transiently in three participants and was treated with topical steroids.[36,37]

## Subgroup Analyses and Heterogeneity

No data were available on any subgroups of interest, including sociodemographic factors (e.g., sex, age, race or ethnicity), severity of vision loss, form of RP (e.g., syndromic, non-syndromic), inheritance pattern (e.g., X-linked, autosomal recessive) and type of genetic mutation (e.g., RPGR).

## Uncertainty and Controversies

There are a number of uncertainties and controversies for sonpiretigene, particularly since this is an emerging evidence base for a new biotechnology to treat a rare disease.

- The evidence base for treatment efficacy consists solely of the RESTORE trial, a 27-participant RCT that has yet to be published nor details fully made publicly available. A single small trial may not generalize to all types of RP and while the reported efficacy may be underpowered for secondary outcomes, these findings may not be replicated in a larger clinical trial since positive treatment effects may be exaggerated with potential for false positives.[55] Further information is needed to fully appraise the evidence.

- RP affects different aspects of vision (peripheral vision, light perception, color perception, acuity) over time and, as such, any single measure of benefit may be inadequate for assessing a given patient and may fluctuate day-to-day unrelated to disease progression. In the RESTORE trial, with only 27 patients, the data are sometimes difficult to interpret and reconcile across various outcome measures. This may reflect some variability in patients' treatment response. Although floor and ceiling effects in the various outcomes contribute to this issue, and some of the outcomes in single patients appear internally inconsistent and may reflect measurement issues (e.g., HD MCO-003 in Figure 3.2 had minimal improvement in visual acuity but maximal improvement in mobility of 6 light levels). Also, a few participants in the sham group had improved mobility and shape discrimination, which raises concerns about the validity of these two outcome measures developed by the manufacturer for low vision populations.

- Given the above issues, we are particularly concerned about unreported data on outcomes that were described in the protocol for RESTORE. Some outcomes were incompletely collected. We would always have concerns about reporting bias in such a situation, but because of the inconsistencies across measures we feel it is particularly important to have complete outcomes data even if there are challenges with interpretation.

- RESTORE randomized participants to treatment of a single eye with the lowest visual acuity. We have uncertainties around the potential gains of treating both eyes although we suspect that this may be the way sonpiretigene will be used clinically if it receives FDA approval. Gains from treating a second eye might be less than treating the first eye for several reasons. These include that functional benefits may rely mainly on vision in the better (after treatment) eye and that injection of one eye apparently results in at least some transfection of bipolar cells in the uninjected eye.

- Long-term durability of treatment benefits is difficult to assess. Experts had differing opinions on durability with some expressing concern that the treatment could lead to accelerated death of transfected bipolar cells. Others felt that improving light sensitivity could help preserve retinal pathways. As seen in Figure 3.1, the actual 100-week data could be interpreted in various ways with regard to the stability of benefits.

- A number of experts expressed skepticism about sonpiretigene based on experiences with other opsin-based treatments, lack of published details from the RESTORE trial, and lack of data from studies in larger animals that better reflect retinal functioning in humans.

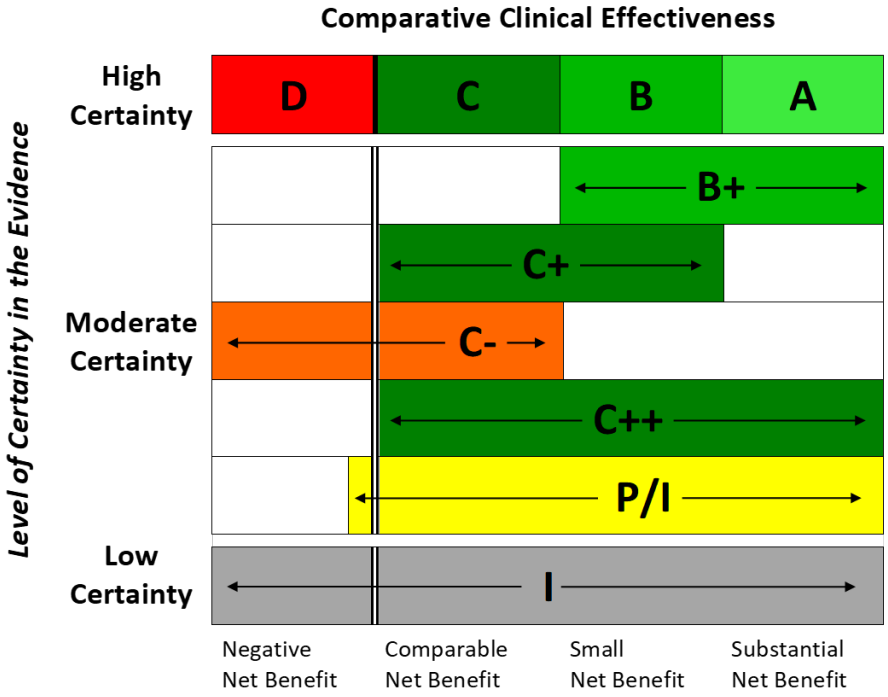
- There is some risk for unmasking with sham intravitreal injections, particularly if participants have experienced prior intravitreal injections. Assessment of masking adequacy was not measured in RESTORE. Additionally, we are uncertain whether there were adequate procedures in place to maintain allocation concealment at the time participants enrolled in the trial.

- While sonpiretigene appeared to have few harms in the RESTORE trial, there was concern for transfection of cells in the untreated eye. This was felt to occur by movement of the vector to the contralateral retina via the optic chiasm. If so, the vector may also be transfecting cells in the brain. It is unclear if this would have harms because of the lack of light exposure, but we note the possibility here.

## 3.3. Summary and Comment

An explanation of the ICER Evidence Rating Matrix (Figure 3.3) is provided here.

**Figure 3.3. 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 Incremental" -*** *Moderate certainty of a comparable or small net health benefit, with high certainty of at least a comparable net health benefit*
***C- = "Comparable or Inferior" –*** *Moderate certainty that the net health benefit is either comparable or inferior with high certainty of at best a comparable 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 small or substantial net health benefit, small (but nonzero) likelihood of a negative net health benefit*
***I = "Insufficient" –*** *Any situation in which the level of certainty in the evidence is low*

Despite the difficulties with interpreting RESTORE, the results appear to show clinically meaningful improvements in vision in sonpiretigene-treated participants compared with sham-treated participants, at least in the short run. Our confidence in these results is reduced by concerns about outcome interpretation, unreported outcomes, the small number of patients, and some uncertainties around masking and allocation concealment. We are uncertain about treatment durability and about potential short-term and long-term harms as the number of treated patients is too small and the duration too short to be confident about safety. We also note that concerns from

some experts about biologic plausibility affect the pre-trial probability of efficacy and thus the post-trial interpretation of outcomes. Given this, for adults with advanced RP and severe vision loss, we rate treatment with sonpiretigene as promising but inconclusive ("**P/I**").

**Table 3.12. Evidence Ratings**

| Treatment | Comparator | Evidence Rating |
|---|---|---|
| **Adults with Advanced Retinitis Pigmentosa** | | |
| **Sonpiretigene Isteparvovec** | Usual Care | P/I: Promising, but Inconclusive |

## New England CEPAC Votes

**Table 3.13. NE CEPAC Votes on Comparative Clinical Effectiveness Questions**

| Question | Yes | No |
|---|---|---|
| ***Patient Population for all questions: People with advanced retinitis pigmentosa (RP) with severe vision loss.*** | | |
| ***Note: Usual care may include low vision aids, mobility training and support, and vision related rehabilitation.*** | | |
| **For patients with advanced RP, is the current evidence adequate to demonstrate that the net health benefit of sonpiretigene is greater than that of usual care?** | 10 | 2 |

A large majority of the panel voted that the current evidence is adequate to demonstrate that the net health benefit of sonpiretigene is greater than that of usual care. While many panelists expressed their concerns about the small trial population, uncertain durability of effect, and the unknown risk of long-term harms, clinical experts and the research team spoke about the low risk of serious harms during the trial and the efficacy of the treatment that appeared to restore some vision for a rare disease with unmet need.

# 4. Long-Term Cost Effectiveness

## 4.1. Methods Overview

The primary aim of this analysis was to estimate the cost-effectiveness of sonpiretigene isteparvovec (sonpiretigene) for people with advanced retinitis pigmentosa and severe vision loss. We used a Markov cohort model that compared sonpiretigene to usual care over a lifetime time horizon. The base-case analysis was conducted from a health care sector perspective (i.e., focus on direct medical care costs only), and patient and caregiver productivity impacts were considered in the modified societal perspective analysis. The model was developed in Microsoft Excel.

A *de novo* decision analytic model was developed for this evaluation, informed by key clinical trials and prior relevant economic models. Costs and outcomes were discounted at 3% per year. The model focused on a hypothetical cohort of patients with advanced retinitis pigmentosa being treated with sonpiretigene or usual care entering the model. Baseline characteristics of patients were aligned with those enrolled in the key clinical trial (RESTORE). Model cycle length was one year and included a half-cycle correction based on what was observed in prior published economic models and the clinical trial data (the primary endpoint of the RESTORE trial was at 52 weeks). Over the lifetime of the model, patients occupied one of six health states based on five levels of visual functioning and a dead state (Figure 4.1). The five levels of visual functioning, from best to worst functioning, include: better than counting fingers, counting fingers, hand motion, light perception, and no light perception. At the start of the model, the distribution of patients into corresponding health states was the same between sonpiretigene and usual care based on a weighted average of patients included in the RESTORE trial.[35,47] Patients remained in the model until they died. All patients could transition to death from all causes from any of the alive health states.

During the development of the model analysis plan, we discussed the preliminary model structure and assumptions with four members of the patient community to ensure their perspectives and experiences were reflected in our analysis. We also discussed the draft model findings with the same four individuals after the posting of our draft report. Full details of the feedback we received and how they informed our model development can be found in the Supplement Section B1 and E1 and as relevant throughout the Report.

Sonpiretigene was assessed under ICER's Value Assessment Framework adaptations for treatments of ultra-rare conditions and for high-impact "single and short-term therapies" (SSTs), and our analysis follows the approach outlined in ICER's Reference Case. Additional details of our methods can be found in the Supplement.

**Figure 4.1. Model Structure**

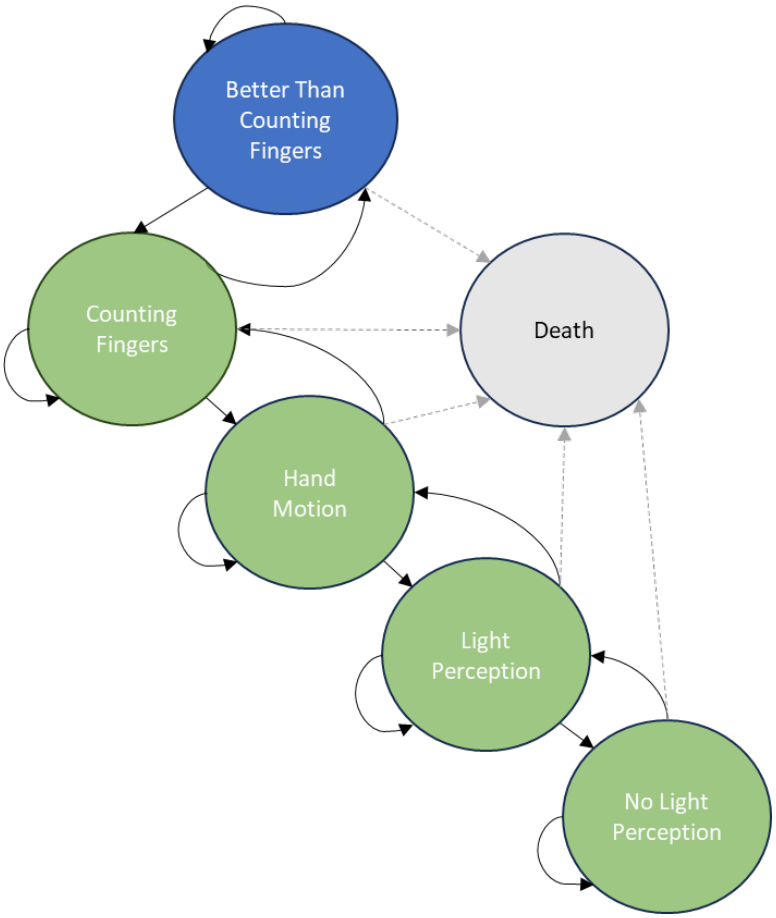



**Figure 4.1 Notes**: Movement of more than one health state may be possible in the model. These transitions are not depicted in the model schematic for simplicity. The model schematic depicts six health states including five health states defined by visual functioning (better than counting fingers, counting fingers, hand motion, light perception and no light perception) and a death state. Green health states (from counting fingers to no light perception) represent the possible starting health states for the intervention and usual care groups. The blue shaded health state (vision better than counting fingers) is a potentially achievable health state for some patients in the model, however, in line with the likely eligible patient population for sonpiretigene, no patients started in better than counting fingers. Transitions between health states (or staying within the same health state) occurred annually, and patients could move to the death state from any level of visual functioning over the lifetime of the model. Please refer to our key model assumptions below for details regarding the data used to inform patient transitions between health states.

Changes to the economic evaluation between the draft Evidence Report and the revised Evidence Report included:

- Removed the patient in the sham control group of the RESTORE trial with a major protocol deviation from the calculations that informed baseline starting distribution and treatment effectiveness at Week 52.

- Revised baseline starting distribution across levels of visual functioning to be equal between sonpiretigene and usual care.

    - In the draft Evidence report, starting distribution was based on what was observed in the RESTORE trial. We revised the baseline distribution of patients across level of visual functioning to be based on a weighted average of patients in the RESTORE trial to remove the impact of any imbalances between intervention and usual care arms.

- Modified approach to calculating week 52 treatment effectiveness to better approximate population-level impact and reduce data sensitivity due to the small sample size.

    - The same principles that were used to derive treatment effectiveness at week 52 in the draft evidence report were used in the revised evidence report with the following changes: instead of applying the direct transitions observed for each individual patient in the trial at week 52, patients were categorized as either staying in the same state, or moving up or down one, two, or three levels of visual functioning based on their starting level of visual functioning. To further smooth the data given the small sample size, the counting fingers and hand motion transitions and the light perception and no light perception transitions were combined into a weighted average based on the number of patients within each starting state. For example, if 50% of patients in light perception stay in light perception at week 52, and 100% of patients in no light perception stay in no light perception at week 52, the percentage of patients staying in their starting state for light perception and no light perception would be 75% assuming that two patients started in each of those states. Likewise, if the remaining 50% of patients in no light perception move up one state to light perception, and 0% patients in light perception move up one state to hand motion, the percentage of patients moving up one state for light perception and no light perception would be 25%. These health state transitions were applied to the revised baseline starting distributions and were meant to help smooth the impact of a single patient driving the results.

- Revised placeholder price of sonpiretigene to $437,500 to remain consistent with the clinical trial protocol and effectiveness results which were based on treatment being administered in only one eye. Our draft evidence report used a placeholder price of $875,000, assuming that both eyes would be treated in practice.

- Revised health state utility for better than counting fingers to 0.54 based on data from the RESTORE trial, in which two patients achieved a higher level of visual functioning than would be represented by the value used in the draft evidence report (0.50).

## 4.2. Key Model Assumptions and Inputs

### Key Model Assumptions

Our model included several assumptions as outlined in Table 4.1.

**Table 4.1. Key Model Assumptions**

| Assumption | Rationale |
|---|---|
| **Treatment effectiveness of sonpiretigene was modeled based on a composite endpoint of best corrected visual acuity (BCVA), multi-luminance Y-mobility testing, and the multi-luminance shape discrimination test at week 52 (year one).** | The primary outcome of the RESTORE trial was the change in visual acuity based on the LogMAR scale at 52 weeks. Due to the limitations of the LogMAR scale in detecting changes in visual function at severe levels of vision loss, we supplemented the results of the BCVA score with the results of the secondary outcomes, the multi-luminance mobility test and the multi-luminance shape discrimination test at 52 weeks, to inform our determination of treatment effectiveness at 52 weeks (see "Clinical Inputs" below). |
| **We used pooled data from the high and low dose arms for sonpiretigene in the RESTORE trial to inform our assessment of the treatment effect.** | Based on individual patient-level data provided by the manufacturer and publicly available data, outcomes appeared similar between high and low dose arms for sonpiretigene. |
| **Treatment effectiveness of sonpiretigene was assumed to last for five years, followed by progressive decline in visual functioning over another five years at which point (year ten) treated patients returned to the vision level of untreated patients.** | There are limited data from the RESTORE trial to inform assumptions about the long-term durability of treatment for sonpiretigene and we heard concerns from clinical experts about anticipated durability. Data from the RESTORE trial suggests possible maintenance of treatment effects for up to 100 weeks and clinical experts suggested that five to seven years was a reasonable expectation of durability. We conducted scenario analyses to assess the impact of alternative assumptions for treatment durability. |

| Assumption | Rationale |
|---|---|
| **Untreated patients and treated patients who returned to the vision level of untreated patients (at year 10) were assumed to experience an exponential decline in visual functioning.** | There are limited data from the RESTORE trial to inform assumptions about progression in visual functioning for untreated patients or treated patients for whom the full treatment effect has been lost. We heard that progression is typically most rapid in the early stages of vision loss suggesting that an exponential function was reasonable. Literature-based estimates for the rate of progression in visual functioning and clinical expert opinion resulted in a realistic estimate for the percentage of patients reaching a state of no light perception over the model time horizon. |
| **Patients receiving sonpiretigene in the model were assumed to receive a one-time intravitreal injection in one eye with the lowest visual acuity.** | Patients receiving sonpiretigene in the RESTORE trial received a one-time intravitreal injection in only one eye. We heard that, in practice, patients are likely to receive treatment in both eyes; however, there is no evidence to inform what impact this might have on patient outcomes. We also heard from clinical experts that patients receiving treatment in only one eye may experience treatment effects in the untreated eye; however, the extent of impact is unclear. It is possible that additional benefit could be seen if both eyes are treated; however no additional benefits were modeled. |
| **Patients with retinitis pigmentosa were assumed to be at the same risk of death as the general United States (US) population. No deaths occurred in year one of the model.** | There is no evidence to suggest that the risk of death would vary across advanced levels of vision loss or to suggest mortality impacts from treatment with sonpiretigene; there were no deaths over 100 weeks in the RESTORE trial. In the absence of a differential effect on mortality and in the absence of direct evidence in advanced retinitis pigmentosa demonstrating an increased risk of mortality, we modeled patients as having a similar risk of death to the general population as an assumption favorable to sonpiretigene since it maximizes the life expectancy during which patients experience treatment benefits. |
| **No serious adverse events associated with sonpiretigene or usual care were modeled. We assumed that mild to moderate inflammation associated with the injection site was managed with prophylactic steroids.** | There is no evidence from the RESTORE trial that sonpiretigene is associated with serious adverse events. Mild to moderate inflammation associated with the injection site has been reported and is typically managed with prophylactic low-dose steroids. |
| **Non-intervention medical costs remained the same across all health states in the model.** | Based on input from the patient community and as observed in the literature, medical visits and diagnostics related to retinitis pigmentosa are not expected to change as patients move between states of visual functioning. |

Table 4.1 Abbreviations - BCVA: best corrected visual acuity, LogMAR: Logarithm of the Minimum Angle of Resolution, US: United States

## Key Model Inputs

Key model inputs are shown in Table 4.2 and outlined below.

### *Baseline Population Characteristics*

Baseline population characteristics were based on the characteristics of patients enrolled in the key clinical trial (RESTORE). The mean age was 56.4 years, 37% of patients were female, and baseline level of visual functioning was 2.21 as measured on the LogMAR scale.

### *Clinical Inputs*

At baseline, patients receiving sonpiretigene or usual care were categorized into one of the five levels of functioning described in the model schematic (Figure 2.1) informed by individual patient-level data[47] provided by the manufacturer (Table 4.2). Baseline distribution was assumed to be the same between sonpiretigene and usual care based on a weighted average of patients included in the RESTORE trial.

Treatment effectiveness was determined based on data from the RESTORE trial at Week 52 including individual patient-level data provided by the manufacturer.[47] One patient in the sham control group had a major protocol deviation and was removed from the analysis. These data showed the results for primary and secondary outcomes of best corrected visual acuity (BCVA), multi-luminance Y-mobility testing, and the multi-luminance shape discrimination test for each patient. Any patient who experienced improvement in at least two of the three measures (or at least one measure when one or two of the other measures was at the ceiling), moved at least one health state. Among those who improved, if the BCVA was one of the two or three measures that improved, and the score suggested the patient experienced an improvement of more than one health state – for example, a move from light perception to counting fingers or a move from light perception to better than counting fingers, a two or three-health state improvement, respectively, was modeled. Similarly, patients who experienced worsening in at least two of the three measures transitioned to a worse health state following the same rule as described for patients who improved. To further smooth the data given the small sample size, the counting fingers and hand motion transitions and the light perception and no light perception transitions were combined into a weighted average based on the number of patients within each starting state. For example, if 50% of patients in light perception stayed in light perception at week 52, and 100% of patients in no light perception stayed in no light perception at week 52, the percentage of patients staying in their starting state for light perception and no light perception would be 75% assuming that two patients started in each of those states. Likewise, if the remaining 50% of patients in no light perception move up one state to light perception, and 0% patients in light perception move up one state to hand motion, the percentage of patients moving up one state for light perception and no light perception would be 25%. These health state transitions were applied to the revised baseline

starting distributions and were meant to help prevent the impact of a single patient driving the results. Transition was assumed to occur half-way through the first model cycle (6 months) using a half-cycle correction, based on data from the RESTORE trial showing gradual visual improvement between baseline and week 52. The remaining patients stayed in the same health state. Health state membership at the end of year one is shown in Table 4.2.

Patients receiving sonpiretigene and usual care were assumed to remain in their year one health state to the end of the second cycle (year two) of the model.[45] Patients receiving sonpiretigene remained at that same level of visual function until model year five followed by progressive loss in visual functioning over another five years. At the end of model year ten, we assumed that patients receiving sonpiretigene had returned to the vision level of untreated patients and would subsequently progress at the same rate as the usual care arm. For patients in the usual care arm, after year two, patients experienced a progressive decline in visual functioning over their lifetime in line with the natural history of disease. To achieve a realistic estimate for the percentage of patients reaching a state of no light perception, we assumed a conservative estimate of 1.75% for the annual rate of decline in patient's level of visual functioning that aligned with clinical expert opinion and supported by published literature. The estimate was based on the lower end of the range reported in Lam et al 2024 (i.e., 3.5%) and further reduced by 50%.[56] The additional reduction in the rate of annual decline resulted in a more reasonable percentage of patients reaching a state of no light perception that aligned with clinical expert opinion and the published literature.[4] The 1.75% annual rate of decline was operationalized in the model as an increase in LogMAR of 1.75% per year and converted to decimal form. The decimal form of the LogMAR score was used to simulate the natural history of disease by creating an exponential function to track visual functioning decline over time. The exponential function was used to determine the annual transition probabilities associated with moving to more progressive health states over time and are represented as years to progression to the next health state in Table 4.2. A summary of health state distributions and transitions for patients for sonpiretigene and usual care is provided in the Supplement Section E2 (Table E2.5).

No treatment discontinuation was modeled for either the intervention or comparator, and the risk of death was based on general population age- and sex-adjusted mortality using United States (US) life tables.[57] The cost of prophylactic steroid use for all patients receiving sonpiretigene was included in the model to prevent mild to moderate inflammation.

### *Health State Utilities*

Health state utilities were derived from a utility elicitation study for retinitis pigmentosa from the UK (better than counting fingers, counting fingers, hand motion, and light perception) and from Brown 2001 to inform the health state utility value for the no light perception health state (Table 4.2).[58,59] We assumed that the better than counting fingers health state in the model was aligned with the "profound impairment" health state defined in O'Brien 2023 which had a utility of 0.5. We adjusted the 0.5 utility to 0.54 to reflect findings from the RESTORE trial that approximately 25% of patients who reached the better than counting fingers health state achieved a level of visual functioning of "severe impairment" which was associated with a utility value of 0.65. Additionally, to reflect what we heard during the focused sessions with patients that there are likely to be meaningful differences in quality of life between patients who experience hand motion compared to being able to perceive light, we adjusted the utility value for hand motion to be the midpoint of the utility values reported for counting fingers and light perception (0.38).

### *Costs*

All costs used in the model were inflated to 2023 US dollars.

We used a placeholder price of US $437,500 for treatment in one eye, which is half of the midpoint of the range estimated by IPD Analytics that assumes treatment of both eyes ($750,000 to $1,000,000).[60] We included a mark-up of 6% of the placeholder price, and an administration cost of $112.18 (CPT Code: 67028, injection eye drug) for sonpiretigene.[61]

Estimates from Frick et al. 2012 were used for non-intervention direct medical costs.[7] Costs are annual and inclusive of related and unrelated medical costs and include inpatient, outpatient, and pharmacy costs from a retrospective claims analysis of US patients (n=2,990) diagnosed with retinitis pigmentosa.[7] The same health state costs were used for the intervention and usual care groups. Additionally, based on the focused sessions with patients, and as observed in the literature, medical visits and diagnostics related to retinitis pigmentosa are not expected to change as visual function changes, and as such, these costs did not vary by health state.

For the modified societal perspective scenario analysis, we used estimates for direct non-medical costs and indirect costs based on a study by Brown et al. 2016[62] and input from patients.[1] During the focused sessions with patients, we heard that direct non-medical costs and indirect costs do not change substantially as their vision changes. The one exception was for non-medical low vision services and devices, where we heard that progression from better than counting fingers to counting fingers or worse represented a significant shift in the level of supportive devices needed for patients to maintain their level of independence (for example, moving beyond only needing magnifiers and glasses). We have captured this difference as a 27% lower cost for low vision services and devices for patients with visual functioning better than counting fingers compared to

patients in a health state of counting fingers or worse. This 27% reduction was used as a proxy based on the lower end of the 95% confidence interval for the overall societal costs reported in Brown 2016, Table 3.[62] Consequently, the direct non-medical costs included in Table 4.2 include annual caregiver costs, transportation costs, and residence costs for assisted living for any unpaid caregiver time ($48,241 in 2023 US dollars) and the cost of low vision services and devices ($3,108 for better than counting fingers; $4,258 for all other health states, in 2023 US dollars).

Full details on model inputs can be found in the Supplement.

**Table 4.2. Key Model Inputs**

| Parameter | Input | | Source |
|---|---|---|---|
| | Sonpiretigene | Usual Care | |
| **Demographic Characteristics** | | | |
| **Mean Age** | 56.4 years | | Boyer 2023[46] |
| **Female, %** | 37% | | |
| **Baseline Health State Classification*** | | | |
| **Better than Counting Fingers** | 0% | | |
| **Counting Fingers** | 4% | | Manufacturer Data on File[47] |
| **Hand Motion** | 38% | | |
| **Light Perception** | 50% | | |
| **No Light Perception** | 8% | | |
| **Natural History of Disease, Average Years to Progression to Next Health State (Assumed LogMAR)†** | | | |
| **Better than Counting Fingers (1.6)** | 10 | | Schulze-Bonsel et al. 2006,[51] Lam et al 2024,[56] and calculation assuming a decline in visual functioning of 1.75% annually. Sonpiretigene arm followed usual care after model year 5. |
| **Counting Fingers (1.95)** | 12 | | |
| **Hand Motion (2.35)** | 12 | | |
| **Light Perception (2.75)** | 29 | | |
| **No Light Perception (3.75)** | N/A‡ | | |
| **Treatment Effectiveness (Health State Classification)*** | | | |
| ***Year 1 and 2*** | | | |
| **Better than Counting Fingers** | 40% | 2% | Manufacturer Data on File[47] and assumptions |
| **Counting Fingers** | 17% | 33% | |
| **Hand Motion** | 10% | 13% | |
| **Light Perception** | 29% | 47% | |
| **No Light Perception** | 4% | 6% | |
| ***Year 3 to 5*** | Maintenance of Year 2 Health State | Variable, based on natural history data (see above) | Clinical expert opinion and assumptions |
| ***Year 10*** | Distribution of patients across health states matches usual care | | Calibration of sonpiretigene health state distribution to that of usual care |
| ***Year >10*** | Variable, based on natural history of disease (see above) | | Clinical expert opinion, and natural history data[56] |

| Parameter | Input | | Source |
|---|---|---|---|
| | Sonpiretigene | Usual Care | |
| **Health State Utilities (SD)*** | | | |
| **Better than Counting Fingers** | 0.54 (0.26) | | O'Brien 2023[58] and calculation using a weighted average of profound impairment (0.50) and severe impairment (0.65) |
| **Counting Fingers** | 0.43 (0.28) | | O'Brien 2023[58] |
| **Hand Motion** | 0.38 (0.27) | | O'Brien 2023,[58] input from patients, and calculation using mid-point of counting fingers and light perception |
| **Light Perception** | 0.33 (0.26) | | O'Brien 2023[58] |
| **No Light Perception** | 0.26 (0.08) | | Brown 2001[59] |
| **Intervention Costs** | | | |
| **Sonpiretigene Acquisition Costs** | $437,500 | N/A | Based on the midpoint of the range reported by IPD Analytics[60] and assuming treatment in one eye only. |
| **Sonpiretigene Mark-Up** | 6% | N/A | ICER Reference Case |
| **Sonpiretigene Administration Costs** | $112.18 | N/A | Centers for Medicare & Medicaid Services[61] |
| **Prophylactic Steroids** | $2.78/kg | N/A | Sadda 2024[35], Regimen: 1 mg/kg/day (Days -3 to 3), 0.5 mg/kg/day (Days 4 to 10), 0.25 mg/kg/day (Day 11 to 17) |
| **Annual Non-Intervention Direct Medical Costs** | | | |
| **All Health States** | $19,327 ($48,935) | | Frick 2012,[7] and input from patients inflated to 2023 US dollars. |
| **Annual Direct Non-Medical Costs** | | | |
| **Better than Counting Fingers** | $51,349 (NA) | | Brown et al 2016,[62] input from patients, and calculation |
| **All Other Health States** | $52,499 (NA) | | |
| **Annual Indirect Costs** | | | |
| **All Health States** | $12,587 ($21,977) | | Brown et al 2016[62] |

Table 4.2 Abbreviations - LogMAR: Logarithmic Minimum Angle of Resolution, kg: kilograms, mg: milligrams, N/A: not applicable, NA: not available, SD: standard deviation

Table 4.2 Footnotes - * Patients in each health state were defined as having a LogMAR calculated as the midpoint of the range of LogMAR reported in the literature[51]: better than counting fingers (1.4 to <1.8), counting fingers (1.8 to <2.1), hand motion (2.1 to <2.6), light perception (2.6 to <2.9), and no light perception (3.0 to 4.5).

† Simulated using a 1.75% annual rate of decline in visual functioning (i.e., an increase in LogMAR scores) applied to a starting LogMAR score of 1.6 (better than counting fingers) and ending at a LogMAR score of 2.5 (hand motion) and fitting an exponential function to the data (y=0.02684e-0.07980x) where y is equal to the decimal form of the LogMAR score and x is equal to time in years.

‡ No light perception represents the most progressed form of vision loss in the model, therefore further progression in visual functioning is not applicable to this health state.

### *Model Outcomes*

Model outcomes included total life years (LYs) gained, quality-adjusted life years (QALYs) gained, equal-value life years (evLYs) gained, and total costs for each intervention over a lifetime time horizon. The model outcomes also included years with vision better than counting fingers gained and years with light perception gained (i.e., years with visual functioning better than no light perception).

## 4.3. Results

### Base-Case Results

Total discounted health outcomes and costs for sonpiretigene and usual care are presented in Tables 4.3 and 4.4. Over the lifetime of the model, sonpiretigene resulted in more QALYs (0.72 discounted incremental QALYs) and higher costs ($464,000 discounted incremental costs) compared to usual care. Patients spent a greater number of years at a level of visual functioning better than counting fingers, and marginally greater number of years with light perception with sonpiretigene compared to usual care. There were no differences in life years, and as such the total QALYs and evLYs are identical. The higher costs for sonpiretigene were driven by intervention acquisition costs as well as mark-up and other intervention-related costs. There were no differences between sonpiretigene and usual care in non-intervention direct medical costs related and unrelated to retinitis pigmentosa. Undiscounted results are reported in the Supplement E3.

The incremental cost-effectiveness ratio for sonpiretigene compared to usual care was $646,000 per QALY and evLY gained. Additional details are reported in Table 4.5.

**Table 4.3. Results for the Base-Case for Sonpiretigene Compared to Usual Care (Health Outcomes)**

| Treatment | QALYs | evLYs | Life Years | Years in Better than Counting Fingers | Years with Light Perception |
|---|---|---|---|---|---|
| **Sonpiretigene** | 6.88 | 6.88 | 17.70 | 3.41 | 15.24 |
| **Usual Care** | 6.17 | 6.17 | 17.70 | 0.18 | 14.67 |
| **Incremental** | 0.72 | 0.72 | 0 | 3.23 | 0.57 |

Table 4.3 Abbreviations - evLYs: equal value of life years gained, QALY: quality-adjusted life year
Table 4.3 Note - Incremental values may not match individual intervention values due to rounding.

**Table 4.4. Results for the Base-Case for Sonpiretigene Compared to Usual Care (Costs)**

| Treatment | Anticipated Intervention Acquisition Costs* | Intervention-Related Costs† | Non-Intervention Costs | Total Costs* |
|---|---|---|---|---|
| **Sonpiretigene** | $437,500 | $26,600 | $342,200 | $806,000 |

| | | | | |
|---|---|---|---|---|
| **Usual Care** | $0 | $0 | $342,200 | $342,000 |
| **Incremental** | $437,500 | $26,600 | $0 | $464,000 |

Table 4.4 Abbreviations - evLYs: equal value of life years gained, QALY: quality-adjusted life year

Table 4.4 Footnotes - * Based on placeholder price.

†Intervention-related costs include markup costs, administration costs, and adverse event prevention costs.

Table 4.4 Note: Incremental values may not match individual intervention values due to rounding. Intervention acquisition costs and intervention-related costs are undiscounted because they occurred in the first year of the model. Non-intervention costs are discounted.

**Table 4.5. Incremental Cost-Effectiveness Ratios for the Base Case**

| Treatment | Cost per QALY Gained* | Cost per evLY Gained* | Cost per additional year in better than counting fingers | Cost per additional year with light perception |
|---|---|---|---|---|
| **Sonpiretigene vs Usual Care** | $646,000 | $646,000 | $144,000 | $811,000 |

Table 4.5 Abbreviations - evLYs: equal value of life years, QALY: quality-adjusted life year

Table 4.5 Footnote - * Based on placeholder price.

Table 4.5 Note: Cost per life year gained is not applicable because there were no incremental differences in life years between sonpiretigene and usual care.

## Sensitivity Analyses

One-way sensitivity analyses were conducted to identify the impact of parameter uncertainty and key drivers of model outcomes. Figure 4.2 presents the results for sonpiretigene compared to usual care from the health care sector perspective. The most influential inputs were the health state utility values for better than counting fingers and light perception the durability of treatment effect for sonpiretigene, and the starting age of the population. Additional details of the analysis and results can be found in the Supplement.

Probabilistic sensitivity analyses were conducted by jointly varying all parameters over 1,000 simulations and then calculating the proportion of simulations that were cost effective over a range of commonly used cost-effectiveness thresholds. Sonpiretigene had a 0% probability of being cost-effective compared to usual care across all thresholds evaluated (Table 4.6). Additional details can be found in the Supplement.

Due to the nature of the data, the short-term treatment efficacy (Year 1 and 2) for sonpiretigene was not included in the deterministic or probabilistic sensitivity analysis and as such, the impact of these data on the uncertainty of the results is not reflected in the tornado diagram or scatter plot

shown in the Supplement. Alternative assumptions for short-term treatment efficacy were explored in scenario analyses (see below).

### Figure 4.2. Tornado Diagram

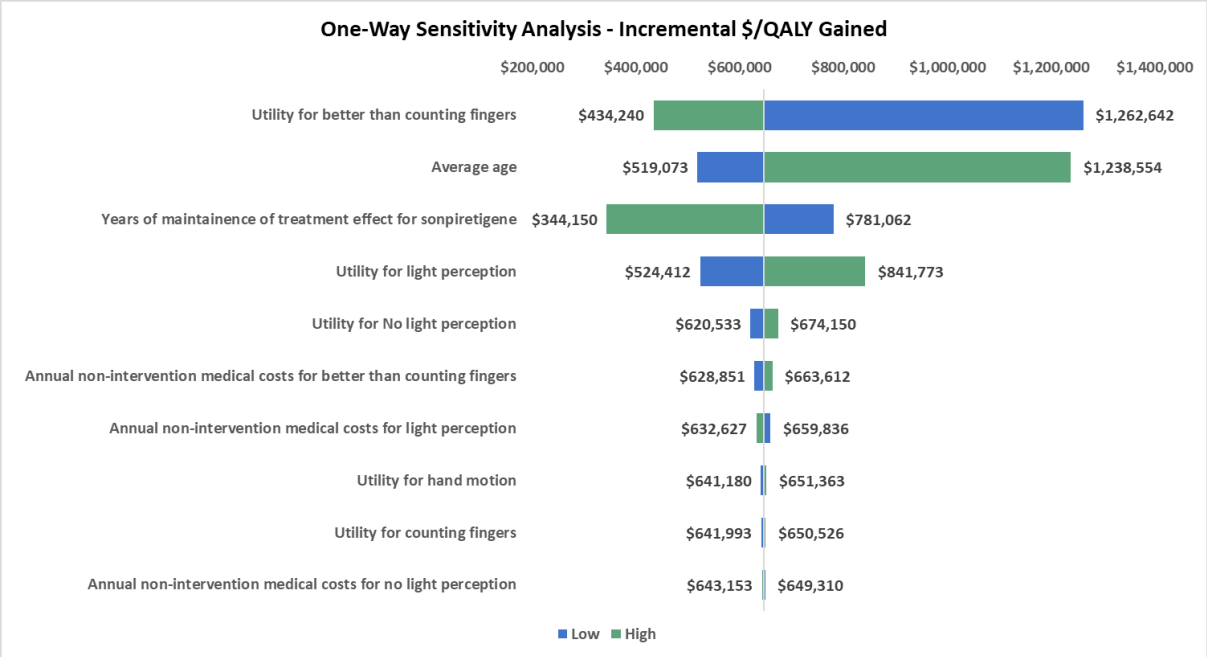



Figure 4.2 Abbreviations - QALY: quality-adjusted life year

Figure 4.2 Note: Due to the nature of the data, the short-term treatment efficacy (Year 1 and 2) for sonpiretigene was not included in the deterministic or probabilistic sensitivity analysis and as such, the impact on the uncertainty of the results is not reflected in the tornado diagram. Alternative assumptions for short-term treatment efficacy were explored in scenario analyses.

### Table 4.6. Probabilistic Sensitivity Analysis Cost per QALY or evLY Gained Results: Sonpiretigene versus Usual Care

| | Cost Effective at $50,000 per QALY or evLY Gained* | Cost Effective at $100,000 per QALY or evLY Gained | Cost Effective at $150,000 per QALY or evLY Gained | Cost Effective at $200,000 per QALY or evLY Gained |
|---|---|---|---|---|
| **Sonpiretigene vs. Usual Care** | 0% | 0% | 0% | 0% |

Table 4.6 Abbreviations - evLY: equal value of life years, QALY: quality-adjusted life year

Table 4.6 Footnote - * Based on placeholder price.

Table 4.6 Note: Due to the nature of the data, the short-term treatment efficacy (Year 1 and 2) for sonpiretigene was not included in the deterministic or probabilistic sensitivity analysis and as such, the impact on the uncertainty of the results is not reflected in the results presented in this table. Alternative assumptions for short-term treatment efficacy were explored in scenario analyses.

## Scenario Analyses

We conducted scenario analyses to examine uncertainty and potential variation in the findings. Scenario analysis included the following:

- Modified societal perspective that includes patient and caregiver productivity costs, transportation costs, and low-visions services and devices.
- An optimistic (A) and conservative (B) benefit scenario analysis which varied assumptions regarding the benefit of treatment. Details of the optimistic and conservative benefit scenarios are included in the Supplement.
- Alternative health state utility values valued by patients with blindness from retinal detachment (Brown et al. 2001).
- Alternative baseline health state classifications based on LogMAR instead of manufacturer-provided classifications.

The results of these scenario analyses are summarized in Table 4.7. Across all scenarios, including more favorable assumptions for treatment durability, incremental cost-effectiveness ratios remained above commonly used cost-effectiveness thresholds. Detailed methods and results are reported in the Supplement. Also in the Supplement is a scenario analysis using unadjusted health-state utility values for hand motion and light perception an a threshold analysis examining the duration of effect in patients receiving short-term benefit that would be needed to achieve cost-effectiveness thresholds.

**Table 4.7. Scenario Analysis Results**

| Base-Case Results | Modified Societal Perspective | Optimistic Benefit Scenario | Conservative Benefit Scenario | Alternative Utility Values | Alternative Baseline Health State Classification |
|---|---|---|---|---|---|
| **Incremental Cost-Effectiveness Ratio (Cost per QALY or evLY gained)** | | | | | |
| $646,000 | $641,000 | $481,000 | $664,000 | $662,000 | $606,000 |

Table 4.7 Abbreviations - evLYs: equal value of life years gained, QALY: quality-adjusted life year, UC: usual care
Table 4.7 Footnote - * Based on placeholder price.

The manufacturer expressed particular concerns about the durability assumptions in the model and felt that ICER should assume lifetime durability of treatment effectiveness. In the following subsection we present results from this scenario in greater detail.

### *Lifetime Durability of Treatment Effect*

**Table 4.8 Results for Sonpiretigene Compared to Usual Care (Health Outcomes) Assuming a Lifetime Durability of Treatment Effect**

| Treatment | QALYs | evLYs | Life Years | Years in Better than Counting Fingers | Years with Light Perception |
|---|---|---|---|---|---|
| **Sonpiretigene** | 7.66 | 7.66 | 17.70 | 6.95 | 16.94 |
| **Usual Care** | 6.17 | 6.17 | 17.70 | 0.18 | 14.67 |
| **Incremental** | 1.49 | 1.49 | 0.00 | 6.77 | 2.27 |

Table 4.8 Abbreviations - evLYs: equal value of life years gained, QALY: quality-adjusted life year

Table 4.8 Note - Incremental values may not match individual intervention values due to rounding.

**Table 4.9 Results for Sonpiretigene Compared to Usual Care (Costs) Assuming a Lifetime Durability of Treatment Effect**

| Treatment | Anticipated Intervention Acquisition Costs* | Intervention-Related Costs† | Non-Intervention Costs | Total Costs* |
|---|---|---|---|---|
| **Sonpiretigene** | $437,500 | $26,600 | $342,000 | $806,300 |
| **Usual Care** | $0 | $0 | $342,000 | $342,000 |
| **Incremental** | $437,500 | $26,600 | $0 | $464,000 |

Table 4.9 Abbreviations - evLYs: equal value of life years gained, QALY: quality-adjusted life year

Table 4.9 Footnotes - * Based on placeholder price

†Intervention-related costs include markup costs, administration costs, and adverse event prevention costs.

Note: Incremental values may not match individual intervention values due to rounding.

**Table 4.10. Incremental Cost-Effectiveness Ratios Assuming a Lifetime Durability of Treatment Effect**

| Treatment | Cost per QALY Gained* | Cost per evLY Gained* | Cost per additional year in better than counting fingers | Cost per additional year with light perception |
|---|---|---|---|---|
| **Sonpiretigene vs Usual Care** | $312,000 | $312,000 | $69,000 | $204,000 |

Table 4.10 Abbreviations - evLYs: equal value of life years, N/A: Not applicable, QALY: quality-adjusted life year

Table 4.10 Footnote - *Based on placeholder price.

Table 4.10 Note - Cost per life year gained is not applicable because there were no incremental differences in life years between sonpiretigene and usual care.

Assuming a lifetime durability of treatment effect would yield prices of $140,000-$210,000 to achieve thresholds of $100,000 to $150,000 per QALY or evLY gained (Table 4.11).

**Table 4.11. QALY and evLY-Based Threshold Analysis Results (Assuming a Lifetime Durability of Treatment Effect)**

| | Anticipated Intervention Acquisition Cost* | Price to Achieve $50,000 per QALY or evLY Gained | Price to Achieve $100,000 per QALY or evLY Gained | Price to Achieve $150,000 per QALY or evLY Gained | Price to Achieve $200,000 per QALY or evLY Gained |
|---|---|---|---|---|---|
| **Sonpiretigene** | $437,500 | $70,000 | $140,000 | $210,000 | $281,000 |

Table 4.11 Abbreviations - evLYs: equal value of life years gained, QALY: quality-adjusted life year, UC: usual care
Table 4.11 Footnote - *Based on placeholder price and represents the cost of treatment for one eye.

## Threshold Analyses

Threshold analyses were conducted for sonpiretigene to calculate the price needed to meet commonly accepted cost-effectiveness thresholds for QALY and evLYs and are shown in Table 4.8. These prices represent the price to treat one eye and were calculated assuming a five-year maintenance of treatment effect. The potential benefit of treating both eyes is unknown, and as such, there is no evidence to support an additional cost for treating a second eye beyond the cost of manufacturing.

**Table 4.12. QALY and evLY-Based Threshold Analysis Results**

| | Anticipated Intervention Acquisition Cost* | Price to Achieve $50,000 per QALY or evLY Gained | Price to Achieve $100,000 per QALY or evLY Gained | Price to Achieve $150,000 per QALY or evLY Gained | Price to Achieve $200,000 per QALY or evLY Gained |
|---|---|---|---|---|---|
| **Sonpiretigene** | $437,500 | $33,500 | $67,400 | $101,300 | $135,200 |

Table 4.12 Abbreviations - evLYs: equal value of life years gained, QALY: quality-adjusted life year, UC: usual care
Table 4.12 Footnote - * Based on placeholder price and represents the cost of treatment for one eye.

## Model Validation

We used several approaches to validate the model. First, we discussed our draft model structure and assumptions with four members of the patient community to ensure their perspectives and experiences were reflected in our model analysis plan. Second, we provided the preliminary model structure, methods, and assumptions to manufacturers, patient groups, and clinical experts. Based on feedback from these groups, we refined data inputs used in the model, as needed. Third, we varied model input parameters to evaluate face validity of changes in results and performed model verification for model calculations using internal reviewers. As part of ICER's efforts in acknowledging modeling transparency, we shared the model with the relevant manufacturer for external verification around the time of publishing the draft report.

## Uncertainty and Controversies

There are several uncertainties related to the modeling assumption and inputs for sonpiretigene as described below:

- The clinical data used to model the primary treatment effect for sonpiretigene were based on a study with a small sample size and a primary outcome measure (BCVA) that has limitations in measuring changes at advanced levels of visual dysfunction. Given the rarity of the disease, we recognize the potential challenges of generating evidence for treatments with a larger sample size. We used the available data and an *a priori* rationale to apply our judgement on how best to represent the treatment effect in the model. We expected the results of the secondary outcomes of the trial to help alleviate concerns about the sensitivity of BCVA in capturing changes in vision for patients with advanced levels of vision loss and have explored alternative assumptions for treatment effects in scenario analyses. We conducted scenario analyses that included alternative assumptions for starting health state classification for patients and alternative assumptions for what threshold of change would be required to obtain an improvement in visual functioning (i.e., number of outcomes for which improvement was documented) in the first year of the model.

- Our model assumed that patients in the sonpiretigene arm received a one-time intravitreal injection in one eye to match the efficacy data from the RESTORE trial in which patients received treatment in the eye with the lower visual acuity. Our placeholder price ($437,500) was also based on the assumption that only one eye would be treated. We heard from clinical experts that in practice, patients are likely to be treated in both eyes; however, we have no data at present to inform the additional benefit that could be achieved from treating both eyes. As discussed in the Comparative Clinical Effectiveness section, there are substantial uncertainties on the magnitude of additional benefits that might be achieved by treating both eyes, if any. If both eyes are treated in practice, there is no evidence to inform an additional payment for treating the second eye beyond the manufacturing costs associated with treatment.

- There were no data beyond Week 100 of the RESTORE trial to inform reasonable estimates for the durability of treatment effect. Given that the average patient in the trial was 56 years of age, and the treatment was modeled over a lifetime time horizon, the majority of the treatment effect was accrued beyond the time for which clinical data was available. A five-year maintenance of treatment effect was believed to be a reasonable estimate for durability given the concerns we heard from clinical experts about potential phototoxicity effects to the transfected bipolar cells. Scenario analyses explored alternative assumptions for treatment durability.

- Although RESTORE was a randomized controlled trial with a usual care comparator group, data were limited to Week 100. We used published literature and clinical expert opinion to determine a reasonable estimate for the rate of progression for the untreated group and as a basis to inform the rate of decline for the treated group after the assumed loss of treatment effect. It is possible that we would obtain different results under alternative assumptions for the rate of visual progression, however, higher rates of progression are anticipated to influence both the treated and untreated groups, and this is unlikely to have a substantial impact on the results. If data suggest differences in medical costs by level of visual functioning, or more substantial differences in quality of life across health states, variation in progression of visual functioning over time may introduce greater uncertainty in the results.

- Our assumption that the distribution of patients across health states for the treated group would match the untreated group at Year 10 of the model required the identification of a calibration target and the subsequent use of a single multiplier to apply to the usual care transition probabilities during the five years of decline in treatment effect. Although we sought to determine a multiplier that generated a match in patient distribution at Year 10, our model contains five health states and an exact match was not possible. For the base case, the health state selected for the calibration target (hand motion) was based on minimizing the absolute difference in the distribution of patients across health states between the intervention and comparator and one that did not systematically disadvantage sonpiretigene by having more patients in a no light perception health state compared to usual care. Furthermore, with each alternative assumption for durability of treatment effect, a calibration target specific to that assumption was calculated; however, the calibration target (i.e., the hand motion health state) remained constant.

- As a result of the limited data to inform treatment effect and associated durability, it was not possible to reliably reflect the uncertainty of all model parameters within the one-way sensitivity analyses or probabilistic sensitivity analyses. As such, the results of the sensitivity analyses should be interpreted alongside the results of the scenario analyses to comprehensively assess the uncertainty in the model findings. It is possible that under extreme assumptions for treatment effect, treatment durability, and alternative utility estimates, results could vary more than that currently represented in the selected sensitivity and scenario analysis.

- The model findings are driven in large part by the health state utility values used in the model. Our base-case analysis used data derived from a utility elicitation study for retinitis pigmentosa from the UK[58] which was believed to be the best source given the recency of the data, the population studied, and the methodology used. We recognize that other studies have reported alternative values across health states, and there are several studies

that do not differentiate quality of life for levels of visual functioning in between light perception and counting fingers. Given the wide range of utility measures and variability in experience heard during our focused sessions with patients, we conducted two additional scenario analyses to explore alternative assumptions for quality of life across levels of visual functioning.

- In response to what we heard during our focused sessions with patients, we included outcome measures for cost per year in better than counting fingers and cost per year with light perception as outcome measures in addition to those defined by quality of life. Sonpiretigene resulted in 3.2 more years in a better than counting fingers health state compared to usual care, a finding that is valuable to consider given the importance to patients.

- Finally, given the marginal incremental differences in QALYs and evLYs observed, small changes in the estimated QALYs can have substantial impacts on the calculated incremental cost-effectiveness ratio.

## 4.4 Summary and Comment

Over a lifetime time horizon, patients treated with sonpiretigene experienced gains in evLYs and a greater number of years with vision better than counting fingers compared to patients receiving usual care. At a placeholder price of $437,500 for treatment in one eye, our analysis suggests that treatment with sonpiretigene would not meet commonly used cost-effectiveness thresholds. Even with more favorable estimates for treatment durability, results remained above commonly used cost-effectiveness thresholds across all sensitivity and scenario analyses.

# 5. Benefits Beyond Health and Special Ethical Priorities

Our reviews seek to provide information on benefits beyond health and special ethical priorities offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that was not available in the evidence base nor could be adequately estimated within the cost-effectiveness model. These elements are listed in the table below, with related information gathered from patients and other stakeholders. Following the public deliberation on this report the appraisal committee will vote on the degree to which each of these factors should affect overall judgments of long-term value for money of the intervention in this review.

**Table 5.1. Benefits Beyond Health and Special Ethical Priorities**

| Benefits Beyond Health and Special Ethical Priorities | Relevant Information |
|---|---|
| **There is substantial unmet need despite currently available treatments.** | There are currently no available therapies to preserve or restore vision in advanced RP.<br><br>To inform unmet need as a benefit beyond health, the results for the absolute and proportional shortfalls have been reported below. The shortfalls were the same, regardless of whether QALY or evLY was used.<br><br>QALY and evLY shortfalls:<br>• Absolute shortfall: 14.9<br>• Proportional shortfall: 70.7%<br><br>The absolute and proportional shortfalls represent the total and proportional health units of remaining quality adjusted life expectancy, respectively, that would be lost due to un- or under-treated illness. Please refer to the ICER Reference Case – Section 2. Quantifying Unmet Need (QALY and evLY Shortfalls) for the shortfalls of other conditions assessed in prior ICER reviews. |
| **This condition is of substantial relevance for people from a racial/ethnic group that have not been equitably served by the health care system.** | There are important health equity implications since adaption of progressive vision loss requires considerable resources that are typically not provided by the health care system. |
| **The treatment is likely to produce substantial improvement in caregivers' quality of life and/or ability to pursue their own education, work, and family life.** | RP itself does not cause morbidity beyond vision loss. Because individuals vary in their ability to adapt, some caregivers may experience more considerable gains in quality of life, time, and finances. |
| **The treatment offers a substantial opportunity to improve access to effective treatment by means of its mechanism of action or method of delivery.** | If not cost prohibitive, a one-time intravitreal injection can substantially improve access. |

ICER did not calculate the Health Distribution Index (HIDI) due to a lack of sufficient data of retinitis pigmentosa rates in racial and ethnic minority populations.

## New England CEPAC Votes

At the public meeting, the New England CEPAC deliberated and voted on the relevance of specific potential other benefits and contextual considerations on judgments of value for the intervention under review. The results of the voting are shown below. Further details on the intent of these votes to help provide a comprehensive view on long-term value for money are provided in the ICER Value Assessment Framework.

**To help inform judgments of overall long-term value for money, please indicate your level of agreement with the following statements:**

**Table 5.2. New England CEPAC Votes on Benefits Beyond Health and Special Ethical Priorities - Condition**

| Benefits Beyond Health and Special Ethical Priorities | Strongly Disagree | Disagree | Neutral | Agree | Strongly Agree |
|---|---|---|---|---|---|
| **There is substantial unmet need despite currently available treatments.** | 0 | 0 | 0 | 2 | 10* |
| **This condition is of substantial relevance for people from a racial/ethnic group that have not been equitably served by the healthcare system.** | 2 | 1 | 5 | 4 | 0 |

* Table 5.2 Note: a vote was mistakenly cast as "strongly disagree" during the public meeting but is corrected here as "strongly agree"

A large majority of the panel voted that they "strongly agree" there is a substantial unmet need despite currently available treatments. The panel heard from patient experts, clinical experts, and the research team about the high unmet need for individuals with RP. It was noted that although patients living with RP are extremely resilient, they are dependent on assistive technology, have limited opportunities within the workforce, and experience social isolation due to having low vision.

Votes from the panel were split and mainly ranged from "neutral" to "agree" with a few votes for "strongly disagree" that RP is of substantial relevance for people from a racial/ethnic group that have not been equitably served by the health care system. While

RP does not differentially affect certain racial/ethnic groups, the panel heard from patient and clinical experts that the ability to successfully adapt to severe vision loss depended on socioeconomic status, digital and health literacy, and geographic access to visual rehabilitation resources and a city-wide infrastructure to successfully navigate, such as public transport.

**To help inform judgments of overall long-term value for money, please indicate your level of agreement with the following statements based on the relative effects of sonpiretigene versus usual care:**

**Table 5.3. New England CEPAC Votes on Benefits Beyond Health and Special Ethical Priorities – Treatment**

| Benefits Beyond Health and Special Ethical Priorities | Strongly Disagree | Disagree | Neutral | Agree | Strongly Agree |
|---|---|---|---|---|---|
| **The treatment is likely to produce substantial improvement in caregivers' quality of life and/or ability to pursue their own education, work, and family life.** | 0 | 2 | 2 | 8 | 0 |
| **The treatment offers a substantial opportunity to improve access to effective treatment by means of its mechanism of action or method of delivery.** | 0 | 1 | 3 | 6 | 2 |

A majority of the panel members voted that they "agree" that the treatment is likely to produce substantial improvement in caregivers' quality of life and/or ability to pursue their own education, work, and family life. The patient experts shared the experience of people with RP who rely on caregivers for daily needs, such as preparations of meals. They shared how a slight increase in independence can improve caregivers' well-being.

Half of the panel voted that they "agree" that the treatment offers a substantial opportunity to improve access to effective treatment by means of its mechanism of action or method of delivery. The panel heard about how this gene therapy would be potentially more accessible compared to usual care. However, there were uncertainties about transportation if the therapy was restricted to a small number of centers with retinal specialists.

# 6. Health Benefit Price Benchmarks

The Health Benefit Price Benchmark (HBPB) for the cost of treating one eye with sonpiretigene is presented in Table 6.1 below. The HBPB for a drug is defined as the price range that would achieve incremental cost-effectiveness ratios between $100,000 per QALY and $150,000 per evLY gained. The HBPB range for sonpiretigene is $67,400 to $101,300. The potential benefit of treating both eyes is unknown, and as such, there is no evidence to support an additional cost for treating a second eye beyond the cost of manufacturing.

**Table 6.1. Annual Cost-Effectiveness Threshold Prices for Sonpiretigene**

| | Price for Treatment of One Eye at $100,000 Threshold | Price for Treatment of One Eye at $150,000 Threshold |
|---|---|---|
| **QALYs Gained** | $67,400 | $101,300 |
| **evLYs Gained** | $67,400 | $101,300 |

Table 6.1 Abbreviations - evLY: equal value life year, QALY: quality-adjusted life year

## New England CEPAC Votes

### New England CEPAC Votes on Long-Term Value for Money at Current Prices

Long-term value for money votes were not taken at the public meeting because a net price for sonpiretigene was not available.

# 7. Potential Budget Impact

## 7.1. Overview of Key Assumptions

Results from the cost-effectiveness model were used to estimate the potential total budgetary impact of sonpiretigene for patients with advanced retinitis pigmentosa and severe vision loss. Potential budget impact is 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 a five-year time horizon. We used a placeholder price of $437,500 and the three threshold prices (at $50,000, $100,000, and $150,000 per evLYG) for sonpiretigene in our estimates of budget impact.

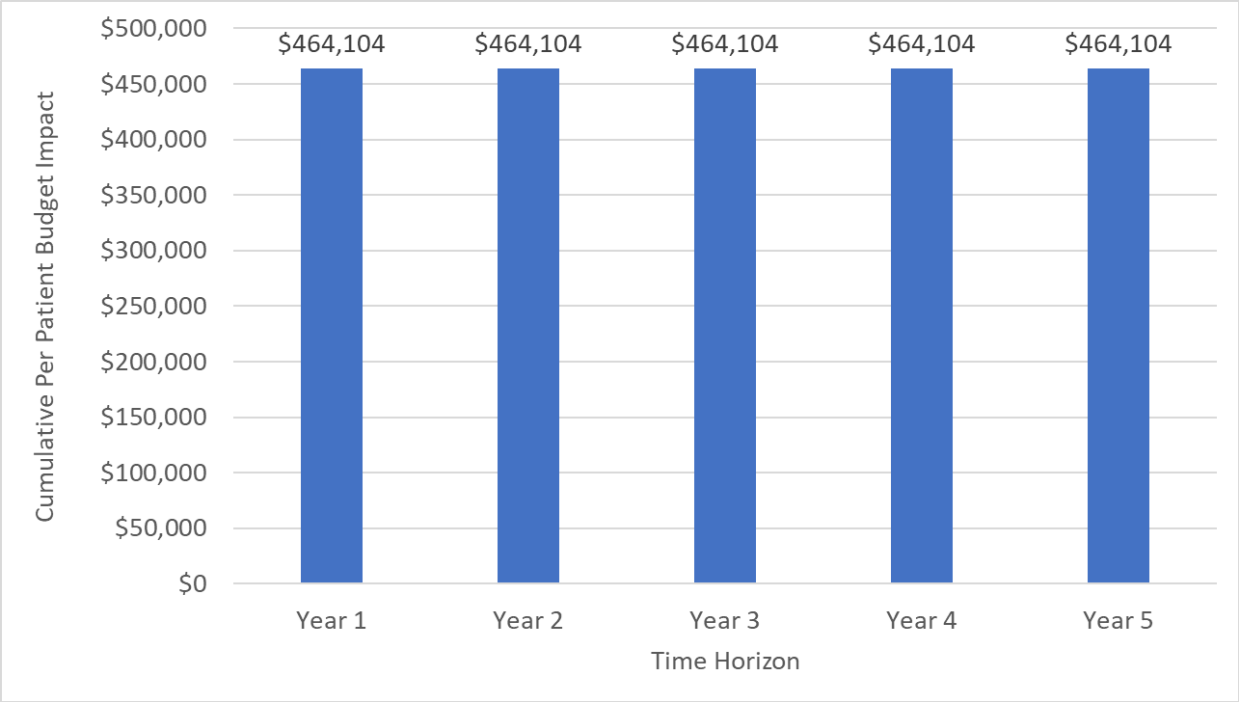
This potential budget impact analysis included the estimated number of individuals in the US who would be eligible for sonpiretigene. To estimate the size of the potential candidate populations for treatment, we used inputs for the prevalence of retinitis pigmentosa in the US (0.025%).[1] To estimate those with severe vision loss, we further applied the percentage of patients with retinitis pigmentosa with visual acuity in the range of "counting fingers or worse" (12%) as a proxy, based on the eligibility criteria of the RESTORE study.[3] It is assumed that all patients with retinitis pigmentosa in this range of vision loss would be eligible for sonpiretigene. However, this assumption may change with the approval and uptake of new gene therapies for retinitis pigmentosa given that treatment with a prior gene therapy was an exclusion criterion for the RESTORE trial. Applying these sources to the total projected US population averaged over the five years (346,449,218) results in estimates of 10,393 eligible patients in the US.[63] For the purposes of this analysis, we assumed that 20% of these patients would initiate treatment each year over five years, or 2,079 patients per year.

## 7.2. Results

Figure 7.1 illustrates the cumulative annual per patient treated population budget impact for sonpiretigene compared to usual care. The cumulative per patient annual budget impact represents the incremental costs of sonpiretigene compared to usual care per patient across all patients treated within a time horizon (including those who initiated sonpiretigene in previous years), assuming sonpiretigene is used with 20% uptake each year over five years.

At sonpiretigene's placeholder price of $437,500 per treatment and assuming both eyes are treated, the average annual budget impact per patient was $464,104 in the first year, with cumulative per patient annual costs remaining the same over longer time horizons. This is because intervention costs are incurred only in the first year, and there is no cost difference between sonpiretigene and usual care thereafter.

**Figure 7.1. Cumulative Per Patient Annual Budget Impact for Sonpiretigene Compared to Usual Care Using a Placeholder Price for Sonpiretigene**




Assuming a 20% uptake of sonpiretigene each year, 91% of patients could be treated over five years at the placeholder price of $437,500 before reaching the ICER potential budget impact threshold of $880 million per year. All potentially eligible patients could be treated over the span of five years at the $50,000, $100,000 and $150,000 per evLY threshold prices ($33,500, $67,400 and $101,300 respectively).

## Access and Affordability Alert

The purpose of an ICER access and affordability alert is to signal to stakeholders and policy makers that the amount of added health care costs associated with a new service may be difficult for the health system to absorb over the short term without displacing other needed services or contributing to rapid growth in health care insurance costs that threaten sustainable access to high-value care for all patients.

ICER is not issuing an access and affordability alert for sonpiretigene. At the placeholder price of $437,500, assuming that treatment is only given in one eye, 91% of patients expected to be eligible for treatment over five years can be treated without crossing the ICER potential budget impact threshold of $880 million per year, and at the $150,000 threshold price of $101,300, 100% of patients could be treated without crossing this threshold.

# 8. Policy Recommendations

Following the New England CEPAC deliberation on the evidence, a policy roundtable discussion was moderated by Sarah Emond, President and CEO at ICER, around how best to apply the evidence on the use of sonpiretigene. The policy roundtable members included two patient organization representatives, two clinical experts, two payers, and one representative from the drug maker. The discussion reflected multiple perspectives and opinions, and therefore, none of the statements below should be taken as a consensus view held by all participants. The top-line policy implications are presented below, and additional information can be found here.

## General Recommendations

### All Stakeholders

***Recommendation 1***

***All stakeholders have a responsibility to make necessary accommodations for individuals with severe vision loss, including designing educational materials and signage suitable for low vision. Low vision should not undermine the tenets of fair access to medical care, to which all patients have a fundamental right.***

There are many challenges for individuals with low vision to navigate the health care system, such as attending clinic visits, reviewing results and messages in electronic health records system, and learning about available clinical trials. All stakeholders emphasized the need to accommodate individuals with low vision to be able to access health care, such as better signage in offices, including in ophthalmology offices, and design of patient portals and other materials, such as the use of alternative text for figures and tables, compatibility with assistive technology, and adoption of electronic forms so that patients can complete them on their own to maintain privacy.

***Recommendation 2***

***Researchers and regulators should partner with patients, clinical specialty societies, and manufacturers to validate and standardize patient-centered outcome measures that capture the full range of perceived visual function in individuals with advanced RP with severe vision loss. These measures should complement visual acuity in registries and future pivotal trials.***

The primary outcome used in the pivotal trial of sonpiretigene was best corrected visual acuity (BCVA). However, individuals with severe vision loss may have no or some light perception and their vision cannot be assessed by BCVA. Furthermore, patients with advanced RP have a myriad of visual symptoms beyond central vision loss, such as loss of color perception, peripheral vision, and contrast sensitivity. To complement the primary outcome of BCVA, all stakeholders play a role in facilitating research and developing regulatory guidance to validate and standardize the use of patient-centered outcome measures for individuals with advanced RP with severe vision loss, including the newly developed tests for mobility (MLYMT) and shape discrimination (MLSDT) used by the manufacturers to evaluate the efficacy of sonpiretigene. Such outcomes may also be useful to evaluate treatments for other inherited retinal disorders with photoreceptor loss.

# Health Equity

## All Stakeholders

***Recommendation 1***

***All stakeholders have a responsibility to increase awareness of and access to low vision aids and vision rehabilitation services for individuals with severe vision loss.***

There is currently no cure or disease-modifying therapies for RP with severe vision loss. The best available treatment for advanced RP includes low vision aids and vision rehabilitation. However, patients and clinical experts highlighted low uptake of these services due to lack of awareness and access to these services, especially for individuals who live in more rural settings or from lower socioeconomic backgrounds who have more limited financial means, time flexibility, and social support. These inequities are driven in large part because they are paid for out-of-pocket since they are not traditionally covered by insurance the way durable medical equipment (i.e. wheelchairs) and physical rehabilitation are covered for medical conditions impairing mobility and physical functioning.

To address these concerns:

<u>Payers should take the following actions:</u>

- Expand the coverage of medically necessary services for individuals with low vision to include assistive devices, such as white canes and magnifiers, and vision rehabilitation services for training in the use of adaptive devices, orientation and mobility, and independent living skills, including vocational adaptations.

Manufacturers should take the following actions:

- Provide educational material to inform individuals with severe vision loss about low vision aids and vision rehabilitation services to successfully adapt to vision loss.

Clinical specialty societies and patient organizations should take the following actions:

- Educate retina specialists, optometrists, ophthalmologists, primary care providers, and patients about low vision services and available rehabilitation centers.
- Explore and develop virtual options to provide vision rehabilitation to further increase access, particularly for individuals who do not have the financial means or ability to travel to attend in person.

## Payers

***Recommendation 1***

***Given that response to sonpiretigene appears to be widely variable across patients and that the durability of response is uncertain, payers that consider implementing outcomes-based contracts using best-corrected visual acuity should have a mechanism for judging meaningful responses that cannot be captured from BCVA. An outcomes-based contract that allows for patient and clinician reported outcomes and allows for refunds or rebates for treatment effects that are not maintained may be appropriate for a gene therapy that is expected to have a high price.***

While variability in response makes an outcomes-based contract a consideration for payers, there are difficulties in developing such contracts for sonpiretigene. The most natural outcome to use for an outcomes-based contract is the best-corrected visual acuity (BCVA). However, this outcome will not be sufficient for everyone since individuals with severe vision loss who have unmeasurable visual acuity below the floor threshold of the BCVA may still have meaningful improvement (such as improvement from no light perception to some light perception). Additionally, advanced RP affects many visual symptoms beyond central vision, such as color vision and contrast sensitivity, which are not assessed by the BCVA. Thus, payers may wish to work with the manufacturer to develop patient-centered outcome measures that capture benefits that could be missed by the BCVA, such as the Michigan Retinal Degeneration Questionnaire, which assesses visual function across seven domains. Clinician and patient input will be important in developing any outcomes-based contracts in this space.

***Recommendation 2***

***When designing coverage policies if sonpiretigene is approved by the FDA, payers should use the inclusion criteria from the pivotal trial as a guide to coverage policy.***

There are no other curative or disease-modifying therapies for advanced RP. The potential alternative therapies to restore vision include photoreceptor transplantation and surgically implanted retinal "chips", which clinical experts we spoke to believe are both earlier in development with less robust evidence and are much more complicated therapies. Given the significant uncertainty that remains about sonpiretigene, it is reasonable for payers to use prior authorization as a component of coverage. Prior authorization criteria should be based on the ultimate FDA label, if the drug is approved, clinical evidence, specialty society guidelines, and input from clinical experts and patient groups. The process for authorization should be clear and efficient for providers and patients. Options for specific elements of coverage criteria within insurance coverage policy are discussed below.

## Manufacturers

***Recommendation 1***

***Manufacturers should set prices that will foster affordability and access for all patients by aligning prices with the value of their treatments. In the setting of a new intervention for advanced RP, while there is considerable hope associated with the promise of sonpiretigene, there also remains substantial uncertainty regarding the durability of treatment effect and longer-term safety. Manufacturer pricing should also reflect these considerations in moderating launch pricing.***

Drug prices that are set well beyond the cost-effective range cause not only financial toxicity for patients and families using the treatment but also contribute to general health care cost growth that pushes families out of the insurance pool, and that causes others to ration their own care in ways that can be harmful.

Manufacturers should therefore price novel treatments in accordance with the demonstrated benefits to patients for their specific therapies and should not benchmark prices to existing gene therapies. In settings of substantial uncertainty, initial pricing should err on the side of being more affordable. This would allow more patients access, while generating additional data on the real-world effectiveness of novel treatments that could be used in future assessment updates. With accumulation of evidence of substantial patient benefit, manufacturers should be allowed to increase pricing in accordance with demonstrating more benefits for patients.

We appreciate the commitment of the manufacturer during the policy roundtable to price their treatment based on value to ensure affordable access. Given that this treatment is mutation agnostic, there may be more patients eligible for treatment than the gene therapy for RP, including those with other inherited retinal diseases with photoreceptor degeneration (i.e. Stargardt disease). As more is learned about the real-world use of the therapy, the manufacturer should consider adjusting the price to reflect its value in a potentially larger population.

***Recommendation 2***

***The manufacturer should follow all participants enrolled in ongoing clinical trials and establish registries that can be used to assess the long-term benefits and harms of all patients receiving this optogenetic therapy.***

Concerns remain about the durability of treatment effect, potential benefits on other aspects of vision not measured in the clinical trial, and long-term harms that may be uncommon. Potential harms include ocular and retinal complications and transfection of cells outside of the injected eye as noted with other gene therapies for inherited retinal disorders. Whether these harms will be seen for this treatment requires larger, long-term follow-up studies, especially since the treatment may be administered to younger adults with advanced RP. Experts emphasized the need to follow all patients currently enrolled in clinical trials to understand the safety profile and the durability of benefits. Additionally, registries of all patients receiving this therapy should collect standardized patient-reported outcome measures to assess benefits across all relevant domains of vision that could be affected by treatment, especially for individuals who have severe vision loss and are at or below the floor threshold for assessing visual acuity.

***Recommendation 3***

***Support access to sonpiretigene by providing specialized delivery services of the therapy to ophthalmology clinics.***

Since restricting prescribing to retinal specialists may not be necessary clinically, to improve availability and access of this treatment to patients with advanced RP, the manufacturer should consider providing “white glove” service which entails a dedicated case manager to oversee the delivery process, and customized logistics with temperature-controlled handling and a clear chain of custody to prevent contamination, mislabeling, or mishandling of this gene therapy that may deter clinicians from obtaining the treatment to administer to their patients.

## Clinicians and Clinical Societies

***Recommendation 1***

***Develop consensus recommendations for treatment of patients with RP.***

Clinical societies should update their consensus recommendations or practice guidelines for managing patients with advanced RP to include newer therapies to help restore vision, such as sonpiretigene and more investigational therapies, such as photoreceptor transplantation and surgically-implanted "chips". Payers base their coverage decisions and utilization management policies to a great extent on clinical guidelines. The American Academy of Ophthalmology (AAO) last updated it guidance on the clinical assessment of patients with inherited retinal degenerations, which includes RP, in 2022. Current recommendations do not discuss treatment. After new therapies are approved by the FDA for the treatment of patients with RP, the AAO should consider issuing a consensus guideline to discuss and provide pragmatic advice as to how sonpiretigene and other FDA-approved therapies should be incorporated into practice. Guidelines should be easy to interpret by clinicians, payers, and patients with vision loss.

## Patient Organizations

***Recommendation 1***

***Patient organizations have a vital role to play to promote objective descriptions of the risks and benefits of new therapies in order to support shared decision-making for every patient. In addition, patient groups have a powerful voice and should apply it to create significant pressure for fair pricing and appropriate insurance coverage across all sectors of the health system.***

Patient groups should endeavor to educate patients about the potential risks and benefits of new therapies, particularly those with uncertainty about durability of effect and long-term safety, and work with other stakeholders to develop and disseminate evidence-based, balanced materials that are accessible to all patients, including those with low health literacy. Patient groups should also accept responsibility to publicly promote access and fair pricing of new therapies.

## Researchers and Regulators

***Recommendation 1***

***Given that some patients did not appear to improve with sonpiretigene, and others had more dramatic responses in visual acuity, researchers should look for sources of heterogeneity in treatment response to optogenetic therapy.***

Better understanding of the causes of heterogeneity in treatment response to optogenetic therapy would be immensely helpful to more precisely target which patients should be considered for treatment. Experts thought differences in the retinal biology were the key drivers of why patients may have differential treatment response to optogenetic therapy. Specifically, experts suspected that shorter duration of photoreceptor degeneration and having sufficient retinal thickness of the inner and middle layers might predict better response. Additionally, experts thought proteomics—the study of proteins produced by retinal cells—was another promising avenue to explore the heterogeneity in treatment response. They were less enthusiastic that differences in treatment response were driven by the underlying genetic mutation and noted that disentangling such heterogeneity would be implausible given the large number of genes and mutations involved in RP.

***Recommendation 2***

***Researchers should study whether sonpiretigene improves vision for individuals with advanced RP who have severe vision loss better than the pivotal trial eligibility criteria.***

The RESTORE trial eligibility was based upon BCVA inclusion criteria (LogMAR 1.9 or worse in treatment eye and BCVA not better than LogMAR 1.6 in the contralateral eye) which may be overly restrictive. To address the potential broader unmet need for other patients with advanced RP but better visual function, future studies should evaluate the efficacy and safety of sonpiretigene for individuals with better BCVA in the treatment eye than the trial criteria, better visual function in the non-treated eye than a LogMAR of 1.6, or have more preserved visual function but very narrow visual fields (less than 10 degrees).

# References


1. Hartong DT, Berson EL, Dryja TP. Retinitis pigmentosa. *The Lancet*. 2006/11/18/ 2006;368(9549):1795-1809. doi:https://doi.org/10.1016/S0140-6736(06)69740-7
2. Garg S. Retinitis pigmentosa: Clinical presentation and diagnosis. In: Connor R, ed. *UpToDate*. Wolters Kluwer; 2024. *Gardiner, Matthew F*.
3. Grover S, Fishman GA, Anderson RJ, et al. Visual acuity impairment in patients with retinitis pigmentosa at age 45 years or older. *Ophthalmology*. Sep 1999;106(9):1780-5. doi:10.1016/S0161-6420(99)90342-1
4. Vezinaw CM, Fishman GA, McAnany JJ. VISUAL IMPAIRMENT IN RETINITIS PIGMENTOSA. *RETINA*. 2020;40(8):1630-1633. doi:10.1097/iae.0000000000002649
5. De Silva SR, Chan HW, Agarwal A, Webster AR, Michaelides M, Mahroo OA. Visual Acuity by Decade in 139 Males with RPGR-Associated Retinitis Pigmentosa. *Ophthalmology Science*. 2024;4(2)doi:10.1016/j.xops.2023.100375
6. Ng QX, Ong C, Yaow CYL, et al. Cost-of-illness studies of inherited retinal diseases: a systematic review. *Orphanet Journal of Rare Diseases*. 2024/02/29 2024;19(1):93. doi:10.1186/s13023-024-03099-9
7. Frick KD, Roebuck MC, Feldstein JI, McCarty CA, Grover LL. Health Services Utilization and Cost of Retinitis Pigmentosa. *Archives of Ophthalmology*. 2012;130(5):629-634. doi:10.1001/archophthalmol.2011.2820
8. Gong J, Cheung S, Fasso-Opie A, et al. The Impact of Inherited Retinal Diseases in the United States of America (US) and Canada from a Cost-of-Illness Perspective. *Clin Ophthalmol*. 2021;15:2855-2866. doi:10.2147/opth.S313719
9. American Foundation for the Blind. Reviewing the Disability Employment Research on People who are Blind or Visually Impaired: Key Takeaways. https://www.afb.org/research-and-initiatives/employment/reviewing-disability-employment-research-people-blind-visually
10. Galvin O, Chi G, Brady L, et al. The Impact of Inherited Retinal Diseases in the Republic of Ireland (ROI) and the United Kingdom (UK) from a Cost-of-Illness Perspective. *Clin Ophthalmol*. 2020;14:707-719. doi:10.2147/opth.S241928
11. Jacobson S, Cideciyan A. Treatment Possibilities for Retinitis Pigmentosa. *New England Journal of Medicine*. 2010;363(17):1669-1671. doi:doi:10.1056/NEJMcibr1007685
12. Sakai D, Tomita H, Maeda A. Optogenetic Therapy for Visual Restoration. *Int J Mol Sci*. Nov 30 2022;23(23)doi:10.3390/ijms232315041
13. Nanoscope Therapeutics Announces Positive Top-line Results from Randomized Controlled Trial of MCO-010 for Retinitis Pigmentosa. 2024. https://nanostherapeutics.com/2024/03/26/nanoscope-therapeutics-announces-top-line-results-from-ph2-trial-of-mco-010-for-retinitis-pigmentosa/
14. Euler T, Haverkamp S, Schubert T, Baden T. Retinal bipolar cells: elementary building blocks of vision. *Nat Rev Neurosci*. Aug 2014;15(8):507-19. doi:10.1038/nrn3783
15. Nanoscope Announces Plans to Submit BLA for MCO-010 to Treat Retinitis Pigmentosa. October 10, 2024, 2024. Accessed October 10, 2024. https://nanostherapeutics.com/2024/10/10/nanoscope-announces-plans-to-submit-bla-for-mco-010-to-treat-retinitis-pigmentosa/

16. Christ SL, Zheng DD, Swenor BK, et al. Longitudinal Relationships Among Visual Acuity, Daily Functional Status, and Mortality. *JAMA Ophthalmology*. 2014;132(12)doi:10.1001/jamaophthalmol.2014.2847
17. Lee DJ, Gomez-Marin O, Lam BL, Zheng DD. Visual acuity impairment and mortality in US adults. *Arch Ophthalmol*. Nov 2002;120(11):1544-50. doi:10.1001/archopht.120.11.1544
18. Na K-H, Kim HJ, Kim KH, et al. Prevalence, Age at Diagnosis, Mortality, and Cause of Death in Retinitis Pigmentosa in Korea—A Nationwide Population-based Study. *American Journal of Ophthalmology*. 2017;176:157-165. doi:10.1016/j.ajo.2017.01.014
19. Duncan J, Branham K, Birch D, et al. *Guidelines on Clinical Assessment of Patients with Inherited Retinal Degenerations*. 2022. https://www.aao.org/education/clinical-statement/guidelines-on-clinical-assessment-of-patients-with
20. Comander J, Weigel DiFranco C, Sanderson K, et al. Natural history of retinitis pigmentosa based on genotype, vitamin A/E supplementation, and an electroretinogram biomarker. *JCI Insight*. Aug 8 2023;8(15)doi:10.1172/jci.insight.167546
21. Sullivan L, Daiger S. Summaries of Genes and Loci Causing Retinal Diseases. https://retnet.org/summaries#a-genes
22. Daiger SP, Bowne SJ, Sullivan LS. Perspective on Genes and Mutations Causing Retinitis Pigmentosa. *Archives of Ophthalmology*. 2007;125(2):151-158. doi:10.1001/archopht.125.2.151
23. O'Neal TB, Luther EE. Retinitis Pigmentosa. *StatPearls*. StatPearls Publishing Copyright © 2024, StatPearls Publishing LLC.; 2024.
24. Nguyen XT, Moekotte L, Plomp AS, Bergen AA, van Genderen MM, Boon CJF. Retinitis Pigmentosa: Current Clinical Management and Emerging Therapies. *Int J Mol Sci*. Apr 19 2023;24(8)doi:10.3390/ijms24087481
25. Banken R, Rind D, Carlson J, et al. *Voretigene Neparvovec for Biallelic RPE65-Mediated Retinal Disease: Effectiveness and Value*. 2018. https://icer.org/wp-content/uploads/2020/10/MWCEPAC_VORETIGENE_FINAL_EVIDENCE_REPORT_02142018.pdf
26. Reichel FF, Seitz I, Wozar F, et al. Development of retinal atrophy after subretinal gene therapy with voretigene neparvovec. *Br J Ophthalmol*. Sep 2023;107(9):1331-1335. doi:10.1136/bjophthalmol-2021-321023
27. Fischer MD, Simonelli F, Sahni J, et al. Real-World Safety and Effectiveness of Voretigene Neparvovec: Results up to 2 Years from the Prospective, Registry-Based PERCEIVE Study. *Biomolecules*. Jan 17 2024;14(1)doi:10.3390/biom14010122
28. Wu KY, Kulbay M, Toameh D, Xu AQ, Kalevar A, Tran SD. Retinitis Pigmentosa: Novel Therapeutic Targets and Drug Development. *Pharmaceutics*. Feb 17 2023;15(2)doi:10.3390/pharmaceutics15020685
29. Prem Senthil M, Khadka J, Pesudovs K. Seeing through their eyes: lived experiences of people with retinitis pigmentosa. *Eye (Lond)*. May 2017;31(5):741-748. doi:10.1038/eye.2016.315
30. Foundation Fighting Blindness. *X-Linked Retinitis Pigmentosa Externally Led Patient-Focused Drug Development Voice of the Patient Report*. 2022. https://www.fightingblindness.org/xlrp-pfdd#voice-of-the-patient-report-1411

31. McDonnall MC, Cmar JL, McKnight ZS. Beyond Employment Rates: Continuity of Employment for People with Visual Impairments. *J Vis Impair Blind*. Mar 2022;116(2):275-80. doi:10.1177/0145482x221091827
32. American Foundation for the Blind. Demographics of Americans with Vision Difficulty. https://www.afb.org/research-and-initiatives/statistics/demographics-americans-vision-difficulty#:~:text=According%20to%20the%202022%20American,3.9%20million%20males%20(45.6%25)
33. Chaumet-Riffaud AE, Chaumet-Riffaud P, Cariou A, et al. Impact of Retinitis Pigmentosa on Quality of Life, Mental Health, and Employment Among Young Adults. *Am J Ophthalmol*. May 2017;177:169-174. doi:10.1016/j.ajo.2017.02.016
34. Cross N, van Steen C, Zegaoui Y, Satherley A, Angelillo L. Retinitis Pigmentosa: Burden of Disease and Current Unmet Needs. *Clin Ophthalmol*. 2022;16:1993-2010. doi:10.2147/opth.S365486
35. Sadda S. MCO-010 Optogenetic Therapy for the Treatment of Advanced Retinitis Pigmentosa RESTORE – Phase 2b Clinical Trial. EURETINA 20242024.
36. Mohanty S. Nanoscope Therapeutics | Samarendra Mohanty, PhD - Co-Founder, President & Chief Scientific Officer. 2021:
37. Chavala S. Intravitreal AAV2 Optogenetic Vision Restoration in retinal degenerative patients with ABCA4 mutation. presented at: Opthalmology Innovation Source Retina at ASRS; 2021; San Antonio, Texas.
38. Sadda S. 52 Week Safety and Efficacy of Optogenetic Therapy for Vision Restoration in Retinitis Pigmentosa Patients. presented at: EURETINA; 2022; Hamburg, Germany.
39. Barone SC, S.H., Koester J, von Tress M, et al. Longitudinal Analysis of BCVA and Near-Field Object Recognition in Low- or High-Dose MCO-010 Mutation Agnostic Optogenetic Therapy for Retinitis Pigmentosa: 12-Month Results From a Phase 2b/3 Randomized, Sham-Controlled, Patient- and Assessor-Masked Clinical Trial (RESTORE). ASGCT: Nanoscope Therapeutics Burnett College of Medicine, Texas Christian University; 2024.
40. Ho A. Longitudinal BCVA analysis of low- or high-dose MCO-010 mutation agnostic optogenetic therapy for retinitis pigmentosa: 12-month results from a Phase 2b/3 clinical trial (RESTORE). ARVO 20242024.
41. Kay C. MCO-010 optogenetic vision restoration in retinitis pigmentosa patients with profound vision loss: A randomized, sham-controlled, multi-center, double-masked clinical trial (RESTORE). Retina Society 20232023.
42. Kay C. Longitudinal BCVA and Safety Analysis of Mutation-Agnostic MCO-010 Optogenetic Therapy for Retinitis Pigmentosa: Patient Case From A Phase 2b/3 Clinical Trial (RESTORE). Retina World Congress 20242024.
43. Loewenstein A. BCVA Analysis of Patients Treated with Low- or High-dose MCO-010 Mutation Agnostic Optogenetic Therapy for Retinitis Pigmentosa: 100-week TOPLINE Results From RESTORE a Phase 2b/3 Clinical Trial. Retina Society 20242024.
44. Monés J. Longitudinal AUC analysis of BCVA in patients treated with low- or high-dose MCO-010 mutation agnostic optogenetic therapy for retinitis pigmentosa: 100-week TOPLINE results from a Phase 2b/3 randomized, sham-controlled clinical trial (RESTORE). EURetina 2024: Institut de la Màcula, Barcelona; 2024.

45. Singer M. BCVA Analysis of Low- or High-dose MCO-010 Mutation-Agnostic Optogenetic Therapy for Retinitis Pigmentosa: FIRST TIME 100-Week TOPLINE Results from a Phase 2b/3 Clinical Trial (RESTORE). ASRS 2024: UT Health San Antonio; 2024.
46. Boyer D. Efficacy and safety of MCO-010 optogenetic therapy for vision restoration in patients with severe vision loss due to retinitis pigmentosa: A phase 2b randomized, sham-controlled, multi-center, multi-dose, double-masked clinical trial (RESTORE). ARVO2023.
47. Nanoscope Therapeutics. Data on File. 2024.
48. ClinicalTrials.gov. Efficacy and Safety of MCO-010 Optogenetic Therapy in Adults With Retinitis Pigmentosa [RESTORE] (RESTORE). https://clinicaltrials.gov/study/NCT04945772?cond=%E2%80%A2%09NCT04945772&rank=1&page=1&limit=10
49. ClinicalTrials.gov. Non-Interventional Long Term Follow-up Study of Participants Previously Enrolled in the RESTORE Study (REMAIN). https://clinicaltrials.gov/study/NCT06162585?cond=NCT06162585&rank=1
50. Bach M. Visual Acuity "Cheat Sheet" for high and low vision. https://michaelbach.de/sci/acuity.html
51. Schulze-Bonsel K, Feltgen N, Burau H, Hansen L, Bach M. Visual acuities "hand motion" and "counting fingers" can be quantified with the freiburg visual acuity test. *Invest Ophthalmol Vis Sci*. Mar 2006;47(3):1236-40. doi:10.1167/iovs.05-0981
52. Vignal-Clermont C, Girmens JF, Audo I, et al. Safety of Intravitreal Gene Therapy for Treatment of Subjects with Leber Hereditary Optic Neuropathy due to Mutations in the Mitochondrial ND4 Gene: The REVEAL Study. *BioDrugs*. Mar 2021;35(2):201-214. doi:10.1007/s40259-021-00468-9
53. Chung DC, McCague S, Yu ZF, et al. Novel mobility test to assess functional vision in patients with inherited retinal dystrophies. *Clin Exp Ophthalmol*. Apr 2018;46(3):247-259. doi:10.1111/ceo.13022
54. Agboola FW, AC. A Framework for Evaluating the Diversity of Clinical Trials. *Journal of Clinical Epidemiology*. 2024:111299.
55. Pocock SJ, Stone GW. The Primary Outcome Is Positive — Is That Good Enough? *New England Journal of Medicine*. 2016;375(10):971-979. doi:doi:10.1056/NEJMra1601511
56. Lam BL, Scholl HPN, Doub D, Sperling M, Hashim M, Li N. A SYSTEMATIC LITERATURE REVIEW OF DISEASE PROGRESSION REPORTED IN RPGR -ASSOCIATED X-LINKED RETINITIS PIGMENTOSA. *Retina*. Jan 1 2024;44(1):1-9. doi:10.1097/iae.0000000000003920
57. Social Security Administration. Period Life Table, 2021, as used in the 2024 Trustees Report. https://www.ssa.gov/oact/STATS/table4c6.html
58. O'Brien P, Enstone A, Bridge D, Wyn R, Banhazi J. Elicitation of Health State Utility Values in Retinitis Pigmentosa by Time Trade-off in the United Kingdom. *Clinicoecon Outcomes Res*. 2023;15:29-39. doi:10.2147/ceor.S385094
59. Brown MM, Brown GC, Sharma S, Kistler J, Brown H. Utility values associated with blindness in an adult population. *Br J Ophthalmol*. Mar 2001;85(3):327-31. doi:10.1136/bjo.85.3.327
60. IPD Analytics. Payer & Provider Insights. https://www.ipdanalytics.com
61. Centers for Medicare & Medicaid Services. Physician Fee Schedule. https://www.cms.gov/medicare/physician-fee-schedule/search?Y=0&T=0&HT=0&CT=0&H1=67028&M=5

62. Brown MM, Brown GC, Lieske HB, Tran I, Turpcu A, Colman S. SOCIETAL COSTS ASSOCIATED WITH NEOVASCULAR AGE-RELATED MACULAR DEGENERATION IN THE UNITED STATES. *Retina*. Feb 2016;36(2):285-98. doi:10.1097/iae.0000000000000717
63. US Census Bureau. 2017 National Population Projections Datasets. Accessed Jan. 15, 2025. https://www.census.gov/data/datasets/2017/demo/popproj/2017-popproj.html
64. Lee W, Kim JH, Lee S, Kim K, Kang TS, Han YS. Estimation of best corrected visual acuity based on deep neural network. *Sci Rep*. Oct 24 2022;12(1):17808. doi:10.1038/s41598-022-22586-2
65. Igoe JM, Lam BL, Gregori NZ. Update on Clinical Trial Endpoints in Gene Therapy Trials for Inherited Retinal Diseases. *J Clin Med*. Sep 18 2024;13(18)doi:10.3390/jcm13185512
66. Bach M. The Freiburg Visual Acuity test--automatic measurement of visual acuity. *Optom Vis Sci*. Jan 1996;73(1):49-53. doi:10.1097/00006324-199601000-00008
67. Bach M. Manual of the Freiburg Vision Test 'FrACT$_{1}$ $_{o}$' version 2025-01-05. Updated January 05, 2025. Accessed January 10, 2025, https://michaelbach.de/fract/manual.html
68. Ottersen T, Førde R, Kakad M, et al. A new proposal for priority setting in Norway: Open and fair. *Health Policy*. Mar 2016;120(3):246-51. doi:10.1016/j.healthpol.2016.01.012
69. van de Wetering EJ, Stolk EA, van Exel NJ, Brouwer WB. Balancing equity and efficiency in the Dutch basic benefits package using the principle of proportional shortfall. *Eur J Health Econ*. Feb 2013;14(1):107-15. doi:10.1007/s10198-011-0346-7
70. Stolk EA, van Donselaar G, Brouwer WB, Busschbach JJ. Reconciliation of economic concerns and health policy: illustration of an equity adjustment procedure using proportional shortfall. *Pharmacoeconomics*. 2004;22(17):1097-107. doi:10.2165/00019053-200422170-00001
71. American Academy of Opthalmology. *Guidelines on Clinical Assessment of Patients with Inherited Retinal Degenerations - 2022*. 2022. https://www.aao.org/education/clinical-statement/guidelines-on-clinical-assessment-of-patients-with
72. Cook DJ, Mulrow CD, Haynes RB. Systematic reviews: synthesis of best evidence for clinical decisions. *Ann Intern Med*. Mar 1 1997;126(5):376-80.
73. Higgins J, Thomas, J, Chandler, J, Cumpston, M, Li, T, Page, MJ, Welch, VA. Cochrane Handbook for Systematic Reviews of Interventions version 6.1 (updated September 2020). https://training.cochrane.org/handbook/current
74. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. Mar 29 2021;372:n71. doi:10.1136/bmj.n71
75. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019;366:l4898. doi:10.1136/bmj.l4898
76. Ollendorf D, Pearson, SD. ICER Evidence Rating Matrix: A User's Guide. Updated January 31, 2020. https://icer.org/evidence-rating-matrix/
77. Ollendorf DA, Pearson SD. An integrated evidence rating to frame comparative effectiveness assessments for decision makers. *Medical care*. Jun 2010;48(6 Suppl):S145-52. doi:10.1097/MLR.0b013e3181d9913b
78. ClinicalTrials.gov. Dose-Escalation Study to Evaluate the Safety and Tolerability of Intravitreal vMCO-I in Patients With Advanced Retinitis Pigmentosa. https://clinicaltrials.gov/study/NCT04919473

79. ClinicalTrials.gov. A Long-Term Follow-Up Study in Subjects Who Received vMCO-I Administered Via Intravitreal Injection (EXTEND). https://clinicaltrials.gov/study/NCT05921162?term=NCT05921162&rank=1
80. ClinicalTrials.gov. Non-interventional Long Term Follow-up Study of Participants Previously Enrolled in the STARLIGHT Study (SUSTAIN). https://clinicaltrials.gov/study/NCT06048185?term=NCT06048185&rank=1
81. Confalonieri F, La Rosa A, Ottonelli G, et al. Retinitis Pigmentosa and Therapeutic Approaches: A Systematic Review. *Journal of Clinical Medicine*. 2024;13doi:https://doi.org/10.3390/jcm13164680
82. Sanders GD, Neumann PJ, Basu A, et al. Recommendations for Conduct, Methodological Practices, and Reporting of Cost-effectiveness Analyses: Second Panel on Cost-Effectiveness in Health and Medicine. *Jama*. Sep 13 2016;316(10):1093-103. doi:10.1001/jama.2016.12195
83. Pickard AS, Law EH, Jiang R, et al. United States Valuation of EQ-5D-5L Health States Using an International Protocol. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research*. Aug 2019;22(8):931-941. doi:10.1016/j.jval.2019.02.009
84. Lloyd A, Piglowska N, Ciulla T, et al. Estimation of impact of RPE65-mediated inherited retinal disease on quality of life and the potential benefits of gene therapy. *Br J Ophthalmol*. Nov 2019;103(11):1610-1614. doi:10.1136/bjophthalmol-2018-313089
85. Farris M, Goodall S, De Abreu Lourenco R, et al. Estimating Australian Population Utilities for Inherited Retinal Disease Using Time Trade-Off. *Pharmacoecon Open*. Nov 2024;8(6):911-922. doi:10.1007/s41669-024-00515-5
86. Johnson S, Buessing M, O'Connell T, Pitluck S, Ciulla TA. Cost-effectiveness of Voretigene Neparvovec-rzyl vs Standard Care for RPE65-Mediated Inherited Retinal Disease. *JAMA Ophthalmol*. Oct 1 2019;137(10):1115-1123. doi:10.1001/jamaophthalmol.2019.2512
87. Uhrmann MF, Lorenz B, Gissel C. Cost Effectiveness of Voretigene Neparvovec for RPE65-Mediated Inherited Retinal Degeneration in Germany. *Transl Vis Sci Technol*. Aug 2020;9(9):17. doi:10.1167/tvst.9.9.17
88. Viriato D, Bennett N, Sidhu R, et al. An Economic Evaluation of Voretigene Neparvovec for the Treatment of Biallelic RPE65-Mediated Inherited Retinal Dystrophies in the UK. *Adv Ther*. Mar 2020;37(3):1233-1247. doi:10.1007/s12325-020-01243-y
89. Bhadhuri A, Dröschel D, Guldimann M, et al. Cost-effectiveness of voretigene neparvovec in the treatment of patients with inherited retinal disease with RPE65 mutation in Switzerland. *BMC Health Serv Res*. Jun 28 2022;22(1):837. doi:10.1186/s12913-022-08211-y
90. Schwander B. Early health economic evaluation of the future potential of next generation artificial vision systems for treating blindness in Germany. *Health Econ Rev*. Dec 2014;4(1):27. doi:10.1186/s13561-014-0027-1
91. Vaidya A, Borgonovi E, Taylor RS, et al. The cost-effectiveness of the Argus II retinal prosthesis in Retinitis Pigmentosa patients. *BMC Ophthalmol*. Apr 14 2014;14:49. doi:10.1186/1471-2415-14-49
92. Retinal Prosthesis System for Advanced Retinitis Pigmentosa: A Health Technology Assessment Update. *Ont Health Technol Assess Ser*. 2017;17(13):1-62.
93. Institute for Clinical and Economic Review. 2020-2023 Value Assessment Framework. https://icer.org/our-approach/methods-process/value-assessment-framework/

94. Pearson SD. The ICER Value Framework: Integrating Cost Effectiveness and Affordability in the Assessment of Health Care Value. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research*. Mar 2018;21(3):258-265. doi:10.1016/j.jval.2017.12.017
95. Pearson SD, Towse A, Lowe M, Segel CS, Henshall C. Cornerstones of 'fair'drug coverage: appropriate cost sharing and utilization management policies for pharmaceuticals. *Journal of Comparative Effectiveness Research*. 2021;10(7):537-547.

# Supplemental Materials

# A. Background: Supplemental Information

## A1. Definitions

**Retinitis Pigmentosa**: A group of inherited retinal diseases characterized by progressive degeneration of photoreceptor cells in the retina. This loss of photoreceptor cells results in decreased night vision, loss of peripheral vision, and near total blindness with the loss of central vision in advanced stages of disease.[1,2]

**Best Corrected Visual Acuity (BCVA)**: BCVA is a validated measure of visual acuity that evaluates the best vision achievable using corrected lenses. It is commonly used in clinical practice and clinical trials. BCVA is typically assessed by having individuals identify letters of varying size on a chart.[64,65]

**Freiberg Visual Acuity and Contrast Test (FrACT)**: The FrACT is a validated measure of visual acuity. This computerized tool displays visual aids such as a letter displayed at varying sizes and orientations for the individual to identify to determine their visual acuity.[66,67] FrACT can assess individuals with very low vision to the range of semiquantitative categories of "counting fingers" (equivalent to approximately 1.9 LogMAR) and even "hand motion" (approximately 2.3 LogMAR).[51]

**Logarithmic Minimum Angle of Resolution (LogMAR)**: LogMAR is a unit of measurement of visual acuity ranging from -0.3 to 2.25 for the FrACT test used in the RESTORE trial.[45] A LogMAR of zero corresponds to 20/20 vision with values increasing above zero indicating worsening visual acuity. In the RESTORE trial, an improvement by at least -0.3 LogMAR, or three lines gained, is considered clinically meaningful.[35,46]

**Multi-Luminance Y-Mobility Test (MLYMT)**: This manufacturer-developed outcome measure evaluates a person's ability to navigate a Y-shaped course with three obstacles (to the left, right, and in front of the participant) to locate a lighted panel. The MLYMT consists of six levels of illumination ranging from 100 lux (similar to an overcast day) to 0.3 lux (dark night sky). Successful completion of the test at each illumination level is defined as correct identification of the lighted panel three different times.[46] Scoring is as follows:

| Score | -1 | 0 | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|---|---|
| **Interpretation** | Failing at 100 lux (brightest) | Passing at 100 lux | Passing at 32 lux | Passing at 10 lux | Passing at 3 lux | Passing at 1 lux | Passing at 0.3 lux (dimmest) |

**Multi-Luminance Shape Discrimination Test (MLSDT)**: The MLSDT is a novel manufacturer-developed outcome measure that evaluates a person's ability to identify three different shapes at five different illumination levels ranging from 21 lux (dimly lit room) to 0.2 lux (dark night sky).

Successful completion of the test at each illumination level was defined as correct identification of the shapes three different times[46] Scoring is as follows:

| Score | 0 | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|---|
| **Interpretation** | Failing at 21 lux (brightest) | Passing at 21 lux | Passing at 7 lux | Passing at 2.1 lux | Passing at 0.7 lux | Passing at 0.2 lux (dimmest) |

### *Other Relevant Definitions*

**Absolute and Proportional Shortfalls:** Absolute and proportional shortfalls are empirical measurements that capture different aspects of society's instincts for prioritization related to the severity or burden of an illness. The absolute shortfall is defined as the total absolute amount of future health patients with a condition are expected to lose without the treatment that is being assessed.[68] The ethical consequences of using absolute shortfall to prioritize treatments is that conditions that cause early death or that have very serious lifelong effects on quality of life receive the greatest prioritization. Thus, certain kinds of treatments, such as treatments for rapidly fatal conditions of children, or for lifelong disabling conditions, score highest on the scale of absolute shortfall. The proportional shortfall is measured by calculating the proportion of the total health units of remaining life expectancy that would be lost due to untreated illness.[69,70] The proportional shortfall reflects the ethical instinct to prioritize treatments for patients whose illness would rob them of a large percentage of their expected remaining lifetime. As with absolute shortfall, rapidly fatal conditions of childhood have high proportional shortfalls, but high numbers can also often arise from severe conditions among older adults who may have only a few years left of average life expectancy but would lose much of that to the illness without treatment. Details on how to calculate the absolute and proportional QALY and evLY shortfalls can be found in ICER's reference case. Shortfalls will be highlighted when asking the independent appraisal committees to vote on unmet need despite current treatment options as part of characterizing a treatment's benefits beyond health and special ethical priorities (Section 5).

**Health Improvement Distribution Index (HIDI)**: The HIDI identifies a subpopulation that has a higher prevalence of the disease of interest and therefore, creates an opportunity for proportionately more health gains within the subpopulation. This opportunity may be realized by achieving equal access both within and outside the identified subpopulation to an intervention that is known to improve health. The HIDI is defined as the disease prevalence in the subpopulation divided by the disease prevalence in the overall population. For example, if a disease has a prevalence of 10% among Black Americans whereas the disease prevalence among all Americans is 4%, then the Health Improvement Distribution Index is 10%/4%=2.5. In this example, a HIDI of 2.5 means that Black Americans as a subpopulation would benefit more on a relative basis (2.5 times more) from a new effective intervention compared with the overall population. HIDIs above 1.0

suggest that more health may be gained on the relative scale in the subpopulation of interest when compared to the population as a whole. The HIDI may be helpful in characterizing a treatment's benefits beyond health and special ethical priorities (Section 5).

ICER did not calculate the HIDI for this report due to a lack of sufficient data of retinitis pigmentosa rates in racial and ethnic minority populations.

## A2. Potential Cost-Saving Measures in Retinitis Pigmentosa

ICER includes 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.org/our-approach/methods-process/value-assessment-framework/). These services are ones that would not be directly affected by therapies for retinitis pigmentosa (e.g., requirement for assistive devices for low visual acuity), as these services will be captured in the economic model. Rather, we are seeking services used in the current management of retinitis pigmentosa beyond the potential offsets that arise from a new intervention. During stakeholder engagement and public comment periods, ICER encouraged all stakeholders to suggest services (including treatments and mechanisms of care) currently used for patients with retinitis pigmentosa that could be reduced, eliminated, or made more efficient. No suggestions on wasteful or lower-value services were received.

## A3. Research, Development, and Manufacturing Costs

We asked for information on this topic from the manufacturer but did not receive any input on research, development, and manufacturing costs for this patient population.

## A4. Patient Input on Clinical Trial Design

Manufacturers were asked to submit a written explanation of how they engaged patients in the design of their clinical trials, including the methods used to gather patient experience data and how they determined the outcomes that matter most to patients. ICER did not receive input on this specific inquiry.

# B. Patient Community Insights: Supplemental Information

## B1. Methods

We spoke with and received feedback from patients, patient advocacy organizations, clinical experts, and the manufacturer of the product throughout the review.

We spoke with representatives from two patient advocacy organizations, Foundation Fighting Blindness and Prevent Blindness, who provided information and resources about the retinitis pigmentosa community. Foundation Fighting Blindness and Prevent Blindness helped ICER recruit people living with retinitis pigmentosa for interviews. We spoke with nine people living with retinitis pigmentosa who had varying levels of vision degeneration. Insight from these discussions directly informed the patient community insights section of our report.

We also spoke with five clinical experts with expertise ranging from diagnosing and treating retinal degenerative diseases to optogenetics.

***Pilot Project to Explore Patient Engagement in Cost Effective Analysis***

We discussed the preliminary model structure and assumptions with four members of the patient community as part of a pilot project to explore enhanced patient engagement in the cost-effectiveness analysis of sonpiretigene for advanced retinitis pigmentosa. The pilot consisted of three one-hour discussions held virtually over the Zoom meeting platform. Two sessions (Sessions 1 and 2) were completed prior to the posting of the Draft Evidence Report. The third session (Session 3) was an optional discussion for participants that took place following Draft Evidence Report posting for ICER to share the findings from the cost-effectiveness analysis and the impact of patient engagement in the modeling effort. Specific aims of the pilot project were to:

1. Engage in education and information-sharing with participants regarding the goals of cost-effectiveness analysis as part of a broader health technology assessment process.

2. Work with participants on a proposed draft analysis plan to ensure that the patient's experience with retinitis pigmentosa and goals for treatment are reflected in ICER's cost-effectiveness analysis structure, data, and key assumptions.

3. Obtain feedback from participants to understand the value of patient engagement, opportunities for improvement, challenges or barriers to engagement, and the impact of the discussions on the final results of the cost-effectiveness analysis and ICER report more broadly.

The first session provided background information on the role of cost-effectiveness analysis in health technology assessment and provided a summary of ICER's draft analysis plan for the retinitis pigmentosa review. The second session consisted of a semi-structured group discussion with open-ended questions to ensure that the draft analysis plan reflected the perspectives and experiences of patients living with retinitis pigmentosa. Following the second session, an additional one-hour session was scheduled with participants (Session 2b) to address a few outstanding questions that could not be addressed during the initial hour (Session 2a). Three of the four participants were available to participate in Session 2b.

Discussion questions in Session 2 (Session 2a and 2b) included the following:*

Levels of Visual Functioning

- Do the levels of visual functioning match your experience of living with retinitis pigmentosa? Are there any levels we missed?
- Do you experience or think about your visual functioning differently than the levels presented?
- How would you describe your level of visual functioning before getting to the point of being able to count fingers?

Outcomes of Interest for the Model

- If a new gene therapy could improve any aspect of your vision, what types of improvements to your vision would be most impactful in your life?

Key Data Inputs for the Model (Quality of Life)

- The literature tells us that individuals who can see hand motion experience the same quality of life as individuals that can perceive light. How would you describe changes in your quality of life, if any, if you went from being able to view hand motion to being able to perceive light? Would there be a meaningful impact on your quality of life? If so, please describe the impact.
- More generally, how has your quality of life (for example, level of independence, moving through your home, choosing clothes) changed as your visual functioning has changed?

Key Data Inputs for the Model (Medical Costs)

- What types of medical costs do you have related to retinitis pigmentosa?
- How have your medical costs changed, if at all, as your visual function has changed?
- Have you had more hospital visits or clinic visits as your visual function has changed?

Key Data Inputs for the Model (Other Costs)

- In addition to health and medical-related costs, are there other financial impacts that you experience? For example, do you experience any lost time at school or work? How has that changed as your vision has changed?
- Do you have one or more family members or friends who take time away from school or work to help you out? Do you think their quality of life is impacted?

Managing Uncertainties of the Model

- If the new gene therapy only helped your visual functioning for a short time (one-two years), would you still want to try it? Over what time period would you want to see benefit for you to try it?
- What has your experience been with visual functioning over time -for example, has your vision changed consistently over time, or have there been stages that have changed faster than others?

Final Thoughts

- Are there any choices that ICER has made for the Model Analysis Plan that you disagree with?
- What have we not yet discussed that you were hoping to share?
- What is the most important thing that you don't want ICER to miss as we finalize our Model Analysis Plan for the new gene therapy for retinitis pigmentosa?

* Note: Given the semi-structured nature of the discussion, not all prepared questions may have been discussed during Session 2 (Session 2a and 2b). The impact of participant involvement on the development of the model is described in Section E below and as relevant throughout the report.

Session 3 provided a refresher of the introductory information from Sessions 1 and 2, a summary of ICER's cost-effectiveness methods used and how the input from participants impacted our model, a summary of ICER's cost-effectiveness analysis results, and time for questions and discussion. All four participants were available to participate in Session 3.

Questions for discussion included:

- Were there any choices that ICER made for the model analysis that you disagree with?
- What surprised you as we presented the results?
- What would you like the committee to know about retinitis pigmentosa, your experience, and your expectations for treatment when they deliberate on the evidence during the public meeting?

# C. Clinical Guidelines

No clinical guidelines for the diagnosis and management of retinitis pigmentosa were available at the time of this report. We summarized a clinical statement on the assessment of inherited retinal disease (IRD) by the American Academy of Ophthalmology below.

## Clinical Assessment of Patients with Inherited Retinal Degenerations[71]

The American Academy of Ophthalmology published a Clinical Statement on the assessment of inherited retinal degenerations in 2022. The Statement provides recommendations for different testing procedures for different classes of IRD, including rod-cone degenerations, which includes retinitis pigmentosa. The Statement highlights a list of important considerations when evaluating a patient with an IRD. Recommendations include conducting an ocular/medical history, molecular genetic testing, clinical evaluations (e.g., testing best corrected visual acuity, biomicroscopy, dilated ophthalmoscopy), imaging (e.g., standard color or wide-field fundus photography, optical coherence tomography), visual field testing, and electrophysiology. For rod-cone degenerations, such as retinitis pigmentosa, these clinical evaluations are recommended during an initial visit and a follow-up visit every one to two years. The Statement highlights the importance of genetic testing as it can confirm a patient's diagnosis, improve disease management, and confirm eligibility for clinical trial enrollment.

# D. Comparative Clinical Effectiveness: Supplemental Information

## D1. Detailed Methods

### PICOTS

#### *Population*

The population of focus for the review was people with advanced retinitis pigmentosa with severe vision loss.

Data permitting, we evaluated the evidence for treatment effect modification by subpopulations defined by:

- Sociodemographic factors (e.g., sex, age, race/ethnicity)
- Extent of vision loss
- Form of RP (e.g., syndromic, non-syndromic)
- Inheritance pattern (e.g., X-linked, autosomal recessive)
- Genetic mutation (e.g., RPGR)

#### *Interventions*

The included intervention is as follows:

- Sonpiretigene isteparvovec (Nanoscope Therapeutics)

#### *Comparators*

We compared sonpiretigene isteparvovec to usual care, which included low vision aids, mobility training and support, and vision-related rehabilitation.

#### *Outcomes*

The outcomes of interest are described in the list below.

- Patient-Important Outcomes
    - Improvements in vision, including:
        - Visual acuity
        - Peripheral vision
        - Night vision
        - Central vision
        - Shape discrimination
    - Slowing of disease progression
    - Independence in daily life, including:
        - Picking up objects
        - Attending to personal hygiene
        - Attending social engagements, school, work
        - Mobility (e.g., walking without assistance, identifying exit doors and lighted entryways)
    - Quality of life
    - Mortality
    - RP-related health concerns
        - Cataracts, glaucoma, macular edema, physical injuries, mental health
- Other Outcomes
    - Health care utilization
    - Adverse events (AE), including:
        - Worsening of vision loss
        - Ocular hypertension
        - Ischemic optic neuropathy
        - Intraocular inflammation
        - Treatment-administration-related AEs
        - Ocular infection
        - Retinal detachment
        - Hemorrhage
        - Inflammation

***Timing***

Evidence on intervention effectiveness was derived from studies of any duration.

***Settings***

All relevant settings were considered, including inpatient, clinic, and office settings, but with a focus on the outpatient setting.

**Table D1.1 PRISMA 2020 Checklist**

| Section and Topic | Item # | Checklist Item |
|---|---|---|
| **TITLE** | | |
| **Title** | 1 | Identify the report as a systematic review. |
| **ABSTRACT** | | |
| **Abstract** | 2 | See the PRISMA 2020 for Abstracts checklist. |
| **INTRODUCTION** | | |
| **Rationale** | 3 | Describe the rationale for the review in the context of existing knowledge. |
| **Objectives** | 4 | Provide an explicit statement of the objective(s) or question(s) the review addresses. |
| **METHODS** | | |
| **Eligibility Criteria** | 5 | Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses. |
| **Information Sources** | 6 | Specify all databases, registers, websites, organizations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted. |
| **Search Strategy** | 7 | Present the full search strategies for all databases, registers and websites, including any filters and limits used. |
| **Selection Process** | 8 | Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process. |
| **Data Collection Process** | 9 | Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process. |
| **Data Items** | 10a | List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g., for all measures, time points, analyses), and if not, the methods used to decide which results to collect. |
| | 10b | List and define all other variables for which data were sought (e.g., participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information. |
| **Study Risk of Bias Assessment** | 11 | Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process. |
| **Effect Measures** | 12 | Specify for each outcome the effect measure(s) (e.g., risk ratio, mean difference) used in the synthesis or presentation of results. |

| Section and Topic | Item # | Checklist Item |
|---|---|---|
| **Synthesis Methods** | 13a | Describe the processes used to decide which studies were eligible for each synthesis (e.g., tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)). |
| | 13b | Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions. |
| | 13c | Describe any methods used to tabulate or visually display results of individual studies and syntheses. |
| | 13d | Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used. |
| | 13e | Describe any methods used to explore possible causes of heterogeneity among study results (e.g., subgroup analysis, meta-regression). |
| | 13f | Describe any sensitivity analyses conducted to assess robustness of the synthesized results. |
| **Reporting Bias Assessment** | 14 | Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases). |
| **Certainty Assessment** | 15 | Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome. |
| **RESULTS** | | |
| **Study Selection** | 16a | Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram. |
| | 16b | Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded. |
| **Study Characteristics** | 17 | Cite each included study and present its characteristics. |
| **Risk of Bias in Studies** | 18 | Present assessments of risk of bias for each included study. |
| **Results of Individual Studies** | 19 | For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g., confidence/credible interval), ideally using structured tables or plots. |
| **Results of Syntheses** | 20a | For each synthesis, briefly summarize the characteristics and risk of bias among contributing studies. |
| | 20b | Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g., confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect. |
| | 20c | Present results of all investigations of possible causes of heterogeneity among study results. |
| | 20d | Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results. |
| **Reporting Biases** | 21 | Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed. |
| **Certainty of Evidence** | 22 | Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed. |

| DISCUSSION | | |
|---|---|---|
| **Section and Topic** | **Item #** | **Checklist Item** |
| **Discussion** | 23a | Provide a general interpretation of the results in the context of other evidence. |
| | 23b | Discuss any limitations of the evidence included in the review. |
| | 23c | Discuss any limitations of the review processes used. |
| | 23d | Discuss implications of the results for practice, policy, and future research. |
| **OTHER INFORMATION** | | |
| **Registration and Protocol** | 24a | Provide registration information for the review, including register name and registration number, or state that the review was not registered. |
| | 24b | Indicate where the review protocol can be accessed, or state that a protocol was not prepared. |
| | 24c | Describe and explain any amendments to information provided at registration or in the protocol. |
| **Support** | 25 | Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review. |
| **Competing Interests** | 26 | Declare any competing interests of review authors. |
| **Availability of Data, Code, and Other Materials** | 27 | Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review. |

From: Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *PLoS Med.* 2021;18(3):e1003583.

## Data Sources and Searches

Procedures for the systematic literature review assessing the evidence on new therapies for retinitis pigmentosa followed established best research methods.[72,73] We conducted the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[74] The PRISMA guidelines include a checklist of 27 items (see Table D1.1).

We searched MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials for relevant studies. Each search was limited to English-language studies of human subjects and excluded articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news items. We included abstracts from conference proceedings identified from the systematic literature search. All search strategies were generated utilizing only the Intervention and Study Design elements described above to capture as many relevant references as possible. The proposed search strategies included a combination of indexing terms (MeSH terms in MEDLINE and EMTREE terms in EMBASE), as well as free-text terms.

To supplement the database searches, we performed manual checks of the reference lists of included trials and systematic reviews and invited key stakeholders to share references germane to the scope of this project. We also supplemented our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature when the evidence met ICER standards (for more information, see the Policy on Inclusion of Grey Literature in Evidence Reviews. Where feasible and deemed necessary, we also accepted data submitted by manufacturers "in-confidence," in accordance with ICER's published guidelines on acceptance and use of such data).

**Table D1.2. Ovid MEDLINE(R) ALL, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews Search Strategy for Sonpiretigene isteparvovec**

| # | Search Term |
|---|---|
| 1 | ("MCO 010" or "MCO010" or "MCO-010" or "Sonpiretigene Isteparvovec" or "virally-carried Multi-Characteristic Opsin" or "vMCO 010" or "VMCO 1" or "VMCO-010" or "VMCO1" or "VMCO-1").ti,ab. |
| 2 | 1 not (animals not (humans and animals)).sh. |
| 3 | 2 not (addresses or autobiography or bibliography or biography or comment or congresses or consensus development conference or dictionary or directory or duplicate publication or editorial or encyclopedia or guideline or interactive tutorial).pt. |
| 4 | limit 3 to English language |
| 5 | remove duplicates from 4 |

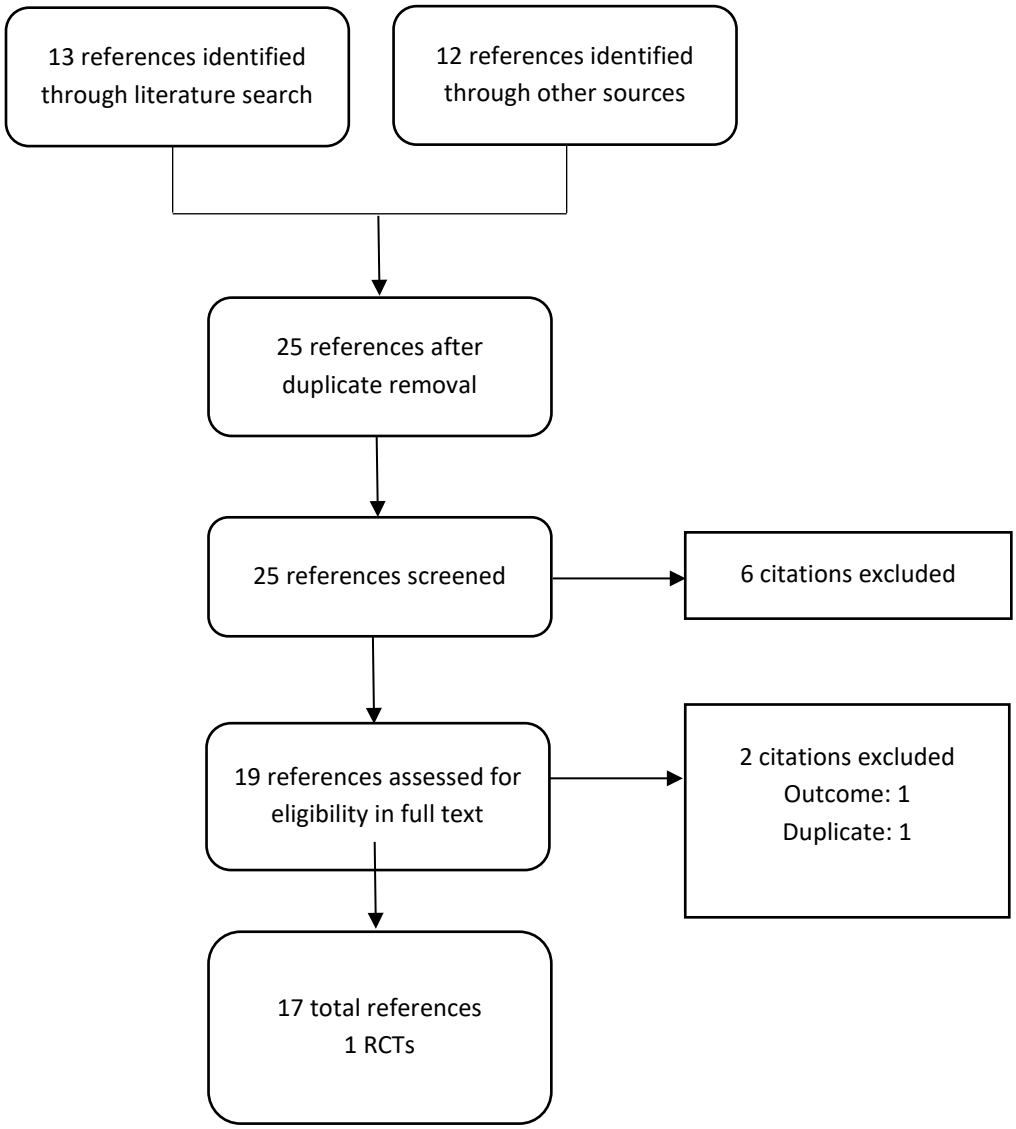
Date of latest search: February 25, 2025

**Table D1.3 EMBASE Search Strategy for Sonpiretigene Isteparvovec**

| # | Search Term |
|---|---|
| **1** | 'sonpiretigene isteparvovec'/exp |
| **2** | ("MCO 010' OR 'MCO010' OR 'MCO-010' OR 'Sonpiretigene Isteparvovec' OR 'virally-carried Multi-Characteristic Opsin' OR 'vMCO 010' OR 'VMCO 1' OR 'VMCO-010' OR 'VMCO1' OR 'VMCO-1"):ti,ab |
| **3** | #1 OR #2 |
| **4** | ('animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp) NOT 'human'/exp |
| **5** | #3 NOT #4 |
| **6** | #5 NOT ('chapter'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it) |
| **7** | #6 AND [english]/lim |

Date of latest search: February 25, 2025

**Figure D1.1. PRISMA Flow Chart Showing Results of Literature Search for Sonpiretigene Isteparvovec for Retinitis Pigmentosa**



## Study Selection

We performed screening at both the abstract and full-text level. Two investigators independently screened all titles and abstracts identified through electronic searches according to the inclusion and exclusion criteria described earlier using Nested Knowledge (Nested Knowledge, Inc, St. Paul, MN); a third reviewer worked with the initial two reviewers to resolve any issues of disagreement through consensus. We did not exclude any study at abstract-level screening due to insufficient information. For example, an abstract that did not report an outcome of interest would be accepted for further review in full text. We retrieved the citations that were accepted during abstract-level screening for full text appraisal. One investigator reviewed full papers and provided justification for exclusion of each excluded study.

We also included documents related to sonpiretigene isteparvovec submitted by the manufacturer. All literature that did not undergo a formal peer review process is described separately.

## Data Extraction

Data were extracted into Microsoft Excel. The basic design and elements of the extraction forms followed those used for other ICER reports. Elements included a description of patient populations, sample size, duration of follow-up, funding source, study design features, interventions (agent, dosage, frequency, schedules), concomitant therapy allowed and used (agent, dosage, frequency, schedules), outcome assessments, results, and risk of bias for each study. The data extraction was performed in the following steps:

1. One reviewer extracted information from the full articles or conference abstracts, and a second reviewer validated the extracted data.
2. Extracted data were reviewed for logic, and a random proportion of data were validated by a third investigator for additional quality assurance.

## Risk of Bias Assessment

We examined the risk of bias for each randomized trial in this review using criteria published in the Cochrane Risk of Bias Assessment Tool Version 2.[73,75] Risk of bias was assessed by study outcome for each of the following aspects of the trials: randomization process, deviation from the intended interventions, missing outcome data, measurement of the outcome, selection of the reported results, and overall risk of bias. Two reviewers independently assessed these domains. Any disagreements were resolved through discussion or by consulting a third reviewer.

To assess the risk of bias in trials, we rated the categories as: “low risk of bias,” “some concerns,” or “high risk of bias.” Guidance for risk of bias ratings using these criteria is presented below:

***Low risk of bias**: The study is judged to be at low risk of bias for all domains for this result.*

***Some concerns**: The study is judged to raise some concerns in at least one domain for this result, but not to be at high risk of bias for any domain.*

***High risk of bias**: The study is judged to be at high risk of bias in at least one domain for this result or the study is judged to have some concerns for multiple domains in a way that substantially lowers confidence in the result.*

We examined the risk of bias for the following outcomes: Best corrected visual acuity (BCVA) measured by the Frieberg Visual Acuity Test (FrACT), multi-luminance Y-mobility test (MLYMT), and multi-luminance shape discrimination test (MLSDT) (Table D1.4).

**Table D1.4. Risk of Bias Assessment for the RESTORE Trial**

| Trial Outcome | Randomization Process | Deviation from the Intended Interventions | Missing Outcome Data | Measurement of the Outcome | Selection of the Reported Result | Overall Risk of Bias |
|---|---|---|---|---|---|---|
| **BCVA** | Low | Some concern | Low | Some concern | Low | Some Concern |
| **MLYMT** | Low | Some concern | Low | Some concern | Some concern | Some Concern |
| **MLSDT** | Low | Some concern | Low | Some concern | Some concern | Some Concern |

Table D1.4 Abbreviations - BCVA: Best Corrected Visual Acuity, MLSDT: multi-luminance shape discrimination test, MLYMT: multi-luminance Y-mobility test

Table D1.4 Note: During this assessment, the RESTORE trial had not yet been published in a peer-reviewed journal. Instead, information from slide-deck presentations, academic-in-confidence data, and a research protocol shared by the manufacturer informed our review.

## Evaluation of Clinical Trial Diversity

We sought to evaluate the demographic diversity of the clinical trial using the ICER-developed Clinical Trial Diversity rating (CDR) Tool.[54] However, the lack of prevalence estimates for this rare condition precluded the evaluation. As described in our VAF, trials of rare diseases with no reliable disease specific prevalence estimate will not be rated on clinical trial diversity. Instead, a qualitative description of the demographic characteristics of participants in the clinical trial will be presented. The demographic information for the pivotal trial of sonpiretigene isteparvovec (RESTORE) is described below.

The RESTORE trial enrolled 27 participants with a mean age of 56 (range: 23 to 84). Information on the number of participants over the age of 65 is not publicly available. There were more male participants (63%) enrolled compared to female participants (37%). The participants were predominantly white (93%) with one Asian participant and one participant whose race was categorized as "other" (see Supplement Table D3.2).

Please refer to our website for information on the Clinical Trial Diversity Rating (CDR) Tool.

## Assessment of Level of Certainty in Evidence

We used the ICER Evidence Rating Matrix to evaluate the level of certainty in the available evidence of a net health benefit among each of the interventions of focus (see Appendix D).[76,77]

## 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 these newer treatments, we scanned the ClinicalTrials.gov site to identify studies completed more than two years ago. Search terms include: "sonpiretigene isteparvovec," "MCO-010", and "retinitis pigmentosa". We selected studies which would have met our inclusion criteria, and for which no findings have been published. We provided a qualitative analysis of the objectives and methods of these studies to ascertain whether there may be a biased representation of study results in the published literature.

## Data Synthesis and Statistical Analyses

Evidence Tables in Section D2 provide a summary of the key outcomes from the therapy, which are further synthesized qualitatively in the report. We assessed the feasibility of quantitative synthesis but determined it was not possible due to there being a single trial and no alternative treatment options to compare against.

# D2. Additional Clinical Evidence

## Additional Methods

### Evidence Base

#### *Phase I/II SAD*

SAD was a Phase I/II open-label, non-randomized, dose-escalation study that evaluated the safety and tolerability of two doses of sonpiretigene isteparvovec. The trial was conducted in India and enrolled 11 patients with advanced RP. Of the 11 patients, three received a low-dose of sonpiretigene ($0.6x10^{11}$ genome copies/eye) and eight received a high-dose ($1.2x10^{11}$ genome copies/eye).[78]

Patients were eligible to enroll in the trial if they had a confirmed diagnosis of advanced RP, a clinical diagnosis of advanced retinal dystrophy and documentation of rod-cone photoreceptor degeneration, a Snellen's visual acuity equivalent to "light perception" or "no light perception" in the study eye and "no-better-than finger counting" in the non-study eye. Patients were ineligible to enroll if they had participation in a past clinical study in the past six months, glaucoma or other diseases affecting the optic nerve, or presence of other complicating systemic diseases that could affect central nervous system functioning.[78]

The primary outcome was the safety and tolerability of sonpiretigene at week 16. Secondary outcomes included changes in visual acuity, mobility, shape recognition, and optical flow at week 52.[78]

## Additional Results

#### *Phase IIb/III RESTORE*

*BCVA: Change From Baseline*

Best corrected visual acuity (BCVA) was also reported as change from baseline using an area under the curve (AUC) analysis at week 52. Participants treated with sonpiretigene had a significant improvement in BCVA AUC compared to sham at week 52 (13.55 versus 3.16 LogMAR*weeks; p=0.01). Significant improvements over sham were observed up to week 100.[40,44]

*BCVA: Individual Participant Data at Week 76*

At week 76, eight sonpiretigene-treated patients continued to show improvements in BCVA (Figure D2.1). Two participants who showed improvement at week 52 had no further improvement in BCVA between weeks 52 and 76. One participant who showed the greatest improvement in BCVA at week 52 (change from baseline [CFB]: -1.83 LogMAR), had a worsening of +0.60 in LogMAR between week 52 and 76. The eight sonpiretigene-treated participants who showed no detectable change in BCVA at week 52 continued to have no detectable changes in BCVA at week 76.[43]

In the sham group, one participant who showed no change in BCVA at week 52 had an improvement of -0.69 LogMAR at week 76. The one sham participant who had a minimally worse BCVA at week 52 than baseline (CFB: +0.01 LogMAR), continued to worsen by week 76 (CFB: +0.24 LogMAR). One sham participant who had a slight improvement at week 52 had a minimal improvement at week 76. The sham participant who had a significant improvement at week 52 (CFB: -0.80), which was determined to be a protocol deviation with an incorrectly recorded BCVA, had a worsening of +0.29 in LogMAR between weeks 52 and 76. Lastly, five sham participants who showed no detectable change in BCVA at week 52 continued to exhibit no detectable changes in BCVA at week 76.[43]

**Figure D2.1. Individual Participant Data for Changes in Visual Acuity at Week 76**

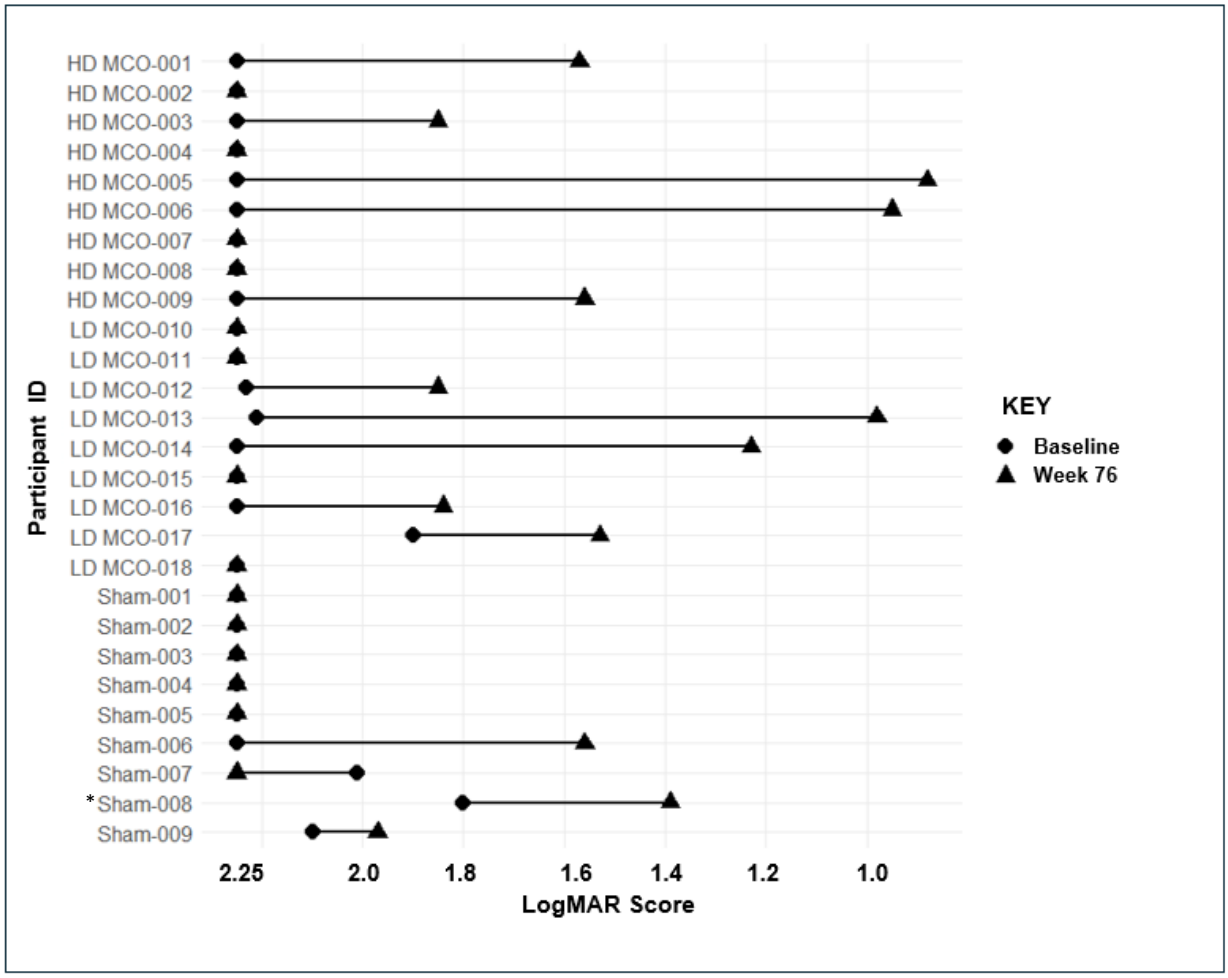



Figure D2.1 Abbreviations – HD: high-dose, LD: low-dose, LogMAR: logarithmic minimum angle of resolution, MCO: sonpiretigene isteparvovec

Figure D2.1 Footnote - * Major protocol deviation related to incorrect recording of BCVA

Source: Data from a presentation by Loewenstein 2024[43]

### *Phase I/II SAD*

In the open-label SAD trial, the mean baseline LogMAR was 1.96 for the participants who received high dose sonpiretigene, which is roughly equivalent to a person being able to count fingers. This was not reported for the low-dose group. At 16 weeks, high-dose sonpiretigene-treated participants had a greater than 0.6 increase in LogMAR compared to a 0.08 change in the low-dose group. At week 52, the mean BCVA score was 1.46 LogMAR for high-dose treated participants. This data was not presented for the low-dose arm.[36]

## Additional Harms

### *Phase I/II SAD*

In the SAD trial, no serious-treatment-emergent adverse events or adverse events leading to study discontinuation were reported.[36-38]

# D3. Evidence Tables

**Table D3.1. Study Design[48,78]**

| Trial & Design | Interventions (n) | Inclusion & Exclusion Criteria | Primary Outcome |
|---|---|---|---|
| **RESTORE (NCT04945772)**<br><br>**Phase IIb/III, Randomized, Double-Masked, Sham-Controlled**<br><br>**N=27**<br><br>**Follow-Up: 100 Weeks** | **Low-Dose:** $0.9x10^{11}$ gc/eye sonpiretigene (n=9)<br><br>**High-Dose:** $1.2x10^{11}$ gc/eye sonpiretigene (n=9)<br><br>Sham injection (n=9) | **Inclusions:**<br>- Age ≥ 18 years.<br>- Diagnosed with Advanced Retinitis Pigmentosa (RP) based on clinical examination, dilated fundus examination, and genetic testing.<br>- Best-Corrected Visual Acuity (BCVA) < 1.9 LogMAR in the study eye.<br>- BCVA > 1.6 LogMAR in the non-study eye.<br>**Exclusions**:<br>- Prior participation in gene therapy program.<br>- Pre-existing conditions in the study eye such as glaucoma, diseases affecting the optic nerve causing significant visual field loss, active uveitis, corneal or lenticular opacities.<br>- Active ocular inflammation, recurrent history of idiopathic or autoimmune associated uveitis<br>- Presence of any complicating systemic diseases such as malignancies whose treatment could affect central nervous system function<br>- Received retinal prothesis (e.g., ARGUS-II), any gene or stem cell therapy (ocular/non-ocular) | Efficacy of a single IVT of sonpiretigene as assessed by best corrected visual acuity (BCVA) [52 weeks] |
| **SAD (NCT04919473)**<br><br>**Phase I/IIa, Open-Label, Dose-Escalation**<br><br>**N=11**<br><br>**Follow-Up: 52 Weeks** | **Low-Dose:** $0.6x10^{11}$ gc/eye sonpiretigene (n=3)<br><br>**High-Dose:** $1.2x10^{11}$ gc/eye sonpiretigene (n=8) | **Inclusions:**<br>- Age ≥ 18 years.<br>- Diagnosed with Advanced Retinitis Pigmentosa (RP) using fundus photographs.<br>- Snellen's visual acuity equivalent light-perception/no light-perception in study eye.<br>- Visual acuity in the non-study eye of no-better-than finger counting.<br>**Exclusions:**<br>- Participation in investigational drug clinical trials, agent or therapy or any gene or stem cell therapy in the past six months<br>- Pre-existing eye conditions such as glaucoma, diseases affecting the optic nerve causing significant visual field loss, active uveitis, corneal or lenticular opacities.<br>- Ocular surgery in the study eye within three months prior to Day 0.<br>- Presence of disorders of the ocular media which interfere with visual acuity and other ocular assessments, including OCT, during the study period.<br>- Presence of vitreo-macular adhesion or traction, epiretinal membrane, macular pucker and macular hole, evident by ophthalmoscopy and/or by OCT examinations<br>- Current evidence of retinal detachment significantly affecting central vision.<br>- Active ocular inflammation, recurrent history of idiopathic or autoimmune associated uveitis. | The safety and tolerability of escalating doses of sonpiretigene administered via a single IVT in subjects with advanced RP [16 weeks] |

Table D3.1 Abbreviations - IVT: intravitreal treatment, gc: genome copies, LogMAR: logarithmic minimum angle of resolution, n: number of participants, N: total number, OCT: optical coherence tomography, RP: retinitis pigmentosa

### Table D3.2. RESTORE Baseline Characteristics[46]

| Arm | | Low-Dose Sonpiretigene | High-Dose Sonpiretigene | Combined Sonpiretigene | Sham Control |
|---|---|---|---|---|---|
| **N** | | 9 | 9 | 18 | 9 |
| **Mean Age** | | 52.2 | 60.4 | 56.3 | 56.7 |
| **Female, n (%)** | | 3 (33.3) | 3 (33.3) | 6 (33.3) | 4 (44.4) |
| **Race, n (%)** | Asian | 1 (11.1) | 0 | 1 (5.6) | 0 |
| | Black and African American | 0 | 0 | 0 | 0 |
| | White | 7 (77.8) | 9 (100) | 16 (88.9) | 9 (100) |
| | Other | 1 (11.1) | 0 | 1 (5.6) | 0 |
| **Ethnicity, n (%)** | Hispanic or Latino | 4 (44.4) | 3 (33.3) | 7 (38.9) | 4 (44.4) |
| | Non-Hispanic or Latino | 5 (55.6) | 6 (66.7) | 11 (61.1) | 5 (55.6) |
| **Inheritance Pattern, n (%)** | Syndromic Disease | 3 (33.3) | 4 (44.4) | 7 (38.9) | 4 (44.4) |
| | Non-Syndromic Disease | 6 (66.7) | 5 (55.6) | 11 (61.1) | 5 (55.6) |
| | X-linked | 2 (22.2) | 1 (11.1) | 3 (16.7) | 1 (11.1) |
| | Autosomal recessive | 5 (55.6) | 6 (66.6) | 11 (61.1) | 6 (66.7) |
| | Autosomal-dominant | 2 (22.2) | 2 (22.2) | 4 (22.2) | 2 (22.2) |
| **Baseline Visual Functioning, Mean Score (SE)** | Best-Corrected Visual Acuity (BCVA) | 2.21 (NR) | 2.3 (NR) | 2.229 (0.02) | 2.172 (0.05) |
| | Visual field (e.g., degrees) | 2.0 | 0.5 | 1.3 | 0.8 |
| | Multi-luminance Y- Mobility Test (MLYMT) | 0.77 (NR) | 1.55 (NR) | 1.2 (0.6) | 1.0 (1.0) |
| | Multi-Luminance Shape Discrimination Test (MLSDT) | 1.44 (NR) | 0.22 (NR) | 0.83 (0.4) | 1.7 (0.6) |

Table D3.2 Abbreviations - %: percent, n: number, N: total number, NR: not reported, SE: standard error

**Table D3.3. RESTORE Efficacy Outcomes[35,39-41,43-46]**

| Arm | | | Low-Dose Sonpiretigene | High-Dose Sonpiretigene | Combined Sonpiretigene | Sham Control |
|---|---|---|---|---|---|---|
| **N** | | | 9 | 9 | 18 | 9 |
| **Freiburg BCVA Score, LogMAR** | **Baseline** | Mean Baseline Score (SEM) | 2.21 (NR) | 2.3 (NR) | 2.229 (0.02) | 2.172 (0.05) |
| | 52 weeks | Mean Score (SEM); p-value vs. baseline | 1.823 (NR); NR | 1.964 (NR); NR | NR | NR |
| | | LSM Change from Baseline (SEM); p-value vs. sham | -0.382 (0.1244); 0.0290 | -0.337 (0.829); 0.0209 | NR | -0.050 (0.0717); NA |
| | | Responders, n (%) | 3 (33) | 4 (44) | 7 (39) | 1 (11) |
| | 76 weeks | Mean Score (SEM); p-value vs. baseline | NR | NR | NR | NR |
| | | LSM Change from Baseline (SEM); p-value vs. sham | -0.374 (0.1332); 0.0652 | -0.539 (0.1032); 0.0014 | NR | -0.078 (0.0783); NA |
| | | Responders, n (%) | NR | NR | 10 (56) | NR |
| | 100 weeks | Mean Score (SEM); p-value vs. baseline | NR | NR | NR | NR |
| | | LSM Change from Baseline (SEM); p-value vs. sham | *-0.21 (0.13);* NR | *-0.24 (0.10);* NR | NR | *-0.07 (0.08)*; NR |
| | | Responders, n (%) | NR | NR | 5 (28) | NR |
| **BCVA AUC Analysis (LogMAR*week)** | 52 weeks | Change from Baseline; p-value vs. sham | 16.14 (5.93); 0.0386 | 10.91 (4.02); 0.0885 | 13.55 (NR); 0.0101 | 3.16 (NR) |
| | 76 weeks | Change from Baseline p-value vs. sham | 25.45 (8.61); 0.0268 | 22.00 (5.78); 0.0105 | NR | 5.369 (2.72) |
| | 100 weeks | Change from Baseline; p-value vs. sham | 31.67 (11.3); 0.0306 | 31.49 (7.52); 0.00250 | NR | 6.120 (3.37); NA |
| **MLYMT Score** | **Baseline** | Mean Baseline Score (SE) | 0.77 (NR) | 1.55 (NR) | 1.167 (0.612) | 1.0 (1.0) |
| | 52 weeks | N at the ceiling | NR | NR | 5 (28) | 3 (33) |
| | | Mean Score (SEM); p-value vs. baseline | NR | NR | 4.167 (0.43); p<0.0001 | 3.0 (1.0); p=0.0805 |
| | | Mean Change from Baseline (SEM); p-value vs. sham | NR | NR | 3.00 (0.59); 0.1977 | 2.00 (1.00); NA |
| | | Responders, n (%) | 6 (66.7) | 6 (66.7) | 12 (67) | 3 (33) |
| | | Light Level Improvement | +2 light levels | +2 light levels | +2 light levels | +2 light levels |

| Arm | | | Low-Dose Sonpiretigene | High-Dose Sonpiretigene | Combined Sonpiretigene | Sham Control |
|---|---|---|---|---|---|---|
| N | | | 9 | 9 | 18 | 9 |
| MLSDT Score | **Baseline** | Mean Baseline Score (SE) | 1.44 (NR) | 0.22 (NR) | 0.8333 (0.364) | 1.667 (0.624) |
| | 36 weeks | Responders, n (%) | 5 (55.6) | 3 (33.3) | 8 (44.4) | 0 |
| | 52 weeks | N at the ceiling | NR | NR | NR | NR |
| | | Mean Score (SEM); p-value vs. baseline | NR; 0.2721 | NR; 0.0265 | 2.444 (0.5); 0.0235 | 1.889 (0.772); 0.8632 |
| | | Mean Change from Baseline (SEM); p-value vs. sham | 1.33 (NR); NR | 1.89 (NR); NR | 1.94 (0.59); 0.1657 | 0.22 (0.86); NA |
| | | Responders, n (%) | 5 (56) | 5 (56) | 10 (56) | 2 (22) |
| | | Light Level Improvement | +2 light levels | +2 light levels | +2 light levels | +2 light levels |
| Clinically Meaningful Improvement in Composite Endpoints | 52 weeks | MLYMT or MLSDT, n (%); p-value vs. sham | 8 (88.9); 0.1312 | 8 (88.9); 0.1312 | 16 (89); 0.024 | 4 (44) |
| | | MLYMT or BCVA, n (%); p-value vs. sham | NR | NR | 17 (94); 0.008 | 4 (44) |
| | | MLSDT or BCVA, n (%); p-value vs. sham | NR | NR | 13 (72); 0.09 | 3 (33) |
| | | MLYMT or MLSDT or BCVA, n (%); p-value vs. sham | NR | NR | 18 (100); 0.007 | 5 (56) |
| | | MLYMT and MLSDT, n (%) | NR | NR | 6 (33) | 1 (11) |
| | | MLYMT and BCVA, n (%) | NR | NR | 2 (11) | 0 (0) |
| | | MLSDT and BCVA, n (%) | NR | NR | 4 (22) | 0 (0) |
| | | MLYMT and MLSDT and BCVA, n (%) | NR | NR | 1 (6) | 0 (0) |

Table D3.3 Abbreviations - AUC: area under the curve, BCVA: Best-Corrected Visual Acuity, CI: confidence interval, LSM: least-squares mean, LogMAR: logarithmic minimum angle of resolution, MLSDT: Multi-Luminance Shape Discrimination Test, MLYMT: Multi-Luminance Y-Mobility Test, n: number, NA: not applicable, NR: not reported, SE: standard error, SEM: standard mean error, %: percent

Table D3.3 Note: Italicized data has been digitized or calculated

**Table D3.4. RESTORE Safety Outcomes[40-46]**

| Arm | | Timepoint | Low-Dose Sonpiretigene | High-Dose Sonpiretigene | Combined Sonpiretigene | Sham Control |
|---|---|---|---|---|---|---|
| N | | | 9 | 9 | 18 | 9 |
| **Adverse Events, n (%)** | Overall | 52 weeks | 9 (100.0) | 8 (88.9) | 17 (94.4) | 8 (88.9) |
| | Serious | 52 weeks | 0 | 0 | 0 | 1 (11.1) |
| | Grade 3/4 | 52 weeks | 0 | 0 | 0 | 1 |
| | Leading to study discontinuation | 52 weeks | 0 | 0 | 0 | 0 |
| **Ocular Adverse Events, n (%)** | Overall | 52 weeks | 9 (100.0) | 8 (88.9) | 17 (94.4) | 6 (66.7) |
| | | 100 weeks | 9 (100.0) | 8 (88.9) | 17 (94.4) | 7 (77.8) |
| | Serious | 52 weeks | 0 | 0 | 0 | 0 |
| **Adverse Events of Special Interest, n (%)** | Asymptomatic COVID-19 | 52 weeks | 0 | 2 (22.2) | 2 (11.1) | 0 |
| | Hypertension | 52 weeks | 0 | 3 (33.3) | 3 (16.7) | 2 (22.2) |
| | Anterior chamber cell | 52 weeks | 6 (66.7) | 2 (22.2) | 8 (44.4) | 2 (22.2) |
| | | 100 weeks | 6 (66.7) | 3 (33.3) | 9 (50.0) | 1 (11.1) |
| | Ocular hypertension | 52 weeks | 4 (44.4) | 3 (33.3) | 7 (38.9) | 1 (11.1) |
| | | 100 weeks | 4 (44.4) | 4 (44.4) | 8 (44.4) | 1 (11.1) |
| | Retinitis | 52 weeks | 0 | 0 | 0 | 0 |
| | | 100 weeks | 0 | 0 | 0 | NR |
| | Hypotony | 52 weeks | 0 | 0 | 0 | 0 |
| | | 100 weeks | 0 | 0 | 0 | NR |
| | Vasculitis | 52 weeks | 0 | 0 | 0 | 0 |
| | | 100 weeks | 0 | 0 | 0 | NR |
| | Conjunctival hemorrhage | 52 weeks | 4 (44.4) | 3 (33.3) | 7 (38.9) | 0 |
| | | 100 weeks | 4 (44.4) | 3 (33.3) | 7 (38.9) | 0 |
| | Vitreous haze | 52 weeks | 3 (33.3) | 2 (22.2) | 5 (27.8) | 0 |
| | | 100 weeks | 3 (33.3) | 2 (22.2) | 5 (27.7) | 0 |
| | Keratic precipitates | 52 weeks | 3 (33.3) | 1 (11.1) | 4 (22.2) | 0 |
| | | 100 weeks | 2 (22.2) | 1 (11.1) | 3 (16.7) | 0 |
| | Vitreous disorder | 52 weeks | 3 (33.3) | 0 | 3 (16.7) | 1 (11.1) |
| | | 100 weeks | 3 (33.3) | 0 | 3 (16.7) | 1 (11.1) |
| | Iritis | 52 weeks | 0 | 2 (22.2) | 2 (11.1) | 1 (11.1) |
| | | 100 weeks | 0 | 2 (22.2) | 2 (11.1) | 1 (11.1) |

| Arm | | Timepoint | Low-Dose Sonpiretigene | High-Dose Sonpiretigene | Combined Sonpiretigene | Sham Control |
|---|---|---|---|---|---|---|
| N | | | 9 | 9 | 18 | 9 |
| **Adverse Events of Special Interest, n (%)** | Vitreal cells | 52 weeks | 1 (11.1) | 2 (22.2) | 3 (16.7) | 0 |
| | | 100 weeks | 1 (11.1) | 2 (22.2) | 3 (16.7) | 0 |
| | Anterior chamber flare | 52 weeks | 1 (11.1) | 1 (11.1) | 2 (11.1) | 0 |
| | | 100 weeks | 1 (11.1) | 0 | 1 (5.6) | 0 |
| | Conjunctival hyperemia | 52 weeks | 1 (11.1) | 1 (11.1) | 2 (11.1) | 0 |
| | | 100 weeks | 1 (11.1) | 1 (11.1) | 2 (11.1) | 0 |
| | Eye pain | 52 weeks | 1 (11.1) | 1 (11.1) | 2 (11.1) | 0 |
| | | 100 weeks | 0 | 2 (22.2) | 2 (11.1) | 0 |
| | Iridocyclitis | 52 weeks | 0 | 2 (22.2) | 2 (11.1) | 0 |
| | | 100 weeks | 0 | 2 (22.2) | 2 (11.1) | 0 |
| | Photophobia | 52 weeks | 1 (11.1) | 1 (11.1) | 2 (11.1) | 0 |
| | | 100 weeks | 1 (11.1) | 1 (11.1) | 2 (11.1) | 0 |
| | Photopsia | 52 weeks | 1 (11.1) | 0 | 1 (5.6) | 1 (11.1) |
| | | 100 weeks | 1 (11.1) | 0 | 1 (5.6) | 1 (11.1) |
| | Punctate keratitis | 52 weeks | 1 (11.1) | 0 | 1 (5.6) | 1 (11.1) |
| | | 100 weeks | 1 (11.1) | 0 | 1 (5.6) | 1 (11.1) |
| | Vitreous floaters | 52 weeks | 1 (11.1) | 0 | 1 (5.6) | 1 (11.1) |
| | | 100 weeks | 1 (11.1) | 0 | 1 (5.6) | 1 (11.1) |
| | Vitreous detachment | 100 weeks | 1 (11.1) | 0 | 1 (5.6) | 1 (11.1) |
| | Altered visual depth perception | 100 weeks | 0 | 0 | 0 | 1 (11.1) |
| | Blepharitis | 100 weeks | 1 (11.1) | 0 | 1 (5.6) | 0 |
| | Cataract nuclear | 100 weeks | 0 | 0 | 0 | 1 (11.1) |
| | Conjunctival edema | 100 weeks | 0 | 0 | 0 | 1 (11.1) |
| | Corneal edema | 100 weeks | 0 | 1 (11.1) | 1 (5.6) | 0 |
| | Cystoid macular edema | 100 weeks | 0 | 0 | 0 | 1 (11.1) |
| | Eye discharge | 100 weeks | 0 | 1 (11.1) | 1 (5.6) | 0 |
| | Eyelid pain | 100 weeks | 1 (11.1) | 0 | 1 (5.6) | 0 |
| | Foreign body sensation in eyes | 100 weeks | 1 (11.1) | 0 | 1 (5.6) | 0 |
| | Keratitis | 100 weeks | 1 (11.1) | 0 | 1 (5.6) | 0 |
| | Lacrimation increased | 100 weeks | 1 (11.1) | 0 | 1 (5.6) | 0 |

| Arm | | Timepoint | Low-Dose Sonpiretigene | High-Dose Sonpiretigene | Combined Sonpiretigene | Sham Control |
|---|---|---|---|---|---|---|
| N | | | 9 | 9 | 18 | 9 |
| | Choroiditis | 100 weeks | 0 | 0 | 0 | NR |
| | Vasculitis | 100 weeks | 0 | 0 | 0 | NR |
| | Ischemic Neuropathy | 100 weeks | 0 | 0 | 0 | NR |
| | Hypopyon | 100 weeks | 0 | 0 | 0 | NR |
| **Intraocular Inflammation, n (%)** | Treatment with topical or oral steroids | 52 weeks | NR | NR | 2 (11.1) | 2 (22.2) |
| | | 100 weeks | NR | NR | 1 (5.6) | 2 (22.2) |

Table D3.4 Abbreviations - AEs: adverse events, n: number, N: total number, NR: not reported, TEAE: treatment-emergent adverse event, %: percent

**Table D3.5 RESTORE Individual Participant Data for Key Efficacy Outcomes at Week 52[35,41,42,45]**

| Participant ID | Change from Baseline at Week 52 | | |
|---|---|---|---|
| | BCVA*, LogMAR | MLYMT, Light Levels | MLSDT, Light Levels |
| **MCO 001** | -0.58 | No improvement detected | + 3 |
| **MCO 002** | No improvement detected† | + 5 | + 5 |
| **MCO 003** | -0.04 | + 6 | + 2 |
| **MCO 004** | No improvement detected† | + 6 | + 4 |
| **MCO 005** | -0.69 | + 1 | No improvement detected |
| **MCO 006** | -0.69 | + 3 | No improvement detected |
| **MCO 007** | No improvement detected† | + 6 | No improvement detected |
| **MCO 008** | No improvement detected† | + 2 | No improvement detected |
| **MCO 009** | -0.58 | + 1 | + 5 |
| **MCO 010** | No improvement detected† | No improvement detected | + 3 |
| **MCO 011** | No improvement detected† | + 2 | No improvement detected |
| **MCO 012** | -0.15 | +2 | + 4 |
| **MCO 013** | -1.83 | No improvement detected | + 1 |
| **MCO 014** | -1.02 | No improvement detected | + 4 |
| **MCO 015** | No improvement detected† | + 6 | No improvement detected |
| **MCO 016** | -0.37 | + 6 | + 4 |
| **MCO 017** | -0.11 | + 6 | + 4 |
| **MCO 018** | No improvement detected† | + 5 | No improvement detected |
| **Sham 001** | No improvement detected† | + 6 | + 5 |
| **Sham 002** | No improvement detected† | + 6 | No improvement detected |
| **Sham 003** | No improvement detected† | No improvement detected | No improvement detected |
| **Sham 004** | No improvement detected† | No improvement detected | No improvement detected |
| **Sham 005** | No improvement detected† | No improvement detected | No improvement detected |
| **Sham 006** | No improvement detected† | No improvement detected | + 3 |
| **Sham 007** | +0.01 | + 6 | No improvement detected |
| **Sham 008‡** | -0.80 | No improvement detected | + 1 |
| **Sham 009** | -0.10 | No improvement detected | No improvement detected |

Table D3.5 Abbreviations - BCVA: best corrected visual acuity, LogMAR: logarithmic minimum angle of resolution, MLSDT: multi-luminance shape discrimination test, MLYMT: multi-luminance Y-mobility test

Table D3.5 Footnotes - *A negative change in BCVA indicates an improvement, a positive change indicates a worsening of BCVA. † Baseline BCVA measurement was 2.25 (floor of FrACT test). ‡Major protocol deviation related to incorrect recording of BCVA

**Table D3.6. SAD Baseline Characteristics, Efficacy and Safety Outcomes*[36-38]**

| Arm | | Low-Dose Sonpiretigene | High-Dose Sonpiretigene | Combined Sonpiretigene |
|---|---|---|---|---|
| **N** | | **3** | **8** | **11** |
| **Efficacy Outcomes: Freiburg BCVA Score (LogMAR)** | | | | |
| **Baseline** | Mean Score | NR | 1.95 | NR |
| **16 Weeks** | Mean Score | NR | NR | NR |
| | Change from Baseline | *0.08* | >0.6 | NR |
| | Responders, n (%) | NR | NR | NR |
| **52 Weeks** | Mean Score | NR | 1.46 | NR |
| **Safety Outcomes** | | | | |
| **16 Weeks** | Serious TEAE | 0 | 0 | 0 |
| | AEs leading to study discontinuation | 0 | 0 | 0 |

Table D3.6 Abbreviations - AEs: adverse events, BCVA: best corrected visual acuity, LogMAR: logarithmic minimum angle of resolution, n: number, NR: not reported, SE: standard error, SEM: standard mean error, TEAEs: treatment-emergent adverse event, %: percent

Table D3.6 Footnote: * No data was reported for baseline characteristics, change from baseline and responders for BCVA at week 52, or for the Multi-Luminance Y-Mobility Test (MLYMT) and Multi-Luminance Shape Discrimination Test (MLSDT).

Table D3.6 Note: Italicized data has been digitized or calculated

# D4. Ongoing Studies

**Table D4.1. Ongoing Studies for Sonpiretigene Isteparvovec[49,79,80]**

| Title/Trial Sponsor | Study Design | Comparators | Patient Population | Primary Outcomes | Estimated Completion Date |
|---|---|---|---|---|---|
| **REMAIN**<br><br>**NCT06162585**<br><br>**Nanoscope Therapeutics** | Observational, non-interventional, long-term safety follow-up.<br><br>Estimated enrollment: N=18 | **Arm 1:**<br>$1.2x10^{11}$ gc/eye of sonpiretigene (high-dose)<br>**Arm 2:**<br>$0.9x10^{11}$ gc/eye of sonpiretigene (low-dose) | **Inclusions**:<br>- Previously enrolled in study NTXMCO-002 (RESTORE) and received sonpiretigene.<br>- Agree to participate for the full 3-year duration of follow-up to the best of their ability and barring any unforeseen circumstances. | Assessment of the long-term safety of previous treatment with a single IVT of sonpiretigene [156 weeks]. | September 2027 |
| **EXTEND**<br><br>**NCT05921162**<br><br>**Nanoscope Therapeutics** | Observational, non-interventional, long-term safety follow-up.<br><br>Estimated enrollment: N=11 | **Arm 1:**<br>$1.2x10^{11}$ gc/eye of sonpiretigene<br>**Arm 2:**<br>$0.6 x10^{11}$ gc/eye of sonpiretigene | **Inclusion**:<br>- Previously enrolled in study NSCT/CT/18/01 (SAD) and received sonpiretigene. | Assessment of the long-term safety profile and efficacy of a single IVT of sonpiretigene [240 weeks]. | December 2024 |
| **SUSTAIN**<br><br>**NCT06048185**<br><br>**Nanoscope Therapeutics** | Observational, non-interventional, long-term safety follow-up.<br><br>Estimated enrollment: N=6 | **Arm 1:**<br>Sonpiretigene | **Inclusions**:<br>- Previously enrolled in study NTXMCO-004 (STARLIGHT for Stargardt Disease) and received sonpiretigene.<br>- Agree to participate for the full 4-year duration of follow-up to the best of their ability and barring any unforeseen circumstances. | Assessment of the long-term safety profile of a single IVT of sonpiretigene [204 weeks]. | July 2027 |

Source: www.ClinicalTrials.gov

Table D4.1 Abbreviations - gc/eye: genome copies per eye, IVT: intravitreal injection, N: number of participants

## D5. Previous Systematic Reviews and Technology Assessments

We identified one previously conducted systematic literature review and no health technology assessments. The systematic literature review is briefly summarized below.

**Confalonieri F, La Rosa A, Ottonelli G, et al. Retinitis Pigmentosa and Therapeutic Approaches: A Systematic Review. *Journal of Clinical Medicine*. 2024.[81]**

This systematic review aimed to investigate the efficacy and safety of emerging treatment modalities for retinitis pigmentosa (RP), including gene therapy, mesenchymal-cell-based approaches, and supplementary interventions. The primary focus was to determine the current therapeutic approaches evaluated by clinical trials for RP. Four databases were searched for randomized controlled trials (RCTs), non-randomized studies, and case series that evaluated the efficacy of any therapeutic interventions and clinical outcomes for patients with RP. The researchers included 13 studies (11 RCTs and two non-randomized) and were narratively summarized. Gene therapy was supported as a promising therapeutic approach by two studies that reported favorable outcomes in the preservation of visual function and stabilization of disease progression. Mesenchymal-cell-based therapies presented potential benefits across six studies, although existing evidence remains heterogenous and limited. Supplementary interventions, including nutritional supplements and neuroprotective agents, demonstrated variable and conflicting efficacy across studies. Overall, gene therapy emerged as the most promising therapeutic approach for RP in improving visual function and slowing disease progression. The review acknowledges limitations such as insufficient long-term safety and efficacy data and the genetic heterogeneity of RP and emphasizes the need for further research to identify optimal treatment modalities and ensure patient accessibility.

# E. Long-Term Cost Effectiveness: Supplemental Information

## E1. Detailed Methods

**Table E1.1. Impact Inventory**

| Sector | Type of Impact (Add Additional Domains, as Relevant) | Included in This Analysis from […] Perspective? | | Notes on Sources (if Quantified), Likely Magnitude & Impact (if Not) |
|---|---|---|---|---|
| | | Health Care Sector | Societal | |
| **Formal Health Care Sector** | | | | |
| **Health Outcomes** | Longevity effects | X | X | |
| | Health-related quality of life effects | X | X | |
| | Adverse events | X | X | |
| **Medical Costs** | Paid by third-party payers | X | X | |
| | Paid by patients out-of-pocket | ☐ | X | Cost of low vision services and devices |
| | Future related medical costs | X | X | |
| | Future unrelated medical costs | X | X | |
| **Informal Health Care Sector** | | | | |
| **Health-Related Costs** | Patient time costs | NA | X | |
| | Unpaid caregiver-time costs | NA | X | |
| | Transportation costs | NA | X | |
| **Non-Health Care Sector** | | | | |
| **Productivity** | Labor market earnings lost | NA | X | |
| | Cost of unpaid lost productivity due to illness | NA | X | |
| | Cost of uncompensated household production | NA | ☐ | |
| **Consumption** | Future consumption unrelated to health | NA | ☐ | |
| **Social Services** | Cost of social services as part of intervention | NA | ☐ | |
| **Legal/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 home improvements, remediation | NA | ☐ | |
| **Environment** | Production of toxic waste pollution by intervention | NA | ☐ | |
| **Other** | Other impacts (if relevant) | NA | ☐ | |

Table E1.1 Abbreviations - NA: not applicable

Table E1.1 Notes - The "X" within the table shows that the domain was included in the analysis. The square in the table represents a potentially applicable domain that was not included in the analysis. Adapted from Sanders et al[82]

## Description of evLY Calculations

The equal value life year (evLY) considers any extension of life at the same "weight" no matter what treatment is being evaluated or what population is being modeled. Below are the stepwise calculations used to calculate the evLY.

1. First, we attribute a utility of 0.851, the age- and sex-adjusted utility of the general population in the US that are considered healthy.[83]
2. We calculate the evLY for each model cycle.
3. Within a model cycle, if using the intervention results in additional life years versus the primary comparator, we multiply the general population utility of 0.851 with the additional life years gained (ΔLY gained) within the cycle.
4. The life years shared between the intervention and the comparator use the conventional utility estimate for those life years within the cycle.
5. The total evLY for a cycle is calculated by summing steps three and four.
6. The evLY for the comparator arm is equivalent to the QALY for each model cycle.
7. The total evLYs are then calculated as the sum of evLYs across all model cycles over the time horizon.

Finally, the evLYs gained is the incremental difference in evLYs between the intervention and the comparator arm.

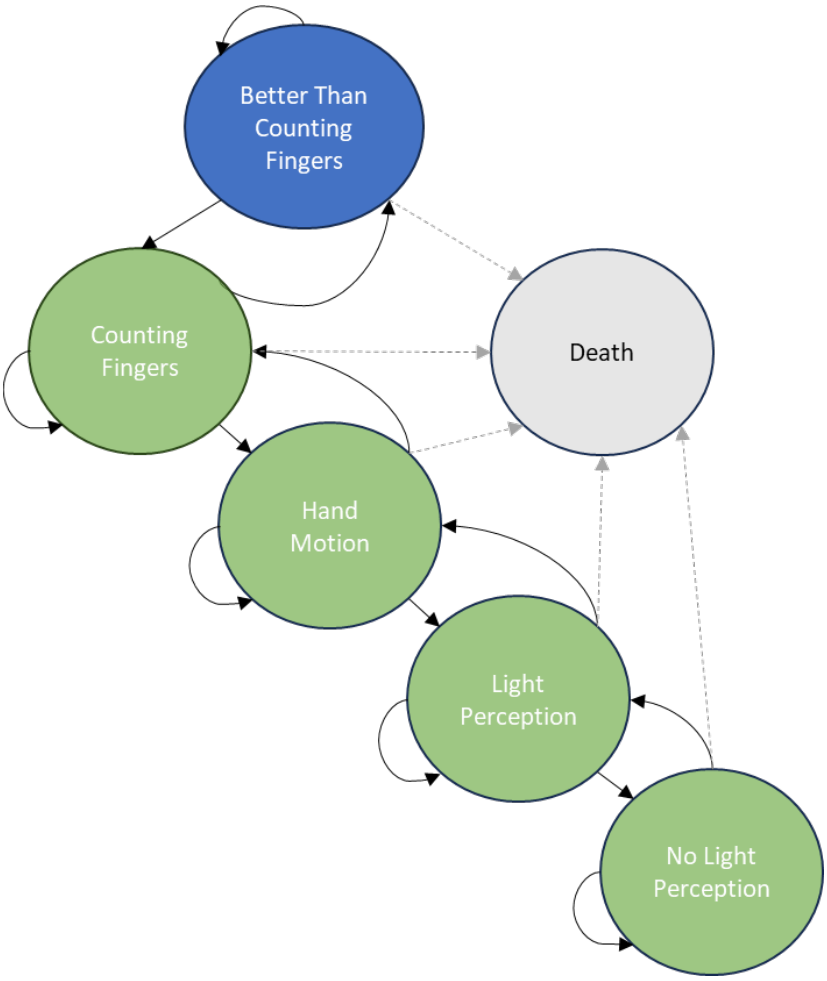
## Overview and Model Structure

We developed a *de novo* decision analytic model for this evaluation, informed by key clinical trials and prior relevant economic models. Costs and outcomes were discounted at 3% per year.

The model focused on a hypothetical cohort of patients with advanced retinitis pigmentosa being treated with sonpiretigene or usual care entering the model. Model cycle length was one year based on what was observed in prior published economic models and the clinical trial data (the primary endpoint of the RESTORE trial was at 52 weeks). Over the lifetime of the model, patients occupied one of six health states based on five levels of visual functioning and a dead state (Figure E1.1). The five levels of visual functioning, from best to worst functioning, included: better than counting fingers, counting fingers, hand motion, light perception, and no light perception. At the start of the model, the distribution of patients into corresponding health states was the same between sonpiretigene and usual care based on a weighted average of patients included in the RESTORE trial.[35]

Patients remained in the model until they die. All patients could transition to death from all causes from any of the alive health states.

**Figure E1.1. Model Schematic**




**Notes**: Movement of more than one health state may be possible in the model. These transitions are not depicted in the model schematic for simplicity. The model schematic depicts six health states including five health states defined by visual functioning (better than counting fingers, counting fingers, hand motion, light perception and no light perception) and a death state. Green health states (from counting fingers to no light perception) represent the possible starting health states for the intervention and usual care groups). The blue shaded health state (vision better than counting fingers) is a potentially achievable health state for some patients in the model, however, in line with the likely eligible patient population for sonpiretigene isteparvovec, no patients started in better than counting fingers. Transitions between health states (or staying within the same health state) occur annually, and patients could move to the death state from any level of visual functioning over the lifetime of the model. Please refer to our key model assumptions below for details regarding the data used to inform patient transitions between health states.

## Target Population

The population of focus for the economic evaluation included patients with advanced retinitis pigmentosa with severe vision loss. Baseline patient characteristics were based on the population enrolled in the key clinical trial (RESTORE) as reported in Table 2.2. No data were available for baseline visual field, only for visual acuity, shape discrimination, and mobility testing.

**Table E1.2. Baseline Population Characteristics**

| | Sonpiretigene Isteparvovec (High and Low Dose) | Usual Care | Source and Notes |
|---|---|---|---|
| **Demographic Characteristics** | | | |
| **Mean Age, Range** | 56.4 (23 to 83) | | Boyer 2023[46] |
| **Female, %** | 37% | | Boyer 2023[46] |
| **Baseline Visual Functioning** | | | |
| **Baseline BCVA, LogMAR, mean (SE)** | 2.229 (0.018) | 2.17 (0.05) | Sadda 2024[35] |
| **MLYMT, Luminance Level, mean (SE)** | 1.17 (0.61) | 1.0 (1.0) | Ho 2024[40] |
| **MLSDT, Luminance Level, mean (SE)** | 0.83 (0.36) | 1.67 (0.62) | Sadda 2024[35] |

Table E1.2 Abbreviations - BCVA: best corrected visual acuity, LogMAR: logarithmic minimum angle of resolution, MLSDT: multi-luminance shape discrimination test, MLYMT: multi-luminance Y-mobility test, NR: not reported, SD: standard deviation, SE: standard error

### *Treatment Strategies*

The list of interventions was developed with input from patient organizations, clinicians, manufacturers, and payers on which treatments to include. The intervention of interest is sonpiretigene isteparvovec (Nanoscope Therapeutics) and the comparator is usual care, which may include low vision aids, mobility training and support, and vision-related rehabilitation.

## Impact of Patient Involvement on Model Development

As described in Section B above, during the development of the model analysis plan, we discussed the preliminary model structure and assumptions with four members of the patient community to ensure their perspectives and experiences were reflected in our model analysis plan. The feedback received informed the following aspects of our model development:

- **Model Structure (progression in visual acuity):** We heard from patients that our proposed model structure, as described, reflected how their visual acuity has, or could, progress over time. However, we also heard that patients could find themselves identifying with more than one level of visual functioning depending on the environmental conditions or proximity and positioning relative to a light source or motion at a given time. For example, under ideal lighting conditions, a patient may be able to see fingers, while under less ideal conditions, they may be limited to only hand motion or light perception. The model assumed that a patient will occupy one health state based on what they experience most of the time, but the fluidity in the level of visual acuity noted by patients was primarily captured in the quality of life and cost estimates we used in the model.

- **Model Structure (highest level of visual acuity):** We defined the health state with the best level of visual functioning as "better than counting fingers." This health state is intended to represent the best level of visual acuity that a patient may achieve from treatment with sonpiretigene. Patients described this level of visual functioning as "legal blindness," and the literature has referred to it as profound visual impairment. We believe naming the state as "better than counting fingers" achieved the best balance of representing an improvement in level of visual acuity beyond counting fingers while not being mistaken for representing a state that could extend to unrealistically high levels of visual acuity.

- **Model Outcomes (cost per clinical outcome achieved):** Participants expressed their experience with retinitis pigmentosa as one that requires constant change to adjust to new levels of visual functioning. Patients valued a treatment that could offer stability or maintenance of their current level of visual functioning. In addition to reporting incremental costs per quality adjusted life year gained, equal-value of life year gained, and life-year gained, we reported the incremental costs per year with visual acuity better than counting fingers gained, and the incremental costs per year with light perception gained.

- **Health State Utilities**: The literature suggests that there are limited to no differences in the health-related quality of life that patients experience at levels of visual functioning between being able to count fingers, seeing hand motion, and being able to perceive light. We heard from patients with more advanced vision loss that the literature findings align with their experience, and we also heard from patients with less advanced vision loss that progression through counting fingers, hand motion, and light perception would represent meaningful quality of life changes. Given the variability in patient perspectives, we conducted a scenario analysis to assess the impact of no differences in health-related quality of life at levels of visual functioning between counting fingers, hand motion, and light perception, as well as a scenario using an alternative source of utility values.

- **Direct Medical Costs**: The literature suggests that there are no differences in direct medical costs according to level of visual functioning at advanced stages of vision loss. This was validated by participating patients.

- **Direct Non-Medical Costs**: We heard from participants that non-medical costs for support such as screen readers, visual aids, and other assistive technology were ongoing and did not change as their vision changed. The one exception to this was progressing from better than counting fingers to counting fingers or worse. Although not captured by participants as being an overly substantial difference, the progression to counting fingers did represent a significant shift in the level of supportive devices needed to maintain their level of independence (for example, moving beyond only needing magnifiers and glasses). We captured the differences in direct non-medical costs between the better than counting fingers health state and all other health states in the model in the modified societal perspective analysis.

- **Indirect Costs:** The literature suggested that there are no differences in productivity costs for patients and carers with varying degrees of advanced vision loss. This was validated by participating patients.
    - Although there may not be substantive changes in productivity costs as visual functioning declined, it was highlighted by participants that the impact on their ability to work was highly dependent on the level of support received from their employer and their creativity and adaptability to managing their vision loss. The impact on their carers' ability to work was similarly not substantively changed as their vision progressed; however, there was variability in the absolute level of impact or sacrifice felt by carers across participant's experiences.

During Session 3, as described in Section B above, we shared the findings from the cost-effectiveness analysis and the impact of patient engagement on the modeling effort. The session offered an opportunity for ICER to provide further clarity on the assumptions of the model and for participants to reinforce their experience with retinitis pigmentosa and expectations for treatment. Key areas of discussion included:

- **Durability of treatment effect:** Participants asked for clarity regarding the durability of treatment effect assumed in the model given the lack of long-term published data. It was emphasized that this assumption was tested extensively in sensitivity and scenario analyses.

- **Anticipated cost of sonpiretigene:** Participants were surprised by the anticipated cost of sonpiretigene (which at the time of the draft report was based on the placeholder price of $875,000 for treating both eyes). It was clarified that the anticipated placeholder price was based on the presumption that pricing will be similar to that of voretigene neparvovec (Luxturna®).

- **Annual medical costs**: Participants reflected that the annual medical costs included in the model seemed high. It was clarified that annual medical costs are the sum of medical costs related and unrelated to retinitis pigmentosa.

- **Interpretation of the cost-effectiveness results:** Participants expressed enthusiasm for the results of the cost-effectiveness analysis which suggested that sonpiretigene was found to offer improvements in quality of life and level of visual functioning compared to usual care. Participants also reinforced the importance of the treatment's ability to halt or slow progression in vision loss. The inclusion of years with visual functioning better than counting fingers and years with light perception were highlighted as an opportunity to feature the impact of treatment on additional outcomes that are important to patients.

# E2. Model Inputs and Assumptions

## Model Assumptions

Our model includes several key assumptions stated below.

### Table E2.1. Key Model Assumptions

| Assumption | Rationale |
|---|---|
| **Treatment effectiveness of sonpiretigene was modeled based on a composite endpoint of best corrected visual acuity (BCVA), multi-luminance Y-mobility testing, and the multi-luminance shape discrimination test at week 52 (year one).** | The primary outcome of the RESTORE trial was the change in visual acuity based on the LogMAR scale at 52 weeks. Due to the limitations of the LogMAR scale in detecting changes in visual function at severe levels of vision loss, we supplemented the results of the BCVA score with the results of the secondary outcomes, the multi-luminance mobility test and the multi-luminance shape discrimination test at 52 weeks, to inform our determination of treatment effectiveness at 52 weeks. (see "Model Inputs" below). |
| **We used pooled data from the high and low dose arms for sonpiretigene in the RESTORE trial to inform our assessment of the treatment effect.** | Based on individual patient-level data provided by the manufacturer and publicly available data, outcomes appeared similar between high and low dose arms for sonpiretigene. |
| **Treatment effectiveness of sonpiretigene was assumed to last for five years, followed by progressive decline in visual functioning over another five years at which point (year 10) treated patients returned to the vision level of untreated patients.** | There are limited data from the RESTORE trial to inform assumptions about the long-term durability of treatment for sonpiretigene and we heard concerns from clinical experts about anticipated durability. Data from the RESTORE trial suggests possible maintenance of treatment effects for up to 100 weeks and clinical experts suggested that five to seven years was a reasonable expectation of durability. We conducted scenario analyses to assess the impact of alternative assumptions for treatment durability. |
| **Untreated patients and treated patients who returned to the vision level of untreated patients (at year 10) were assumed to experience an exponential decline in visual functioning.** | There are limited data from the RESTORE trial to inform assumptions about progression in visual functioning for untreated patients or treated patients for whom the full treatment effect has been lost. We heard that progression is typically most rapid in the early stages of vision loss suggesting that an exponential function was reasonable. Literature-based estimates for the rate of progression in visual functioning and clinical expert opinion resulted in a realistic estimate for the percentage of patients reaching a state of no light perception over the model time horizon. |

| Assumption | Rationale |
|---|---|
| **Patients receiving sonpiretigene in the model were assumed to receive a one-time intravitreal injection in one eye with the lowest visual acuity.** | Patients receiving sonpiretigene in the RESTORE trial received a one-time intravitreal injection in only one eye. We heard that, in practice, patients are likely to receive treatment in both eyes; however, there is no evidence to inform what impact this might have on patient outcomes. We also heard from clinical experts that patients receiving treatment in only one eye may experience treatment effects in the untreated eye; however, the extent of impact is unclear. |
| **Patients with retinitis pigmentosa were assumed to be at the same risk of death as the general United States (US) population. No deaths occurred in year one of the model.** | There is no evidence to suggest that the risk of death would vary across advanced levels of vision loss or to suggest mortality impacts from treatment with sonpiretigene; there were no deaths over 100 weeks in the RESTORE trial. In the absence of a differential effect on mortality and in the absence of direct evidence in advanced retinitis pigmentosa demonstrating an increased risk of mortality, we modeled patients as having a similar risk of death to the general population as an assumption favorable to sonpiretigene since it maximizes the life expectancy during which patients experience treatment benefits. |
| **No serious adverse events associated with sonpiretigene or usual care were modeled. We assumed that mild to moderate inflammation associated with the injection site was managed with prophylactic steroids.** | There is no evidence from the RESTORE trial that sonpiretigene is associated with serious adverse events. Mild to moderate inflammation associated with the injection site has been reported and is typically managed with prophylactic low-dose steroids. |
| **Non-intervention medical costs remained the same across all health states in the model.** | Based on input from the patient community and as observed in the literature, medical visits and diagnostics related to retinitis pigmentosa are not expected to change as patients move between states of visual functioning. |

Table E2.1 Abbreviations - BCVA: best corrected visual acuity, LogMAR: logarithmic minimum angle of resolution, US: United States

## Model Inputs

### *Clinical Inputs*

Key clinical inputs include response to treatment, durability of treatment, and progression in visual functioning over the model time horizon based on data from key clinical trials, a review of the published literature, and conversations with the retinitis pigmentosa community.

### *Clinical Probabilities and Response to Treatment*

At baseline, we categorized patients receiving sonpiretigene or usual care into one of the five levels of functioning described in the model schematic (Figure E1.1). The baseline distribution was informed by individual patient-level data provided by the manufacturer that classified patients as having visual function as better than counting fingers, counting fingers, hand motion, light perception, and no light perception (Table E2.2). These data allowed us to differentiate between very severe levels of visual function at baseline (LogMAR >2.25) and identify changes in visual functioning at Week 52 that otherwise may not be captured using the LogMAR scores alone. Patients with unknown classifications at baseline were assumed to have the average LogMAR score of the trial population (LogMAR 2.21) and were assigned to a health state of hand motion. We used the same baseline distribution of patients across health states for sonpiretigene and usual care based on a weighted average of patients included in the RESTORE trial.[35,47]

**Table E2.2. Baseline Health State Classification**

| Health State | Sonpiretigene Isteparvovec, % | Usual Care, % | Source and Notes |
|---|---|---|---|
| **Better than Counting Fingers** | 0% | | RESTORE trial |
| **Counting Fingers** | 4% | | Manufacturer Data on File[47] |
| **Hand Motion** | 38% | | |
| **Light Perception** | 50% | | |
| **No Light Perception** | 8% | | |

Response to treatment was determined based on data from the RESTORE trial at Week 52 and was used to model patient transitions at year one following treatment. One patient in the sham control group had a major protocol deviation and was removed from the analysis. We assumed that all patients survived up to the end of year one of the model based on data from RESTORE trial where no deaths occurred. Patient transitions were informed by individual patient-level data provided by the manufacturer that showed results for each patient on the primary and secondary outcomes of best corrected visual acuity (BCVA), multi-luminance Y-mobility testing, and the multi-luminance shape discrimination test. Any patient who experienced improvement in at least two of the three measures, or at least one measure when one or two of the other measures was at the ceiling, moved at least one health state. Among those who improved, if the BCVA was one of the two or three measures that improved, and the score suggested the patient experienced an improvement of more than one health state – for example, a move from light perception to counting fingers or a move from light perception to better than counting fingers, a two or three-health state improvement, respectively, was modeled. If improvements were only seen on the multi-luminance mobility test and the multi-luminance shape discrimination test at 52 weeks, only one health state improvement was modeled. Similarly, patients who experienced worsening in at least two of the three measures transitioned to a worse health state following the same rule as described for patients who improved. The remaining patients stayed in the same health state. Patients at the

floor of a measure were assumed to have experienced no further worsening on that measure. Response to treatment was explored in scenario analyses.

To further smooth the data given the small sample size, the counting fingers and hand motion transitions and the light perception and no light perception transitions were combined and applied to both health states conditional on the number of patients within each starting state. For example, if 50% of patients in light perception stayed in light perception at week 52, and 100% of patients in no light perception stayed in no light perception at week 52, the percentage of patients staying in their starting state for light perception and no light perception would be 75% assuming that two patients started in each of those states. Likewise, if the remaining 50% of patients in no light perception move up one state to light perception, and 0% patients in light perception move up one state to hand motion, the percentage of patients moving up one state for light perception and no light perception would be 25%. These health state transitions were applied to the revised baseline starting distributions and were meant to help prevent the impact of a single patient driving the results. These health state transitions were applied to the revised baseline starting distributions and were meant to help prevent the impact of a single patient driving the results.

Patient transition probabilities at year one are shown in Table E2.3 and were half-cycle corrected in the model to assume that transitions occurred on average halfway through each cycle of the model. This was based on data from the RESTORE trial showing gradual visual improvement between baseline and week 52. Health state classifications using the BCVA (LogMAR) were defined as: better than counting fingers (1.4 to <1.8), counting fingers (1.8 to <2.1), hand motion (2.1 to <2.6), light perception (2.6 to <2.9), and no light perception (3.0 to 4.5).[50]

**Table E2.3. Patient Transition Probabilities at Week 52 (Model Year 1)**

| Health State* | Better Than Counting Fingers | Counting Fingers | Hand Motion | Light Perception | No Light Perception |
|---|---|---|---|---|---|
| **Sonpiretigene Isteparvovec** | | | | | |
| **Better than Counting Fingers** | 0% | 0% | 0% | 0% | 0% |
| **Counting Fingers** | 4% | 0% | 0% | 0% | 0% |
| **Hand Motion** | 27% | 11% | 0% | 0% | 0% |
| **Light Perception** | 9% | 5% | 9% | 27% | 0% |
| **No Light Perception** | 0% | 1% | 1% | 1% | 4% |
| **Usual Care** | | | | | |
| **Better than Counting Fingers** | 0% | 0% | 0% | 0% | 0% |
| **Counting Fingers** | 2% | 1% | 1% | 0% | 0% |
| **Hand Motion** | 0% | 19% | 10% | 10% | 0% |
| **Light Perception** | 0% | 13% | 0% | 38% | 0% |
| **No Light Perception** | 0% | 0% | 2% | 0% | 6% |

Table E2.3 Note: Transition probabilities in the table represent the percentage of patients who moved from the starting state (table row) to the ending state (table column) by the end of Year 1 of the model.
Table E2.3 Footnote - * Health state classifications based on BCVA (LogMAR) were defined as: better than counting fingers (1.4 to <1.8), counting fingers (1.8 to <2.1), hand motion (2.1 to <2.6), light perception (2.6 to <2.9), and no light perception (3.0 to 4.5).

### *Durability of Treatment Effect*

Based on data from the RESTORE trial at week 100 that suggested there were no meaningful longer-term changes in BCVA for the intervention or usual care arm, we assumed that patients remained in their year one health state to the end of the second cycle (year two) of the model.[45]

Patients receiving sonpiretigene remained at that same level of visual function until model year five followed by progressive loss in visual functioning over another five years. At the end of model year 10, we assumed that patients receiving sonpiretigene will have returned to the vision level of untreated patients and would subsequently progress at the same rate as the usual care arm. In the absence of data for sonpiretigene after 100 weeks, and with input from clinical experts suggesting that five to seven years was a reasonable expectation of durability, five years of stability in visual functioning followed by progressive loss in visual functioning over another five years was thought to be a realistic assumption. Although prior cost-effectiveness models for voretigene neparvovec modeled a 10-year maintenance of treatment effect,[25] the differences between sonpiretigene and voretigene neparvovec in the underlying mechanism by which they exert their effect limit the confidence we have in extrapolating this evidence to our review of sonpiretigene. Treatment durability assumptions were tested in sensitivity and scenario analyses.

***Progression in Visual Functioning***

*Usual Care*

For patients in the usual care arm, after year two, patients experienced a progressive decline in visual functioning in line with the natural history of disease over their lifetime. There are limited data available to understand the natural history of disease for patients with advanced retinitis pigmentosa, and as such, progressive decline in visual functioning was informed by the literature and by clinical expert input. The percentage of patients likely to have further vision loss and the rate of this vision loss is expected to vary according to stage of visual functioning, so we defined the rate of decline separately for each health state in our model. This information was used to model the progressive decline in visual functioning for usual care after two years.

To achieve a realistic estimate for the percentage of patients reaching a state of no light perception, we assumed that patients progressed at half of the rate of decline suggested by the literature. The rate of decline in visual functioning per year was reported to range from 3.5% to 8.2% in a systematic review of natural history data for RPGR-Associated X-linked retinitis pigmentosa.[56] We selected the low end of the range (3.5%) given that X-linked retinitis pigmentosa is expected to be associated with more rapid progression compared to other forms of retinitis pigmentosa and multiplied the rate by 0.5. This rate of decline (1.75% annually) resulted in a more realistic estimate for the percentage of patients that are anticipated to reach a state of no light perception over their lifetime that aligned with clinical expert opinion and the published literature.[4] The 1.75% annual rate of decline was operationalized in the model as an increase in LogMAR of 1.75% per year and converted to decimal form. The decimal form of the LogMAR score was used to simulate the natural history of disease by creating an exponential function to track visual functioning decline over time. The exponential function was used to determine the annual transition probabilities associated with moving to more progressive health states over time.

**Table E2.4. Progression in Visual Functioning Status**

| Health State (Assumed LogMAR*) | Average Years to Progression to Next State† | Source |
|---|---|---|
| **Better than Counting Fingers (1.6)** | 10 | Schulze-Bonsel et al. 2006[51], Lam et al 2024,[56] and calculation assuming a decline in visual functioning of 1.75% annually. |
| **Counting Fingers (1.95)** | 12 | |
| **Hand Motion (2.35)** | 12 | |
| **Light Perception (2.75)** | 29 | |
| **No Light Perception (3.75)** | N/A‡ | |

Table E2.4 Abbreviations - LogMAR: logarithmic minimum angle of resolution, N/A: not applicable
Table E2.4 Footnotes - * Patients in each health state were defined as having a LogMAR calculated as the midpoint of the range of LogMAR reported in the literature[51]: better than counting fingers (1.4 to <1.8), counting fingers (1.8 to <2.1), hand motion (2.1 to <2.6), light perception (2.6 to <2.9), and no light perception (3.0 to 4.5). † Calculated using a 1.75% annual rate of decline applied to a starting LogMAR score of 1.6 (better than counting fingers) and ending at a LogMAR score of 2.5 (hand motion) and fitting an exponential function to the decimal form of the LogMAR scores (y=0.02684e-0.07980x) where y is equal to the decimal form of the LogMAR score and x is equal to time in years. ‡ No light perception represents the most progressed form of vision loss in the model, therefore further progression in visual functioning is not applicable to this health state.

*Sonpiretigene*

For patients in the intervention arm, after year ten, patients receiving sonpiretigene were assumed to have returned to the level of visual functioning of untreated patients and to then experience a progressive decline in visual functioning in line with the natural history of disease over their lifetime (Table E2.4). We assumed that at year ten of the model, the distribution of patients across each health state in the intervention arm will match as close as possible to that of the usual care arm. We carried out this analysis by calibrating year five to ten annual transition probabilities using the percentage of patients in the hand motion health state of the usual care arm as the calibration target for the base case and all scenario analyses.

### *Summary of Health State Transitions Over Model Time Horizon*

**Table E2.5 Summary of the Health State Assignment and Transitions Over Time for Sonpiretigene and Usual Care**

| | | Health State Assignment and Transitions Over Time | | | | |
|---|---|---|---|---|---|---|
| **Intervention** | **Baseline (Year 0)** | **Year 0-1** | **Year 1-2** | **Year 2-5** | **Year 5-10** | **Year 10+** |
| **Sonpiretigene** | Health state distribution based on the RESTORE trial (Table E2.2) | Health state distribution based on the RESTORE trial (Table E2.3) | Maintain health state | Maintain health state | Gradual progression to match health state distribution of usual care | Gradual progression to the next health state based on years reported in Table E2.4. |
| **Usual Care** | | | | Gradual progression to the next health state based on years reported in Table E2.4. | | |

Table E2.5 Note: Starting in Year 2, patients may transition to the death health state; A half-cycle correction was applied to adjust for the timing of health state transitions to occur in the middle of a model cycle.

### *Discontinuation*

No treatment discontinuation was modeled for either the intervention or comparator. Given that treatment with sonpiretigene is a single administration, all patients in the intervention arm were assumed to receive a full course of treatment.

### *Mortality*

No additional risk of mortality was applied for patients with severe retinitis pigmentosa with advanced vision loss, nor did it vary by treatment or usual care. We assumed that no deaths occurred in the first model cycle (up to one year). For each subsequent model cycle, the risk of death was based on general population age- and sex-adjusted mortality using United States (US) life tables.[57]

### *Adverse Events*

No patients receiving sonpiretigene in the RESTORE trial experienced a serious adverse event.[35] Mild to moderate inflammation has been noted and it is now standard of care to provide prophylactic low dose steroids to prevent occurrence. The regimen consists of 1 mg/kg/day (Days -3 to 3), 0.5 mg/kg/day (Days 4 to 10), 0.25 mg/kg/day (Day 11 to 17) totaling $2.78/kg based on the median WAC of all relevant generic prednisone 1 mg options.[35] We included the cost of prophylactic steroid use for all patients receiving sonpiretigene in the model.

### *Heterogeneity and Subgroups*

There may be differences in treatment efficacy based on the extent of vision loss, form of retinitis pigmentosa, inheritance pattern, and genetic mutation; however, we did not conduct any subpopulation analysis due to lack of data and the small size of the available sample.

### *Health State Utilities*

Health state utilities were derived from a utility elicitation study for retinitis pigmentosa from the UK.[58] The study used time-trade off methodology to value five health states associated with level of visual functioning by conducting interviews with 110 individuals from the UK general population. Health states included moderate impairment, severe impairment, profound impairment, counting fingers, and hand motion/no light perception, and were defined according to visual acuity and visual field functioning. Health state definitions were consistent with those used in other utility elicitation studies.[84,85] We assumed that the better than counting fingers health state in the model was aligned with the "profound impairment" health state defined in O'Brien 2023 which had a utility of 0.5.[58] We adjusted the 0.5 utility to 0.54 to reflect findings from the RESTORE trial that approximately 25% of patients who reached the better than counting fingers health state achieved a level of visual functioning of "severe impairment" which was associated with a utility value of 0.65. Because the health states collapsed the most severe levels of visual functioning (hand motion to no light perception), we used data from Brown 2001[59] to inform the health state utility value for the no light perception health state. Additionally, given that we heard during focused sessions with patients that there is likely to be meaningful differences in quality of life between patients who experience hand motion compared to being able to perceive light, we adjusted the utility value for hand motion to be the midpoint of the utility values reported for counting fingers and light perception (0.38). Health state utilities are reported in Table E2.6. During the focused sessions with patients we also heard that there is variability in health-related quality of life experienced for each level of visual functioning. We, therefore, conducted a scenario analysis to assess the impact of having no differences in health-related quality of life at levels of visual functioning between counting fingers, hand motion, and light perception.

**Table E2.6 Health State Utilities**

| Health State | Value (SD) | Source |
|---|---|---|
| **Better than Counting Fingers** | 0.54 (0.26) | O'Brien 2023[58] and calculation using a weighted average of profound impairment (0.50) and severe impairment (0.65) |
| **Counting Fingers** | 0.43 (0.28) | O'Brien 2023[58] |
| **Hand Motion** | 0.38 (0.27) | O'Brien 2023,[58] calculation for adjustment using mid-point of counting fingers and light perception |
| **Light Perception** | 0.33 (0.26) | O'Brien 2023[58] |
| **No Light Perception** | 0.26 (0.08) | Brown 2001[59] |

Table E2.6 Abbreviations - NA: not available, SD: standard deviation

### *Caregiver Disutilities*

We did not hear from the patient and clinical community that carers of patients with retinitis pigmentosa experience meaningful impacts on their quality of life. As such, we did not include caregiver disutilities in the modified societal perspective analysis.

### *Drug Utilization*

Table E2.7 outlines the treatment regimen and recommended dosage that was used to model drug utilization and associated costs.

**Table E2.7. Treatment Regimen Recommended Dosage**

| | Sonpiretigene Isteparvovec | Source |
|---|---|---|
| **Generic Name** | Sonpiretigene isteparvovec (MCO-010) | RESTORE trial[35] |
| **Manufacturer** | Nanoscope Therapeutics | |
| **Route of Administration** | One-time intravitreal injection into one eye with the lowest visual acuity | |
| **Dosing** | Low dose ($0.9x10^{11}$ gc/eye) and high dose ($1.2x10^{11}$ gc/eye) | |

Table E2.7 Abbreviation: gc/eye: genome copies per eye

### *Economic Inputs*

All costs used in the model were updated to 2023 US dollars.

### *Drug Costs*

A Biologics License Application for sonpiretigene is expected to be submitted to the FDA in Q1 2025, and as such, a price is not yet known. We used a placeholder price of US $437,500 for treatment in one eye, which is half of the midpoint of the range predicted by IPD Analytics ($750,000 to $1,000,000) which assumes treatment of both eyes.[60] This estimate was based on the presumption that pricing will be similar to that of voretigene neparvovec (Luxturna®). Because sonpiretigene will be provider administered, we included a mark-up to the placeholder price. The mark-up is typically calculated as 6% of the placeholder price; however, if additional information becomes available regarding an estimate of the percentage of patients anticipated to be treated in the commercial market and the associated mark-up, this 6% markup is subject to change. If a price becomes known during the course of the ICER review, we will update our estimate accordingly.

No additional costs were assumed for usual care given that no therapeutic alternative is available. Relevant costs are assumed to be captured in other health care costs, indirect costs, and direct non-medical costs for the intervention and comparator arms.

### *Administration Costs*

We included an administration cost of $112.18 (CPT Code: 67028, injection eye drug) for sonpiretigene.[61]

### *Monitoring Costs*

No additional costs for monitoring were included in the model.

### *Other Health Care Costs*

For non-intervention medical costs, we used estimates from Frick et al. 2012 inflated to 2023 dollars.[7] Frick et al. 2012 was a cross-sectional, retrospective claims analysis of patients (n=2,990) diagnosed with retinitis pigmentosa in the US using MarketScan Commercial and Medicare Supplemental Databases.[7] Costs were inclusive of related and unrelated medical costs and include inpatient, outpatient, and pharmacy costs. The same health state costs were used for the intervention and usual care groups. Additionally, based on input from the focused sessions with patients and as observed in the literature, medical visits and diagnostics related to retinitis pigmentosa are not expected to change as visual function changes, and as such, these costs did not vary by health state. Detailed cost inputs are outlined in Table E2.8.

**Table E2.8. Annual Non-Intervention Medical Costs**

| Medical Cost Type | Annual Mean Costs (SD) | Notes |
|---|---|---|
| **Inpatient Costs** | $3,274 ($19,890) | Frick 2012,[7] inflated to 2023 US dollars and patient input. |
| **Outpatient Costs** | $13,654 ($27,033) | |
| **Pharmacy Costs** | $2,398 ($5,645) | |
| **Total Annual Non-Intervention Medical costs** | $19,327 ($48,935) | |

Table E2.8 Abbreviation - SD: standard deviation

### *Direct Non-Medical Costs and Indirect Costs*

For the modified societal perspective analysis, we used estimates for direct non-medical costs and indirect costs based on a study by Brown et al. 2016[62] inflated to 2023 dollars. Brown et al. 2016 estimated direct non-medical costs and indirect costs for patients diagnosed with age-related macular degeneration (n=200) in the US.[62] Costs were analyzed overall and according to four sub-cohorts based on level of visual acuity. We used costs from the most severe sub-cohort (i.e., vision reported as 20/800 to no light perception) for our analysis. Direct non-medical costs included caregiver costs, transportation costs, and residence costs for assisted living for any unpaid caregiver time, estimated in the study to be 60.8% of overall direct non-medical costs ($48,241 in 2023 US dollars). We also included the cost of low vision services and devices ($4,258 in 2023 US dollars), and lost productivity costs include costs for paid and unpaid labor costs for patients ($12,587 in 2023 US dollars) (2009 US dollars reported in Table 8 of Brown et al. 2016).

During the focused sessions with patients, we heard that direct non-medical costs and indirect costs have not changed substantially as their vision changed. The one exception was for non-medical low vision services and devices where we heard that progression from better than counting fingers to counting fingers or worse did represent a significant shift in the level of supportive devices needed for patients to maintain their level of independence (for example, moving beyond only needing magnifiers and glasses). Therefore, for health states of counting fingers, hand motion, light perception, and no light perception, we used the values reported for the most severe sub-cohort, however, for the better than counting fingers health state, we adjusted the cost of low vision services and devices to reflect the lower anticipated cost for this level of visual functioning. We have captured this difference as a 27% lower cost for low vision services and devices (i.e., $4,258 x (1-0.27)=$3,108 in 2023 US dollars) for patients with visual functioning better than counting fingers compared to patients in a health state of counting fingers or worse. This 27% reduction was used as a proxy based on the lower end of the 95% confidence interval for the overall societal costs reported in Brown 2016, Table 3.[62] We assumed that this would represent the approximate costs for the portion of patients with higher levels of visual functioning within the most severe sub-cohort. The total direct non-medical costs and indirect costs that were included in the modified societal perspective analysis are reported in Table E2.9 below.

**Table E2.9. Direct Non-Medical Costs and Indirect Costs**

| Cost Type and Health State | Annual Mean Costs (SD) | Notes |
|---|---|---|
| **Direct Non-Medical Costs** | | |
| **Better than Counting Fingers** | $51,349 (NA) | Brown et al 2016,[62], patient input, and calculation (inclusive of caregiver costs, transportation costs, and residence costs for assisted living for any unpaid caregiver time [$48,241] as well as low vision services and devices [$3,108]) inflated to 2023 dollars. |
| **Counting Fingers** | $52,499 (NA) | Brown et al 2016,[62], patient input, and calculation (inclusive of caregiver costs, transportation costs, and residence costs for assisted living for any unpaid caregiver time [$48,241] as well as low vision services and devices [$4,258]) inflated to 2023 dollars. |
| **Hand Motion** | | |
| **Light Perception** | | |
| **No Light Perception** | | |
| **Indirect Costs** | | |
| **Better than Counting Fingers** | $12,587 ($21,977) | Brown et al 2016[62] (inclusive of paid and unpaid labor costs) and patient input, inflated to 2023 dollars. |
| **Counting Fingers** | | |
| **Hand Motion** | | |
| **Light Perception** | | |
| **No Light Perception** | | |

Table E2.9 Abbreviations - NA: not available, SD: standard deviation

# E3. Results

### Table E3.1. Undiscounted Results for the Base-Case for Sonpiretigene Compared to Usual Care (Health Outcomes)

| Treatment | QALYs | evLYs | Life Years | Years in Better than Counting Fingers | Years with Light Perception |
|---|---|---|---|---|---|
| **Sonpiretigene** | 9.96 | 9.96 | 26.19 | 4.22 | 21.90 |
| **Usual Care** | 9.00 | 9.00 | 26.19 | 0.24 | 20.95 |
| **Incremental** | 0.96 | 0.96 | 0.00 | 3.98 | 0.95 |

Table E3.1 Abbreviations - evLYs: equal value of life years gained, QALY: quality-adjusted life year

Table E3.1 Note - Incremental values may not match individual intervention values due to rounding.

### Table E3.2. Undiscounted Results for the Base-Case for Sonpiretigene Compared to Usual Care (Costs)

| Treatment | Anticipated Intervention Acquisition Costs* | Intervention-Related Costs† | Non-Intervention Costs | Total Costs* |
|---|---|---|---|---|
| **Sonpiretigene** | $437,500 | $26,604 | $506,100 | $970,200 |
| **Usual Care** | $0 | $0 | $506,100 | $506,100 |
| **Incremental** | $437,500 | $26,604 | $0 | $464,100 |

Table E3.2 Abbreviations - evLYs: equal value of life years gained, QALY: quality-adjusted life year

Table E3.2 Footnotes - * Based on placeholder price. †Intervention-related costs include markup costs, administration costs, and adverse event prevention costs.

Table E3.2 Note: Incremental values may not match individual intervention values due to rounding. Intervention acquisition costs and intervention-related costs were also undiscounted in the base case because they occurred in the first year of the model.

# E4. Sensitivity Analyses

We conducted one-way sensitivity analyses to identify the impact of parameter uncertainty and key drivers of model outcomes. We varied input parameters using available measures of parameter uncertainty (i.e., standard errors) or reasonable ranges to evaluate changes in incremental cost-effectiveness ratios. Probabilistic sensitivity analyses were also performed by jointly varying all model parameters over 1,000 simulations, then calculating 95% credible range estimates for each model outcome based on the results. Results of the one-way and probabilistic sensitivity analyses are reported in Tables E4.1 and E4.2.

**Table E4.1. Tornado Diagram Inputs and Results for Sonpiretigene vs. Usual Care**

| | Lower Incremental CE Ratio | Upper Incremental CE Ratio | Lower Input* | Upper Input* |
|---|---|---|---|---|
| **Utility for Better than Counting Fingers** | $434,240 | $1,262,642 | 0.43 | 0.65 |
| **Average Age** | $519,073 | $1,238,554 | 23.00 | 83.00 |
| **Years of Maintenance of Treatment Effect for Sonpiretigene** | $344,150 | $781,062 | 2.00 | 20.00 |
| **Utility for Light Perception** | $524,412 | $841,773 | 0.26 | 0.40 |
| **Utility for No Light Perception** | $620,533 | $674,150 | 0.21 | 0.31 |
| **Annual Non-Intervention Medical Costs for Better than Counting Fingers** | $628,851 | $663,612 | $15,462 | $23,192 |
| **Annual Non-Intervention Medical Costs for Light Perception** | $632,627 | $659,836 | $15,462 | $23,192 |
| **Utility for Hand Motion** | $641,180 | $651,363 | 0.30 | 0.46 |
| **Utility for Counting Fingers** | $641,993 | $650,526 | 0.34 | 0.52 |
| **Annual Non-Intervention Medical Costs for No Light Perception** | $643,153 | $649,310 | $15,462 | $23,192 |

Table E4.1 Abbreviations - CE: cost-effectiveness

Table E4.1 Footnote: * Note lower input may reflect either upper or lower ICER value depending on the direction that the input has on the incremental CE ratio output.

**Figure E4.1. Results of Probabilistic Sensitivity Analysis for Sonpiretigene versus Usual Care**

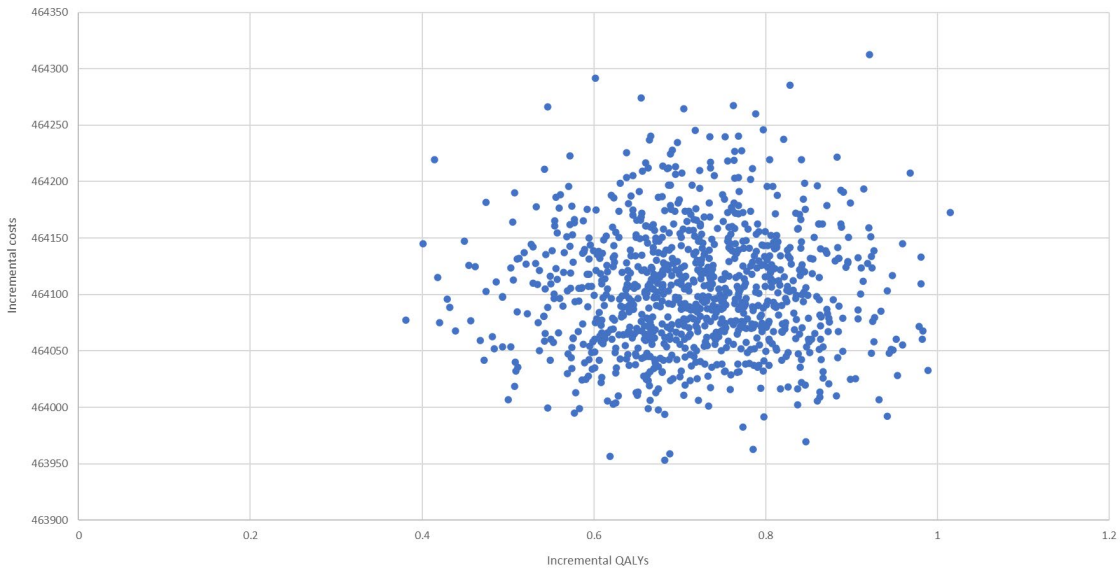



Figure E4.1 Abbreviations - QALY: quality-adjusted life year

Figure E4.1 Note: Due to the nature of the data, the short-term treatment efficacy (Year 1 and 2) for sonpiretigene was not included in the deterministic or probabilistic sensitivity analysis and as such, the impact on the uncertainty of the results is not reflected in the scatterplot. Alternative assumptions for short-term treatment efficacy were explored in scenario analyses.

**Table E4.2. Results of Probabilistic Sensitivity Analysis for Sonpiretigene versus Usual Care**

| | Sonpiretigene | Usual Care | Incremental |
|---|---|---|---|
| **Mean Costs** | $806,310 | $342,206 | $464,104 |
| **Mean QALYs** | 6.90 (6.52, 7.31) | 6.19 (5.75, 6.65) | 0.72 (0.51, 0.92) |
| **Mean evLYs** | 6.90 (6.52, 7.31) | 6.19 (5.75, 6.65) | 0.72 (0.51, 0.92) |
| **Incremental CE Ratio** | | | $ 648,328 |

Table E4.2 Abbreviations - CE: cost-effectiveness, evLYs: equal-value life year, QALY: quality-adjusted life year

# E5. Scenario Analyses

The following scenario analyses were conducted:

1. Modified societal perspective that includes patient and caregiver productivity costs, transportation costs, and low-visions services and devices.

2. In line with the adaptation of the ICER Value Framework for treatments of high-impact "single and short-term therapies" we conducted an A) optimistic and B) conservative benefit scenario analysis which varied assumptions regarding the benefit of treatment. Details of the optimistic and conservative benefit scenarios we included are outlined in Table E5.1 below.

**Table E5.1. Assumptions for Treatment Effect and Durability in the Optimistic and Conservative Benefit Scenarios**

| | Treatment Effect | Treatment Durability |
|---|---|---|
| **Base Case** | Improvement on at least 2/3 outcome measures* | Stability to 5 years |
| **Optimistic Benefit Scenario** | Improvement on at least 2/3 outcome measures* | Stability to 10 years |
| **Conservative Benefit Scenario** | Improvement on at least 3/3 outcome measures* | Stability to 5 years |

Table E5.1 Footnotes - * Includes information submitted by the manufacturer that includes outcomes for best corrected visual acuity, multi-luminance Y-mobility testing, and the multi-luminance shape discrimination test.

3. In addition to assessing the impact of treatment effect and durability on model results within the optimistic and conservative benefit scenario above, we conducted a threshold analysis for duration of effect in patients receiving short-term benefit that would be needed to achieve cost-effectiveness thresholds.

4. Lifetime durability of treatment effect.

5. Unadjusted health-state utility values for hand motion and light perception.

6. Alternative health state utility values valued by patients with blindness from retinal detachment (Brown et al. 2001).

7. Alternative baseline health state classifications based on LogMAR instead of manufacturer provided classifications.

**Table E5.2 Health State Utilities for Scenario Analysis 4 and 5**

| Health State | Base Case Value (SD) | Scenario Analysis 5 Value (SD) | Scenario Analysis 6 Value (SD) |
|---|---|---|---|
| **Better than Counting Fingers** | 0.54 (0.26) | 0.54 (0.26) | 0.65 (0.21) |
| **Counting Fingers** | 0.43 (0.28) | 0.43 (0.28) | 0.47 (0.29) |
| **Hand Motion** | 0.38 (0.27) | 0.33 (0.26) | 0.47 (0.29) |
| **Light Perception** | 0.33 (0.26) | 0.33 (0.26) | 0.47 (0.29) |
| **No Light Perception** | 0.26 (0.08) | 0.26 (0.08) | 0.26 (0.08) |

Table E5.2 Abbreviations - NA: not available, SD: standard deviation

Although we assessed sonpiretigene under an adaptation of the ICER Value Framework for treatments of high-impact "single and short-term therapies" (SSTs), we did not conduct a shared savings scenario analysis or a $150,000 cost offset cap scenario because the comparator for this model is usual care, which may include low vision aids, mobility training and support, and vision-related rehabilitation, rather than a high-cost pharmaceutical and/or other advanced health services. As such, the use of gene therapy in this case does not generate substantial cost savings.

## Scenario Analysis 1: Modified Societal Perspective

**Table E5.3 Results for Sonpiretigene Compared to Usual Care (Health Outcomes)**

| Treatment | QALYs | evLYs | Life Years | Years in Better than Counting Fingers | Years with Light Perception |
|---|---|---|---|---|---|
| **Sonpiretigene** | 6.88 | 6.88 | 17.70 | 3.41 | 15.24 |
| **Usual Care** | 6.17 | 6.17 | 17.70 | 0.18 | 14.67 |
| **Incremental** | 0.72 | 0.72 | 0 | 3.23 | 0.57 |

Table E5.3 Abbreviations - evLYs: equal value of life years gained, QALY: quality-adjusted life year

Table E5.3 Note: Incremental values may not match individual intervention values due to rounding.

### Table E5.4. Results for Sonpiretigene Compared to Usual Care (Costs)

| Treatment | Anticipated Intervention Acquisition Costs* | Intervention-related Costs† | Non-Intervention Costs | Total Costs* |
|---|---|---|---|---|
| **Sonpiretigene** | $437,500 | $26,600 | $1,148,000 | $1,612,400 |
| **Usual Care** | $0 | $0 | $1,152,000 | $1,152,000 |
| **Incremental** | $437,500 | $26,600 | $(4,000) | $460,000 |

Table E5.4 Abbreviations - evLYs: equal value of life years gained, QALY: quality-adjusted life year

Table E5.4 Footnotes - * Based on placeholder price. †Intervention-related costs include markup costs, administration costs, and adverse event prevention costs.

Table E5.4 Note - Incremental values may not match individual intervention values due to rounding.

## Scenario Analysis 2A: Optimistic Benefit Scenario Analysis

### Table E5.5 Results for Sonpiretigene Compared to Usual Care (Health Outcomes)

| Treatment | QALYs | evLYs | Life Years | Years in Better than Counting Fingers | Years with Light Perception |
|---|---|---|---|---|---|
| **Sonpiretigene** | 7.13 | 7.13 | 17.70 | 4.5 | 15.81 |
| **Usual Care** | 6.17 | 6.17 | 17.70 | 0.18 | 14.67 |
| **Incremental** | 0.96 | 0.96 | 0.00 | 4.32 | 1.14 |

Table E5.5 Abbreviations - evLYs: equal value of life years gained, QALY: quality-adjusted life year

Table E5.5 Note: Incremental values may not match individual intervention values due to rounding.

### Table E5.6. Results for Sonpiretigene Compared to Usual Care (Costs)

| Treatment | Anticipated Intervention Acquisition Costs* | Intervention-Related Costs† | Non-Intervention Costs | Total Costs* |
|---|---|---|---|---|
| **Sonpiretigene** | $437,500 | $26,600 | $342,000 | $806,300 |
| **Usual Care** | $0 | $0 | $342,000 | $342,000 |
| **Incremental** | $437,500 | $26,600 | $0 | $464,000 |

Table E5.6 Abbreviations - evLYs: equal value of life years gained, QALY: quality-adjusted life year

Table E5.6 Footnotes - * Based on placeholder price. † Intervention-related costs include markup costs, administration costs, and adverse event prevention costs.

Note: Incremental values may not match individual intervention values due to rounding.

## Scenario Analysis 2B: Conservative Benefit Scenario Analysis

### Table E5.7 Results for Sonpiretigene Compared to Usual Care (Health Outcomes)

| Treatment | QALYs | evLYs | Life Years | Years in Better than Counting Fingers | Years with Light Perception |
|---|---|---|---|---|---|
| **Sonpiretigene** | 6.54 | 6.54 | 17.70 | 2.47 | 14.56 |
| **Usual Care** | 5.84 | 5.84 | 17.70 | 0 | 14.02 |
| **Incremental** | 0.7 | 0.70 | 0.00 | 2.47 | 0.54 |

Table E5.7 Abbreviations - evLYs: equal value of life years gained, QALY: quality-adjusted life year

Table E5.7 Note - Incremental values may not match individual intervention values due to rounding.

### Table E5.8. Results for Sonpiretigene Compared to Usual Care (Costs)

| Treatment | Anticipated Intervention Acquisition Costs* | Intervention-related Costs† | Non-Intervention Costs | Total Costs* |
|---|---|---|---|---|
| **Sonpiretigene** | $437,500 | $26,600 | $342,000 | $806,300 |
| **Usual Care** | $0 | $0 | $342,000 | $342,000 |
| **Incremental** | $437,500 | $26,600 | $0 | $464,000 |

Table E5.8 Abbreviations - evLYs: equal value of life years gained, QALY: quality-adjusted life year

Table E5.8 Footnotes - *Based on placeholder price. †Intervention-related costs include markup costs, administration costs, and adverse event prevention costs.

Table E5.8 Note - Incremental values may not match individual intervention values due to rounding.

## Scenario Analysis 3: Threshold Analysis for Durability of Treatment Benefit

Even if we assumed a lifetime duration of effect for sonpiretigene, the results were substantially above commonly used cost-effectiveness thresholds.

## Scenario Analysis 4: Lifetime Durability of Treatment Effect

### Table E5.9 Results for Sonpiretigene Compared to Usual Care (Health Outcomes)

| Treatment | QALYs | evLYs | Life Years | Years in Better than Counting Fingers | Years with Light Perception |
|---|---|---|---|---|---|
| **Sonpiretigene** | 7.66 | 7.66 | 17.70 | 6.95 | 16.94 |
| **Usual Care** | 6.17 | 6.17 | 17.70 | 0.18 | 14.67 |
| **Incremental** | 1.49 | 1.49 | 0.00 | 6.77 | 2.27 |

Table E5.9 Abbreviations - evLYs: equal value of life years gained, QALY: quality-adjusted life year

Table E5.9 Note - Incremental values may not match individual intervention values due to rounding.

### Table E5.10 Results for Sonpiretigene Compared to Usual Care (Costs)

| Treatment | Anticipated Intervention Acquisition Costs* | Intervention-Related Costs† | Non-Intervention Costs | Total Costs* |
|---|---|---|---|---|
| **Sonpiretigene** | $437,500 | $26,600 | $342,000 | $806,300 |
| **Usual Care** | $0 | $0 | $342,000 | $342,000 |
| **Incremental** | $437,500 | $26,600 | $0 | $464,000 |

Table E5.10 Abbreviations - evLYs: equal value of life years gained, QALY: quality-adjusted life year

Table E5.10 Footnotes - * Based on placeholder price. † Intervention-related costs include markup costs, administration costs, and adverse event prevention costs.

Table E5.10 Note: Incremental values may not match individual intervention values due to rounding.

## Scenario Analysis 5: Unadjusted Health-State Utility Values

### Table E5.11 Results for Sonpiretigene Compared to Usual Care (Health Outcomes)

| Treatment | QALYs | evLYs | Life Years | Years in Better than Counting Fingers | Years with Light Perception |
|---|---|---|---|---|---|
| **Sonpiretigene** | 6.74 | 6.74 | 17.70 | 3.41 | 15.24 |
| **Usual Care** | 6.02 | 6.02 | 17.70 | 0.18 | 14.67 |
| **Incremental** | 0.72 | 0.72 | 0.00 | 3.23 | 0.57 |

Table E5.11 Abbreviations - evLYs: equal value of life years gained, QALY: quality-adjusted life year

Table E5.11 Note - Incremental values may not match individual intervention values due to rounding.

### Table E5.12 Results for Sonpiretigene Compared to Usual Care (Costs)

| Treatment | Anticipated Intervention Acquisition Costs* | Intervention-Related Costs† | Non-Intervention Costs | Total Costs* |
|---|---|---|---|---|
| **Sonpiretigene** | $437,500 | $26,600 | $342,000 | $806,300 |
| **Usual Care** | $0 | $0 | $342,000 | $342,000 |
| **Incremental** | $437,500 | $26,600 | $0 | $464,000 |

Table E5.12 Abbreviations - evLYs: equal value of life years gained, QALY: quality-adjusted life year

Table E5.12 Footnotes - *Based on placeholder price. †Intervention-related costs include markup costs, administration costs, and adverse event prevention costs.

Table E5.12 Note: Incremental values may not match individual intervention values due to rounding.

## Scenario Analysis 6: Alternative Health-State Utility Values

### Table E5.13 Results for Sonpiretigene Compared to Usual Care (Health Outcomes)

| Treatment | | QALYs | evLYs | Life Years | Years in Better than Counting Fingers | Years with Light Perception |
|---|---|---|---|---|---|---|
| **Sonpiretigene** | 8.42 | 8.42 | 17.70 | | 3.41 | 15.24 |
| **Usual Care** | 7.72 | | 7.72 | 17.70 | 0.18 | 14.67 |
| **Incremental** | 0.7 | | 0.70 | 0.00 | 3.23 | 0.57 |

Table E5.13 Abbreviations - evLYs: equal value of life years gained, QALY: quality-adjusted life year

Table E5.13 Note - Incremental values may not match individual intervention values due to rounding.

### Table E5.14 Results for Sonpiretigene Compared to Usual Care (Costs)

| Treatment | Anticipated Intervention Acquisition Costs* | Intervention-Related Costs† | Non-Intervention Costs | Total Costs* |
|---|---|---|---|---|
| **Sonpiretigene** | $437,500 | $26,600 | $342,000 | $806,300 |
| **Usual Care** | $0 | $0 | $342,000 | $342,000 |
| **Incremental** | $437,500 | $26,600 | $0 | $464,000 |

Table E5.14 Abbreviations - evLYs: equal value of life years gained, QALY: quality-adjusted life year

Table E5.14 Footnotes - * Based on placeholder price. † Intervention-related costs include markup costs, administration costs, and adverse event prevention costs.

Table E5.14 Note - Incremental values may not match individual intervention values due to rounding.

## Scenario Analysis 7: Alternative Baseline Health State Classification

### Table E5.15 Results for Sonpiretigene Compared to Usual Care (Health Outcomes)

| Treatment | QALYs | evLYs | Life Years | Years in Better than Counting Fingers | Years with Light Perception |
|---|---|---|---|---|---|
| **Sonpiretigene** | 6.85 | 6.85 | 17.70 | 2.99 | 15.23 |
| **Usual Care** | 6.08 | 6.08 | 17.70 | 0.22 | 14.23 |
| **Incremental** | 0.77 | 0.77 | 0.00 | 2.77 | 1.01 |

Table E5.15 Abbreviations - evLYs: equal value of life years gained, QALY: quality-adjusted life year

Table E5.15 Note - Incremental values may not match individual intervention values due to rounding.

### Table E5.16 Results for Sonpiretigene Compared to Usual Care (Costs)

| Treatment | Anticipated Intervention Acquisition Costs* | Intervention-Related Costs† | Non-Intervention Costs | Total Costs* |
|---|---|---|---|---|
| **Sonpiretigene** | $437,500 | $26,600 | $342,000 | $806,300 |
| **Usual Care** | $0 | $0 | $342,000 | $342,000 |
| **Incremental** | $437,500 | $26,600 | $0 | $464,000 |

Table E5.16 Abbreviations - evLYs: equal value of life years gained, QALY: quality-adjusted life year

Table E5.16 Footnotes - * Based on placeholder price. † Intervention-related costs include markup costs, administration costs, and adverse event prevention costs.

Table E5.16 Note: Incremental values may not match individual intervention values due to rounding.

## Incremental Cost-Effectiveness Ratios for all Scenario Analyses

### Table E5.17. Incremental Cost-Effectiveness Ratios for the Base Case and All Scenario Analyses

| Cost per QALY Gained* | Cost per evLY Gained* | Cost per Additional Year in Better Than Counting Fingers* | Cost per Additional Year with Light Perception* |
|---|---|---|---|
| **Base Case** | | | |
| $646,000 | $646,000 | $144,000 | $811,000 |
| **Scenario 1: Modified Societal Perspective** | | | |
| $641,000 | $641,000 | $143,000 | $805,000 |
| **Scenario 2A: Optimistic Benefit** | | | |
| $481,000 | $481,000 | $108,000 | $406,000 |
| **Scenario 2B: Conservative Benefit** | | | |
| $664,000 | $664,000 | $188,000 | $859,000 |
| **Scenario 3: Threshold Analysis for Durability of Treatment** | | | |
| Results remained above commonly used cost-effectiveness thresholds regardless of assumptions for durability of treatment. | | | |
| **Scenario 4: Lifetime Durability of Treatment Effect** | | | |
| $312,000 | $312,000 | $69,000 | $204,000 |
| **Scenario 5: Unadjusted Utility Values** | | | |
| $643,000 | $643,000 | $144,000 | $811,000 |
| **Scenario 6: Alternative Utility Values** | | | |
| $662,000 | $662,000 | $144,000 | $811,000 |
| **Scenario 7: Alternative Baseline Health State Classification** | | | |
| $606,000 | $606,000 | $168,000 | $462,000 |

Table E5.17 Abbreviations - evLYs: equal value of life years gained, N/A: Not applicable, QALY: quality-adjusted life year

Table E5.17 Footnotes - * Based on placeholder price

Table E5.17 Note - Cost per life year gained is not applicable because there were no incremental differences in life years between sonpiretigene and usual care.

## E6. Heterogeneity and Subgroups

There may be differences in treatment efficacy based on extent of vision loss, form of retinitis pigmentosa, inheritance pattern, and genetic mutation; however, we did not conduct any subpopulation analysis due to lack of data and the small size of the available sample.

## E7. Model Validation

We used several approaches to validate the model. First, we discussed our draft model structure and assumptions with four members of the patient community to ensure their perspectives and experiences were reflected in our model analysis plan. Second, we provided the preliminary model structure, methods, and assumptions to manufacturers, patient groups, and clinical experts. Based on feedback from these groups, we refined data inputs used in the model, as needed. Third, we varied model input parameters to evaluate face validity of changes in results and performed model verification for model calculations using internal reviewers. As part of ICER's efforts in acknowledging modeling transparency, we also shared the model with the relevant manufacturer for external verification around the time of publishing the draft report. Lastly, we compared results to other cost-effectiveness models in this therapy area as described below.

### Prior Economic Models

There are no prior published models to assess the cost-effectiveness of sonpiretigene.

Prior published economic models of treatments for retinitis pigmentosa and related conditions include an ICER assessment of voretigene neparvovec, a gene therapy for *RPE65* mutation-associated retinal dystrophy in February 2018 and four additional assessments of voretigene neparvovec in other jurisdictions.[25,86-89] Other published economic models include assessments of artificial vision devices (e.g., the Argus II Retinal Prosthesis System) for retinitis pigmentosa.[90-92]

The methods and results of economic models assessing voretigene neparvovec are difficult to compare our model to because the target population for voretigene neparvovec are patients with less advanced stages of vision loss and patients are typically treated at a younger age. Consequently, the levels of visual functioning and associated quality of life and costs that patients spend the majority of time in for *RPE65* mutation-associated retinal dystrophy models are different than those considered for patients with advanced RP with severe vision loss.

Three models assessed the cost-effectiveness of artificial vision devices for RP. All analyses were Markov cohort models with time horizons ranging from 20 years to lifetime, conducted from a health care system perspective in Canada, Germany and the European Union. [90-92] Models varied in terms of the health states included in the model, but generally captured variations in levels of visual functioning with a consideration for the ability to perceive light or not. All models acknowledged

the uncertainty in assumptions for the durability of treatment effect due to limited clinical trial data. The methods used in our model aligned with the characteristics of prior RP models in terms of using a Markov cohort model over a lifetime time horizon, an annual cycle length, and health states defined by level of visual functioning. In addition to the treatment-specific differences in model, there were variations in terms of how the health states were defined, the associated utility values and costs used, and the durability of treatment effect assumed.

Compared to our model which found incremental QALYs of 0.72 for sonpiretigene compared to usual care, other models found incremental QALYs of 2.0,[90] 2.9,[91] and 2.6 for artificial vision devices compared to usual care.[92] In addition to the differences in treatment effects between sonpiretigene and artificial vision devices, these differences are likely also driven by including more favorable assumptions for treatment durability,[90,91] using higher utility values for the health states in the model,[90] modeling a younger population,[91,92] assuming a higher mortality for patients with RP,[92] and using a lower discount rate.[92] Given the differences in the interventions and associated costs, a comparison of the incremental costs and the incremental cost-effectiveness ratios between models was not deemed appropriate.

# F. Potential Budget Impact: Supplemental Information

## 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 potential budget impact analysis included the candidate populations eligible for treatment: patients with advanced retinitis pigmentosa and severe vision loss. To estimate the size of the potential candidate populations for treatment, we used inputs for the US population size, the prevalence of retinitis pigmentosa in the US (0.025%),[1] and the percentage of patients with retinitis pigmentosa with visual acuity in the range of "counting fingers or worse" (12%).[3] Applying these sources to the total projected US population averaged over the five years (346,449,218)[63] resulted in estimates of 10,393 eligible patients in the US over five years. For the purposes of this analysis, we assumed that 20% of these patients would initiate treatment each year over five years, or 2,079 patients per year.

ICER's methods for estimating potential budget impact are described in detail elsewhere and have recently been updated.[93,94] The intent of our revised approach to budgetary impact is to document the percentage of patients that could be treated at selected prices without crossing a budget impact threshold that is aligned with overall growth in the US economy.

Once estimates of budget impact are calculated, we compare 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 (Value Assessment Framework), 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.

For 2024-2025, therefore, the five-year annualized potential budget impact threshold that should trigger policy actions to manage access and affordability is calculated to total approximately $880 million per year for new drugs.

# G. Supplemental Policy Recommendations

## Payers

***Coverage Criteria: General***

ICER has previously described general criteria for fair coverage policies that should be considered as cornerstones of any drug coverage policy in the report: Cornerstones of "Fair" Drug Coverage: Appropriate Cost-Sharing and Utilization Management Policies for Pharmaceuticals.

***Drug-Specific Coverage Criteria: Sonpiretigene Isteparvovec***

A one-time, likely costly treatment, combined with uncertain durability, long-term safety, and the potential to adversely interfere with intact visual pathways in the presence of sufficient photoreceptors, may lead payers to develop prior authorization criteria.

None of these criteria, however, should undermine the tenets of fair access to which all patients have a fundamental right.[95] Further, given the expected high cost of this therapy, and the lack of alternative treatments for this condition, patient cost-sharing is not expected to be an appropriate aspect of any coverage policy. To explore the appropriate application of evidence to coverage policy, and to reflect the views of patient experts and clinicians on specific ways that payers might appropriately use coverage policy to manage resources prudently, we present the following perspectives on specific elements of coverage criteria for sonpiretigene.

***Coverage Criteria***

- **Age:** Age criteria should follow the trial, which enrolled adults with severe vision loss, who comprise most individuals with advanced RP. While this treatment is not appropriate for young children since it requires appropriate cortical development to process vision, payers should have efficient mechanisms for clinicians to seek coverage exceptions for patients with serious unmet need who are near the cutoff for the age necessary for coverage.

- **Clinical eligibility**: There was consensus among policy roundtable participants to follow the trial criteria for determining eligibility. Specifically, clinical experts strongly recommended the reliance on a clinically defined diagnosis of advanced RP with severe vision loss. They did not recommend genetic testing be performed since the treatment is mutation agnostic, and because approximately 40% of cases have no identifiable genetic cause. As such, experts recommended a clinical diagnosis of advanced RP. This would entail a history, dilated fundus examination, and imaging (optical coherence tomography) to confirm the presence of an intact retinal inner layer. Eligibility based on trial criteria would require a BCVA worse

than logarithmic minimum angle of resolution (LogMAR) 1.9 in the eye being considered for treatment, and a BCVA no better than LogMAR 1.6 in the contralateral eye. Given the potential for interference with the patient's intact visual system if administered at too early a stage, it would be reasonable for payers to require an attestation by a retinal specialist to confirm the diagnosis and eligibility prior to treatment.

- **Exclusion criteria**: It would be appropriate to follow the pivotal trial's criteria. Experts recommended that a clinical attestation alone would suffice for the exclusion of other mimickers of advanced RP, such as autoimmune disease or presence of ocular complications (i.e. cataracts).

- **Dose:** It would be reasonable for health plans to consider covering treatment of only a single eye, consistent with the available clinical trial evidence. If both eyes are considered for treatment, it would be reasonable to expect the same pricing from the manufacturer as the price for treating one eye in the absence of trial evidence demonstrating added benefit.

- **Provider restrictions**: While some payers may consider a requirement that sonpiretigene be administered by retinal specialists or at a center of excellence for retinal care, clinical experts agreed that most ophthalmologists could administer this treatment in their office given the intravitreal route of injection. While implementing provider restrictions is likely not clinically necessary, payers may prefer to approve therapy by general ophthalmologists only if done so in consultation with a retinal specialist to attest the diagnosis and eligibility for treatment. If payers choose to restrict administration to a retinal specialist or a center of excellence, then it would be incumbent on the health plans to work with the manufacturer to also cover costs related to travel for patients, including transportation and lodging.

***Step Therapy***

There are no other treatments that could be considered a first-line treatment prior to eligibility.

# H. Public Comments

This section includes summaries of the public comments prepared for the New England CEPAC Public Meeting on April 11th, 2025. This summary was prepared by those who delivered a public comment at the meeting. One speaker did not submit a summary of their public comments.

A video recording of all comments can be found here, beginning at minute 00:53. Conflict of interest disclosures are included at the bottom of each statement for each speaker who is not employed by a pharmaceutical manufacturer.

**Samarendra Mohanty, PhD**
**Co-Founder and President, Nanoscope Therapeutics**

Thank you for providing the opportunity to participate in this public meeting. I am Samar Mohanty, President and Chief Scientific Officer for Nanoscope Therapeutics. I am passionate about turning my eye disease research over the past twenty years into innovative therapies, such as *sonpiretigene isteparvovec*, to serve the unmet needs of retinitis pigmentosa (RP) patients with severe vision loss.

RP is a debilitating and life-changing disease caused by hundreds of mutations. The degeneration of vision significantly affects patients' ability to perform routine daily activities and achieve independence, and thus substantially impairs patients' and caregivers' quality of life. This patient population is currently limited to supportive care such as low-vision rehabilitation, including the use of visual aids and guide dogs. Patients and advocacy groups have reiterated that slowing or even halting vision loss is a meaningful treatment goal. A substantial unmet need exists, and currently, no active interventions are available. *Sonpiretigene isteparvovec* is the first transformative and breakthrough mutation-agnostic gene therapy under development for RP patients with severe vision loss. Further, *sonpiretigene* eliminates the need for complex, time-consuming, and costly diagnostics, removing a key access barrier for patients and providers.

In addition to its unique mechanism of action of targeting mature neurons to provide durable efficacy, *sonpiretigene* is administered via a single intravitreal injection, a method that retina specialists are highly familiar with. This procedure can be performed in-office, eliminating the need for hospitalization or surgery. The combination of in-office treatment and a simplified clinical diagnosis process establishes a fundamentally accessible treatment paradigm for *sonpiretigene* intervention that is convenient, efficacious, and safe.

Rare diseases, such as RP with severe vision loss, affect small and widely dispersed patient populations. This makes it challenging to recruit patients, design effective clinical trials, and generate robust data needed for regulatory and commercial launch. RESTORE is a randomized,

sham-controlled trial designed to generate robust evidence of the efficacy and safety of *sonpiretigene* for RP patients with severe vision loss.

*Sonpiretigene* intervention in RESTORE adequately demonstrated meaningful improvements in best-corrected visual acuity at Week 52 and beyond, and is currently being incorporated into a planned BLA submission to the FDA in 2025. The primary endpoint—the change from baseline in best-corrected visual acuity (BCVA) of the study eye at Week 52—was met in *sonpiretigene* cohorts, where mean improvements from baseline were statistically greater than those observed in the sham-control group. At Week 52, 39% of participants treated with *sonpiretigene* and 11% of sham-controlled participants had improvements that reached the threshold of clinical significance of at least 0.3 LogMAR—the equivalent of 3 lines on an eye chart—compared to baseline. At Week 76, 56% of participants treated with *sonpiretigene* improved by at least 3 lines, while 33% had achieved greater than 6 lines of improvement.

Measuring vision improvements by a single outcome in this heterogeneous patient population may be inadequate as different mutations impact central and peripheral vision to varying degrees, making clinical trial design challenging. As ICER noted in the evidence report, in addition to BCVA, *sonpiretigene* demonstrated improvements in vision-guided mobility and shape discrimination that are important for patients' activities of daily living. Analysis of composite measures involving improvement in best-corrected visual acuity or shape discrimination from the RESTORE trial showed that 72% of participants in the combined *sonpiretigene*-treated cohort displayed clinically important improvement. The combined use of all three threshold measures--response in at least one measure of the BCVA, mobility, and shape discrimination--resulted in a 100% response rate of the *sonpiretigene*-treated participants.

Currently, we have 35 patients across multiple clinical trials treated with *sonpiretigene*, and the mechanism of action and clinical data suggest a favorable safety profile and continued durability of the treatment effect. The published preclinical evidence shows a lack of the injected *sonpiretigene* vector in the brain regions. The observed durability of the treatment effect is consistent with the existing nonclinical evidence from large and small animal model data.

Finally, Nanoscope Therapeutics has an interest in ensuring ICER's advanced RP review demonstrates the comprehensive value of *sonpiretigene* to ensure full patient access to therapy. *Sonpiretigene* offers a new beginning for RP patients and caregivers, and empowers retina specialists to not only offer hope but address a long-term unmet need. I truly appreciate the significant amount of work that ICER and its associates have conducted and believe that *sonpiretigene* provides significant and durable value to patients, providers, payers, and the RP community. Thank you.

**Griffin Pinkow**

**CEO and Founder, Foreseeable Future Foundation**

My name is Griffin Pinkow. I'm the Founder and CEO of Foreseeable Future Foundation. I was diagnosed with RP at age 11, and now I'm 32. We actually found out about my vision through sports. I was always an athlete. When my family and I decided to move to California, I made a travel baseball team. One day during practice, I was in the outfield, and I couldn't see the ball off the bat. I'd be running one way. The ball would be going another way.

After going to doctors all over the country, I was finally diagnosed with RP. No one in my family has the condition. No one has vision issues. I always say I was the lucky one in the family being diagnosed with RP. Through my years in middle school and high school. My vision started to deteriorate even more at that time, though I didn't want to use a cane. I didn't want a guide dog. I didn't want to feel like I was different than my peers.

In high school when my vision started to deteriorate even more, my teachers at the time didn't know how to include me in class or make sure I had the assistive technology to be successful. Luckily, my junior year of high school we moved and there really was a huge pivot for me in my life. I had a guidance counselor named Kevin Perone, who said, “Wait a second, you don't have adaptive equipment. You don't have extra time. If you have all the tools, you can be successful. We're going to help you.”

My grades went from F's and D's to A's and B's, and knowing that I could do it, and I had the tools to be successful. I needed the help and the support system, and Kevin was able to help me make sure I had that. Luckily, after graduating from Cold Spring Harbor, I attended Susquehanna University. On campus we did awareness events. We did a dining in the dark. We did a walk to bring awareness, and it really helped make my professional and personal experience at Susquehanna that much better, and got my peers, my teachers, everyone to understand what it was going through, because that was a challenge, and people were mean, or they didn't believe me, or whatever the case may be, so through those things at Susquehanna, I realized that I could really make an impact and help educate and bring awareness to what I'm going through and what other people are going through in my situation. I never really let it stop me from doing anything I wanted to do in life.

My senior year of college I ran the New York City, Marathon. After that I ran Chicago, Boston, and Philadelphia, and realized that I could do something and make a difference. So, after a couple of years from graduation, I started Foreseeable Future Foundation. Our mission is to help the visually impaired and blind live more fulfilling lives through sports and recreation. We do that through a few different programs, and help thousands of kids, young adults and veterans all over the country, making sure that those young individuals and kids have the opportunity to pursue whatever they want, whether it's sports and recreation or just feeling like they're part of a community.

If someone told me that I was going to do all these crazy things and have an organization, Foreseeable Future to give back and help these younger individuals make sure that there's a community for them, and that we can help them. I don't know if I would believe the person if they said I would do those things. Also, getting a cane and a guide dog which I have. Now, Lester, he's incredible. He's a black lab, I think if I embrace those things a little earlier in life, it would probably make personally dealing with the visual impairment a little easier, and getting everyone to understand what I was going through a little bit easier as well, and making them more comfortable.

Finding a cure is the most important thing for myself or anyone dealing with a visual impairment or blindness or RP. At the same time bringing awareness and education to the community, saying that you can do anything. You can be a marathon runner. You can be a tandem cyclist. If you want to be a scientist, you can be a scientist. Adaptations and things that we need to be successful in any role or position, they're available. They can help and show the community that that we're like anyone else.

***No conflicts of interest to disclose.***

# I. Conflict of Interest Disclosures

Tables I1 through I3 contain conflict of interest (COI) disclosures for all participants at the April 11th public meeting of sonpiretigene isteparvovec for advanced retinitis pigmentosa.

**Table I1. ICER Staff and Consultants and COI Disclosures**

| ICER Staff and Consultants* | |
|---|---|
| **Madeline Booth, BA,** Program Manager, ICER | **Sarah Emond, MPP,** President and CEO, ICER |
| **Grace Ham, MSc,** Senior Program and Events Coordinator, ICER | **Belén Herce-Hagiwara, BA**, Research Assistant, ICER |
| **Woojung Lee, PharmD, PhD,** Associate Director of Health Economics and Decision Modeling, ICER | **Anil Makam, MD, MAS**, Assistant Professor of Medicine, University of California San Francisco |
| **Avery McKenna, BS,** Research Lead, ICER | **Marie Phillips, BA**, Health Economics Research Assistant, ICER |
| **Marina Richardson, PhD, MSc,** Associate Director of HTA Methods and Health Economics, ICER | **David Rind, MD, MSc,** Chief Medical Officer, ICER |
| **Sol Sanchez, BS**, Research Assistant, ICER | |

* No conflicts of interest to disclose, defined as individual health care stock ownership (including anyone in the member's household) in any company with a product under study, including comparators, at the meeting in excess of $10,000 during the previous year, or any health care consultancy income from the manufacturer of the product or comparators being evaluated.

**Table I2. New England CEPAC Panel Member Participants and COI Disclosures**

| New England CEPAC Member | Conflict of Interest |
|---|---|
| **Austin Frakt, PhD,** Principal Research Scientist, Harvard T.H. Chan School of Public Health | No conflicts to disclose. |
| **Megan Golden, JD,** Co-Founder and CEO, Mission: Cure | No conflicts to disclose. |
| **Rebecca Kirch, JD, EVP**, Policy and Programs, National Patient Advocate Foundation | No conflicts to disclose. |
| **Stephen Kogut, PhD,** Professor, University of RI | No conflicts to disclose. |
| **Donald M. Kreis, MS, JD**, Consumer Advocate, New Hampshire Office of the Consumer Advocate | No conflicts to disclose. |
| **Julie Kueppers, PhD**, NP, Clinical VP, Alera Group | No conflicts to disclose. |
| **Tara Lavelle, PhD,** Assistant Professor, Tufts Medical Center | No conflicts to disclose. |
| **Aaron Mitchell, MD, MPH**, Assistant Attending, Memorial Sloan Kettering Cancer Center | No conflicts to disclose. |
| **Brian O'Sullivan, MD**, Professor of Pediatrics, Geisel School of Medicine | No conflicts to disclose. |
| **Jo Porter, MPH**, Chief Strategy Officer, NH Center for Justice and Equity | No conflicts to disclose. |
| **Rishi Wadhera, MD, MPP, MPhil,** Associate Professor, Harvard Medical School | No conflicts to disclose. |
| **Jason Wasfy, MD, MPhil,** Associate Professor, Harvard Medical School | No conflicts to disclose. |

**Table I3. Policy Roundtable Participants and COI Disclosures**

| Policy Roundtable Participant | Conflict of Interest |
|---|---|
| **Todd Durham, PhD**, Senior Vice President, Clinical and Outcomes Research, Foundation Fighting Blindness | Foundation Fighting Blindness (FFB) has received sponsorships from various health care companies, including Nanoscope Therapeutics, for their scientific conferences, accounting for<25% of their funding. A member of Dr. Durham's household works in the life sciences industry and receives ≥25% of income from the industry. Additionally, the RD Fund, a venture philanthropy subsidiary of the FFB, has equity interests in several life science companies in its portfolio. |
| **Julie Grutzmacher, MSW, MPH**, Director of Patient Advocacy and Population Health Initiatives, Prevent Blindness | Prevent Blindness receives >25% of funding from health care companies, including Nanoscope Therapeutics. |
| **Hemant Hora, MD, FACP,** Vice President, Medical Affairs, Senior Medical Director, Point32Health | Dr. Hora is a full-time employee of Point32Health. |
| **Vinit B. Mahajan, MD, PhD,** Professor of Ophthalmology, Stanford University | Dr. Mahajan has received funds from Nanoscope Therapeutics, Chigenovo, and Kerna Labs. |
| **Samarendra Mohanty, PhD,** Co-Founder and President, Nanoscope Therapeutics | Dr. Mohanty is a full-time employee of Nanoscope Therapeutics. |
| **Lindsay Rippelmeyer, PharmD**, Senior Director, Supply Chain Finance, Express Scripts by Evernorth | Dr. Rippelmeyer is a full-time employee of Express Scripts. |
| **Stephen Russell, MD,** Professor of Ophthalmology, University of Iowa | Dr. Russell has received funds from Spark Therapeutics, ProQR Therapeutics, Novartis, Digital Diagnostics (IDx, LLC) and has stock ownership in Digital Diagnostics (IDx, LLC). |