Sonpiretigene Isteparvovec for Advanced Retinitis Pigmentosa: Effectiveness and Value

Draft Evidence Report

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Prepared for

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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.

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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.

The economic models used in ICER reports are intended to compare the clinical outcomes, expected costs, and cost-effectiveness of different care pathways for broad groups of patients. Model results therefore represent average findings across patients and should not be presumed to represent the clinical or cost outcomes for any specific patient. In addition, data inputs to ICER models often come from clinical trials; patients in these trials may differ in real-world practice settings.

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*.*

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List of Acronyms and Abbreviations Used in this Report

%	Percent
AAV-2	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 healthcare 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 each 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.[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 (e.g., ≥0.3 LogMAR improvement) improvements 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 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 implausible (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 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 Ratings

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 $875,000 per treatment. 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 small improvements in QALYs (0.36 discounted incremental QALYs) and higher costs ($927,900 incremental costs) compared to usual care. At the placeholder price, assuming that both eyes are 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. Even when halving the placeholder price under an assumption of only one eye being treated and simultaneously assuming a lifetime durability of treatment effect, sonpiretigene remained above commonly used cost-effectiveness thresholds.

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 healthcare 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]

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]

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, 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 each 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.[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 quarter of 2025.[15]

Table 1.1. Interventions 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 each eye	TBD

Table 1.1 Abbreviations - AAV2: adeno-associated virus serotype 2, MCO-010: multi-characteristic opsin, TBD: to be determined

2. Patient and Caregiver Perspectives

ICER engaged with patients, representatives from the Foundation Fighting Blindness and from Prevent Blindness, and clinical experts to understand the perspectives from 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. 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 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, how blindness would affect their personal safety, and described considerable psychosocial and emotional distress.[29]

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.

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.[33]

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 healthcare system with added out-of-pocket costs. A new treatment that preserves or restores vision would have potential health equity gains for those with less financial means, digital literacy, and social network of family, friends, and the community to 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.[33]

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).[34] This was supplemented by data on harms from the Phase I/II SAD dose-escalation trial (see Supplement Section D2).[35-37] Data sources include both publicly available conferences presentations and data submitted confidentially by the manufacturer of sonpiretigene.[34,38-46]

Study Design

RESTORE was a Phase IIb/III trial that evaluated the efficacy and safety of sonpiretigene in 27 adults with advanced RP with severe vision loss. Participants were randomized 1:1:1 to either low-dose sonpiretigene, high-dose sonpiretigene, or a sham procedure in a single eye.[47] 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 had participated in a 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.[47]

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 injection to limit inflammation at the injection site. Sham participants received matching placebo. Participants were followed 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).[48]

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.[45]

Key Outcomes

The primary endpoint of the trial was the change from baseline in BCVA 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.[47] 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 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 and begins at 0 LogMAR (20/20 vision). A greater LogMAR indicates worse vision. While the FrACT is a validated tool to measure visual acuity in people who have low vision, it is unable to capture LogMAR scores below 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).[49] 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.[44,49-51]

Table 3.2. LogMAR and Visual Stage Mapping[49]

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 to account for persons with low vision by creating a simpler obstacle course.[52] 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 for each illumination level was defined as correct identification of the lighted panel three times (see Table 3.3 for scoring).[45]

Table 3.3. Multi-Luminance Y-Mobility Test Scoring[45]

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 for each illumination level was defined as correct identification of the shapes three different times (see Table 3.4 for scoring).[45]

Table 3.4. Multi-Luminance Shape Discrimination Test Scoring[45]

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).[45] 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).[34,40]

Table 3.5. Baseline Characteristics of RESTORE Study Participants[39,45]

	Low-Dose Sonpiretigene (N=9)	High-Dose Sonpiretigene (N=9)	Combined Sonpiretigene (N=18)	Sham Control (N=9)
Age, years, mean (SD)	52.2 (16.2)	60.4 (13.3)	56.3 (15.0)	56.7 (10.9)
Female sex, n (%)	33.3	33.3	33.3	44.4
Race				
White, n (%)	7 (77.8)	9 (100)	16 (88.9)	9 (100)
Asian, n (%)	1 (11.1)	0	1 (5.6)	0
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)	NR	NR	2.2 (0.02)	2.2 (0.05)
MLYMT, mean score (SE)	NR	Redacted Data	1.2 (0.6)	1.0 (1.0)
MLSDT, mean score (SE)	NR	Redacted Data	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.[53] Instead, the demographic diversity of the RESTORE trial is described qualitatively in Supplement D1.

3.2. Results

Clinical Benefits

Best-Corrected Visual Acuity (BCVA)

Change from Baseline in BCVA

At week 52, the low- and high-dose sonpiretigene groups on average had clinically meaningful (≥0.3 LogMAR) and statistically significant improvement in LogMAR versus the sham group, respectively (see Table 3.6).[39] The combined sonpiretigene-treated participants had a mean LogMAR improvement of -0.34 (standard error of the mean [SEM]: 0.49) from baseline compared to -0.05 (SEM: 0.072) for sham participants (p=0.075).[34] 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[34,39]

BCVA Score	Low-Dose Sonpiretigene (N=9)	High-Dose Sonpiretigene (N=9)	Combined Sonpiretigene (N = 18)	Sham Control (N=9)
Mean Score (SEM) – Baseline	NR	NR	2.23 (0.02)	2.17 (0.05)
Mean Score (SEM) – Week 52; p-value vs. baseline	NR	NR	1.89 (0.12); p=0.011	2.07 (0.13); p=0.295
Mean Change from Baseline (SEM)*; p-value vs. sham	-0.38 (0.12); p=0.029	-0.34 (0.08); p=0.021	-0.34 (0.49); p=0.075	-0.05 (0.07)

Table 3.6 Abbreviations - BCVA: best corrected visual acuity, N: total number, NR: not reported, SEM: standard error of the mean

Table 3.6 Footnotes - *Calculated using a linear mixed effects model for repeated measures (MMRM)

At week 76, the eighteen 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).[43] However, 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

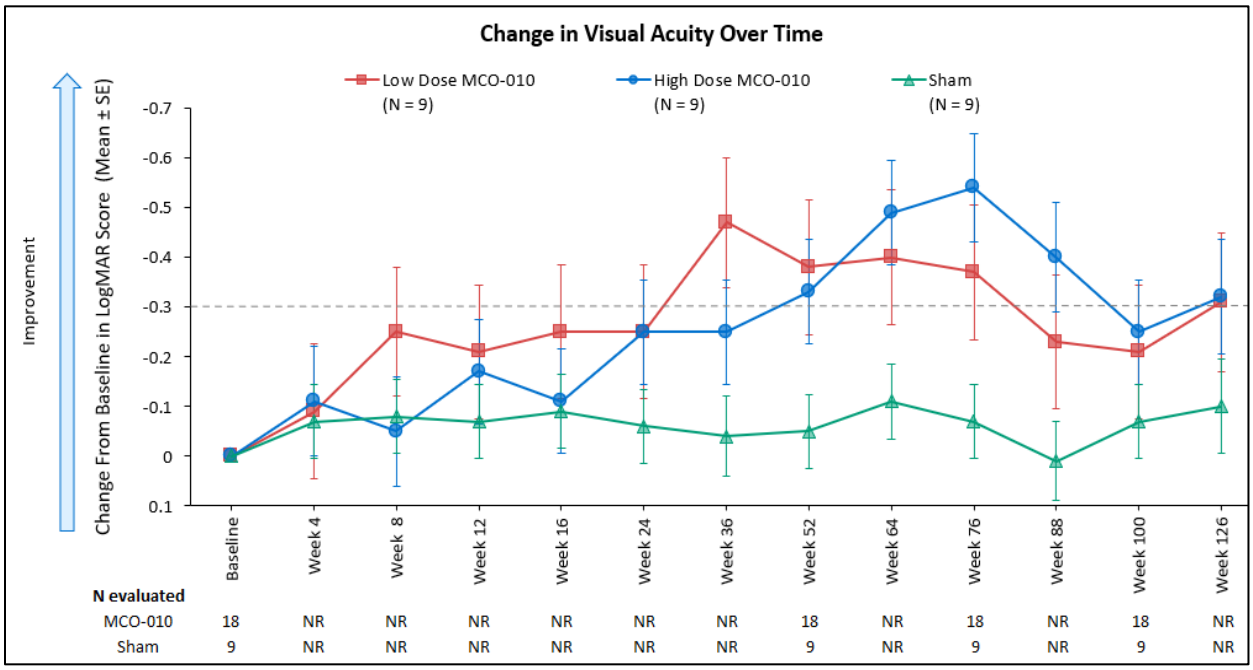


Figure 3.1 Abbreviations – LogMAR: logarithmic minimum angle of resolution, MCO-010: sonpiretigene isteparvovec, N: total number, NR: not reported, SE: standard error

Figure 3.1 Source: Data from a presentation by Monés 2024.[43] 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.[42]

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.[42] 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).[42] 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

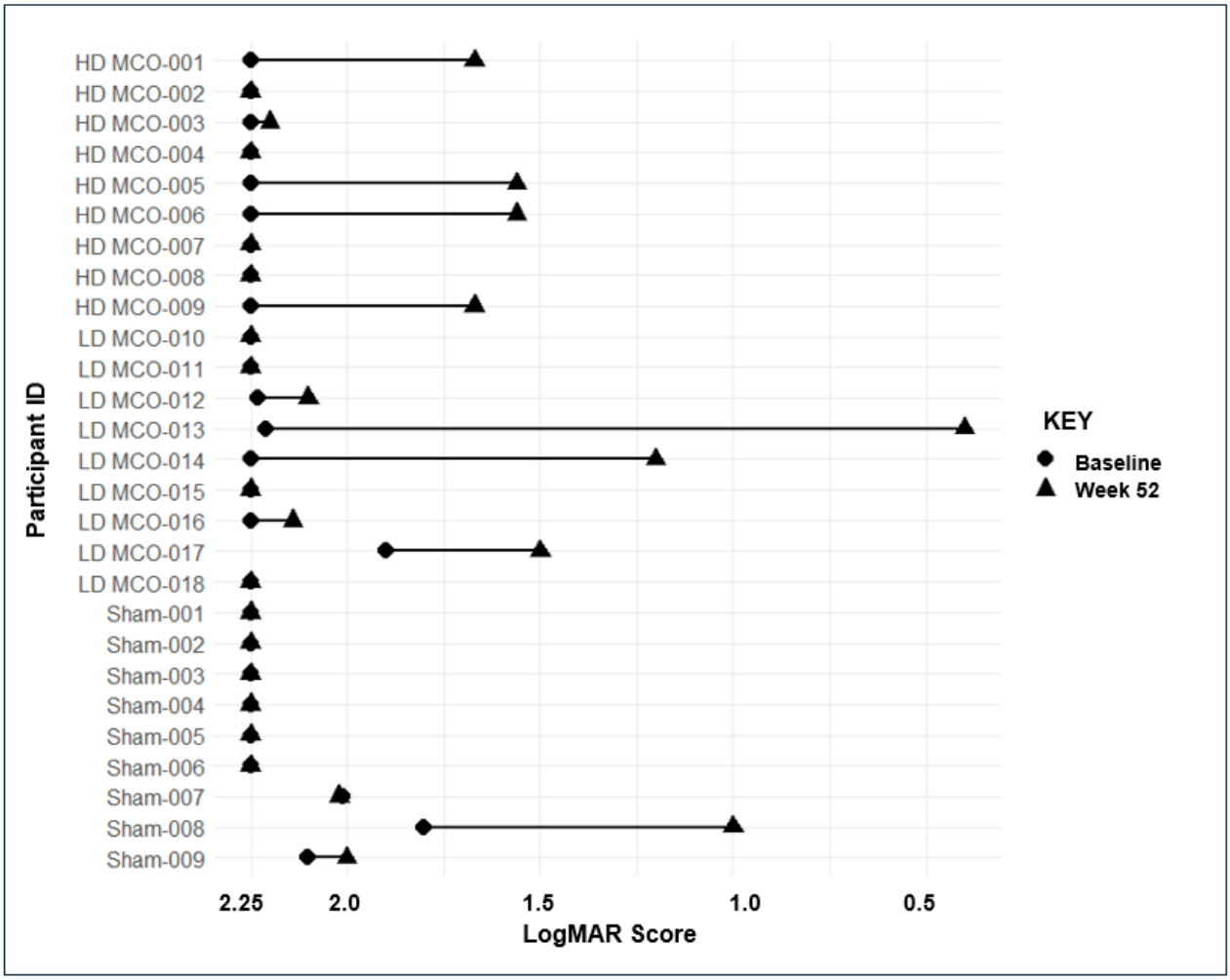


Figure 3.2 Abbreviations - HD: high-dose, LD: low-dose, LogMAR: logarithmic minimum angle of resolution, MCO: sonpiretigene isteparvovec
Figure 3.2 Footnote - * Major protocol deviation related to incorrect recording of BCVA
Source: Data from a presentation by Loewenstein 2024[42]

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 1.17 (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).[40] See Table 3.7. below.

Table 3.7. Mean Changes in Y-Mobility Test Scores[40]

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 (67%) participants in the combined sonpiretigene group achieved a clinically meaningful improvement of at least two light levels in the MLYMT assessment compared to three (33%) participants 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).[34] 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.[34] No participants had a worsened MYLMT score.

Table 3.8. MLYMT: Participants with Light Level Improvement Ranging from 0-6 Levels[34]

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).[40]

Table 3.9. Mean Changes in Shape Discrimination Test Scores[40]

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% vs. 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% vs. 11%; see Table 3.10). Seven sonpiretigene-treated participants (39%) and six sham-treated participants (67%) did not have any detectable improvement.[40]

Table 3.10. MLSDT: Participants with Light Level Improvement Ranging from 0-5 Levels[40]

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.[39] 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.[39] Only one sonpiretigene-treated participant was a responder in all three outcomes.

Table 3.11. Composite Outcomes: Responder Analysis at Week 52[39]

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%).[45] No participants treated with sonpiretigene experienced a serious adverse event.[45] 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%) received topical steroid therapy for intraocular inflammation at week 52.[40] 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).[43] 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.[44] 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.[35,36]

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 the reported efficacy may not be replicated in a larger clinical trial since positive treatment effects may be exaggerated with potential for false positives.[54] 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 implausible and may reflect measurement issues (e.g., LD MCO-013 in Figure 3.2 improved from the floor to 0.5 LogMAR, which is approximately 20/40 vision). 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 these 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.

- 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.

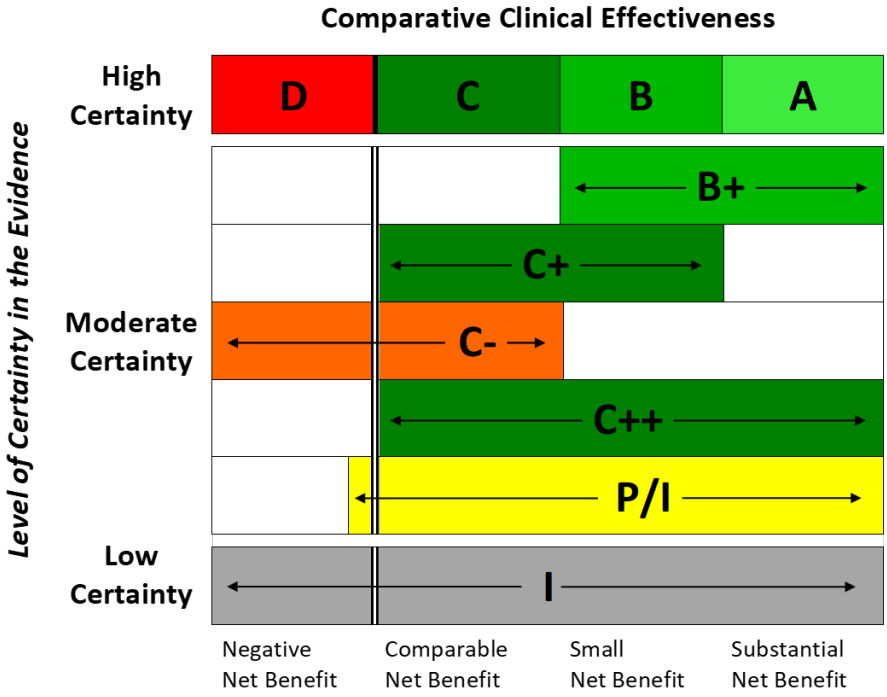
- There is some risk for unmasking with sham intravitreal injections, particularly if participants have experienced prior intravitreal injections. Assessment of masking adequacy was not measured in RESTORE. Additionally, we are uncertain whether there were adequate procedures in place to maintain allocation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

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 an intention-to-treat analysis, with 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 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 based on data from the RESTORE trial.[34,46] 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. 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

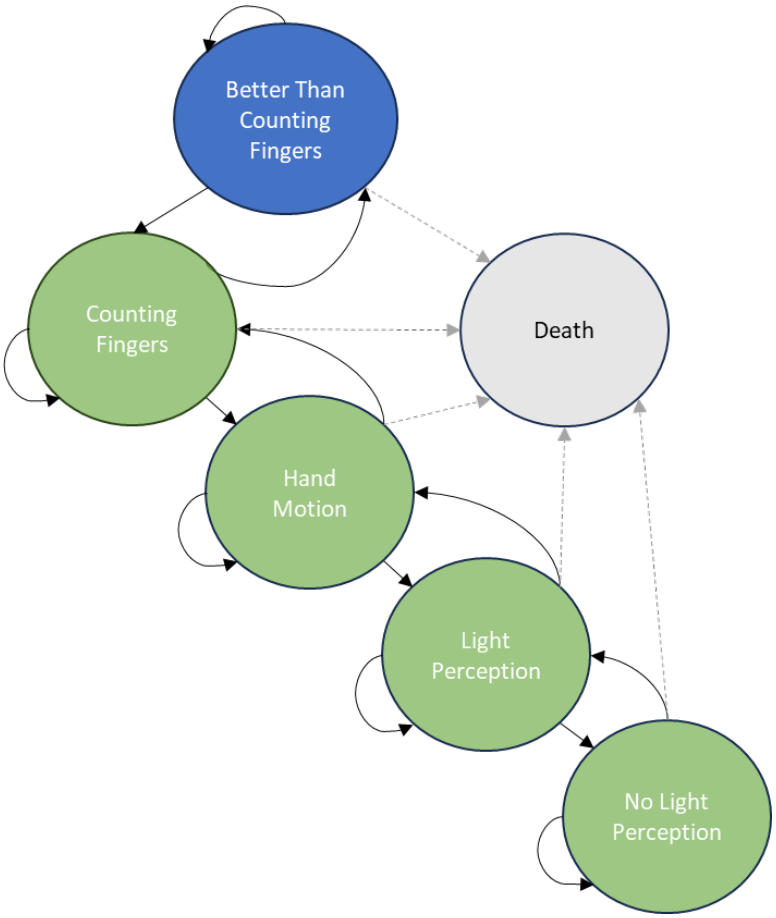


Figure 4.1 Notes: Movement of more than one health state may be possible in the model. These transitions are not depicted in the model schematic for simplicity. The model schematic depicts six health states including five health states defined by visual functioning (better than counting fingers, counting 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.

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 confidential 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.
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 both eyes.	Patients receiving sonpiretigene in the RESTORE trial received a one-time intravitreal injection in only one eye. We heard from clinical experts that patients 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 confidential individual patient-level data[46] provided by the manufacturer (Table 4.2).

Treatment effectiveness was determined based on data from the RESTORE trial at Week 52 including confidential individual patient-level data provided by the manufacturer.[46] 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 (e.g., move from light perception to counting fingers), a two-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. 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.[44] 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%.[55] 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 used to create an exponential function to track visual functioning decline over time based on LogMAR scores. 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.[56] 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).[57,58] To reflect what we heard during the focus group 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 $875,000 per treatment, which is the midpoint of the range estimated by IPD Analytics ($750,000 to $1,000,000 for treatment of both eyes).[59] 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.[60]

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 focus group 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. 20166 and input from patients.[1] During the focus group 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.[61] 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[45]
Female, %	37%		
Baseline Health State Classification*			
Better than Counting Fingers	0%	0%	
Counting Fingers	Redacted Data	Redacted Data	Confidential Data on File[46]
Hand Motion	Redacted Data	Redacted Data	
Light Perception	Redacted Data	Redacted Data	
No Light Perception	Redacted Data	Redacted Data	
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[50], Lam et al 2024,[55] and calculation assuming exponential decline in LogMAR 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	Redacted Data	Redacted Data	Confidential Data on File[46] and assumptions
Counting Fingers	Redacted Data	Redacted Data	
Hand Motion	Redacted Data	Redacted Data	
Light Perception	Redacted Data	Redacted Data	
No Light Perception	Redacted Data	Redacted Data	
Year 3 to 5	Maintenance of Year 2 Health State	Variable, based on natural history data (see above)	Clinical expert opinion and assumptions

Parameter	Input		Source
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[55]
Health State Utilities (SD)*			
Better than Counting Fingers	0.50 (0.27)		O'Brien 2023[57]
Counting Fingers	0.43 (0.28)		O'Brien 2023[57]
Hand Motion	0.38 (NA)		O'Brien 2023,[57] input from patients, and calculation
Light Perception	0.33 (0.26)		O'Brien 2023[57]
	Sonpiretigene	**Usual Care**	
No Light Perception	0.26 (0.08)		Brown 2001[58]
Intervention Costs			
Sonpiretigene Acquisition Costs	$875,000	N/A	IPD Analytics[59]
Sonpiretigene Mark-Up	6%	N/A	ICER Reference Case
Sonpiretigene Administration Costs	$112.18	N/A	Centers for Medicare & Medicaid Services[60]
Prophylactic Steroids	$2.78/kg	N/A	Sadda 2024[34], 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,[61] 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[61]

Table 4.2 Abbreviations - LogMAR: Logarithmic Minimum Angle of Resolution, 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[50]: 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 3.75 (no light perception) and fitting an exponential function to the data (y=0.02684e-0.07980x) where y is equal to the LogMAR score in decimal form 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 marginal improvements in QALYs (0.36 discounted incremental QALYs) and higher costs ($927,900 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 $2,566,000 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	Years in Better than Counting Fingers	Years with Light Perception	QALYs	evLYs	Life Years
Sonpiretigene	3.55	14.90	6.70	6.70	17.70
Usual Care	1.07	14.24	6.33	6.33	17.70
Incremental	2.48	0.66	0.36	0.36	0

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	$875,000	$52,900	$342,200	$1,270,000
Usual Care	$0	$0	$342,200	$342,200
Incremental	$875,000	$52,900	$0	$927,900

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 additional year in better than counting fingers	Cost per additional year with light perception	Cost per QALY Gained*	Cost per evLY Gained*	Cost per Life Year Gained*
Sonpiretigene vs Usual Care	$374,000	$1,410,000	$2,566,000	$2,566,000	N/A

Table 4.5 Abbreviations - evLYs: equal value of life years, N/A: Not applicable, QALY: quality-adjusted life year

Table 4.5 Footnotes - *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, light perception, and counting fingers, 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

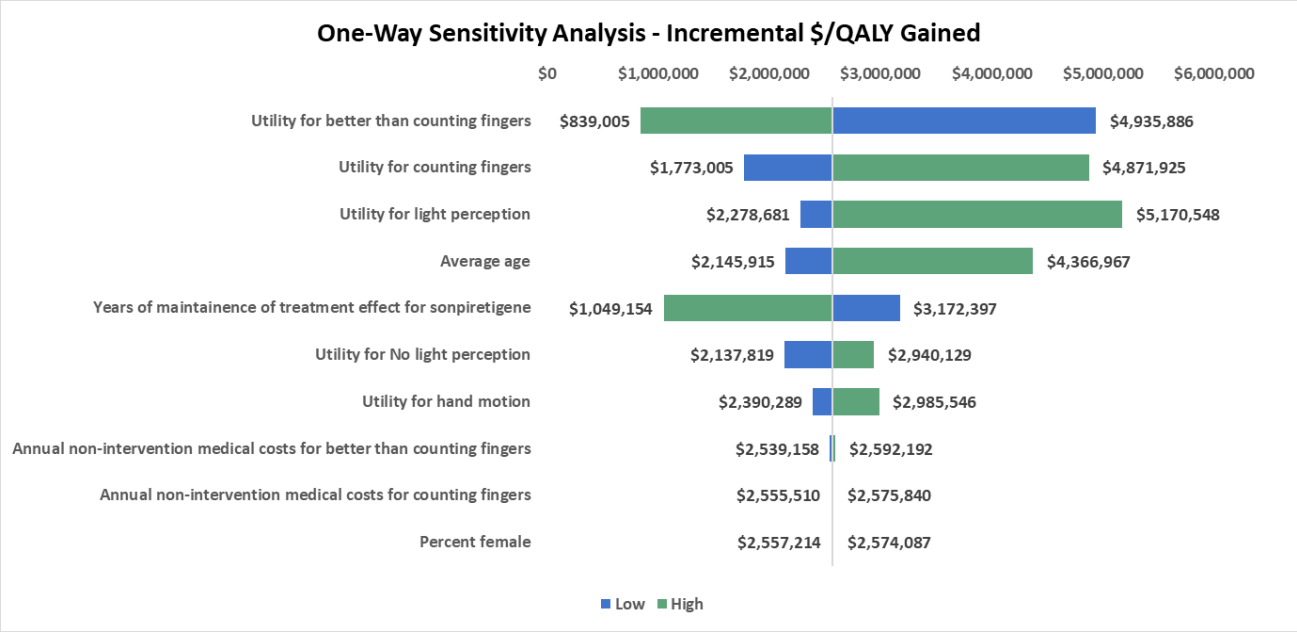


Figure 4.2 Abbreviations: QALY: quality-adjusted life year

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 UC	0%	0%	0%	0%

Figure 4.6 Abbreviations - evLY: equal value of life years, QALY: quality-adjusted life year, UC: usual care

Figure 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.

*Based on placeholder price

Scenario Analyses

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

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

2. A) optimistic and B) conservative benefit scenario analysis which varied assumptions regarding the benefit of treatment. Details of the optimistic and conservative benefit scenarios are included in the Supplement.

3. 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.

The results of selected scenario analyses are presented below, and findings are presented in Tables 4.7 and 4.8. Across all scenarios, including more favorable assumptions for treatment durability, incremental cost-effectiveness ratios remained substantially above commonly used cost-effectiveness thresholds. Detailed methods and results can be found in the Supplement.

Table 4.7. Scenario Analysis Results

Base-Case Results	Modified Societal Perspective	Optimistic Benefit Scenario	Conservative Benefit Scenario	Alternative Utility Values	Lifetime Treatment Durability
Incremental Cost-Effectiveness Ratio (Cost per QALY or evLY gained)					
$2,566,000	$2,558,000	$1,708,000	$2,864,000	$1,587,000	$895,000

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

Threshold Analyses

Threshold analyses were conducted for sonpiretigene to calculate the annual price needed to meet commonly accepted cost-effectiveness thresholds for QALY and evLYs and are shown in Table 4.8.

Table 4.8. QALY and evLY-Based Threshold Analysis Results

	Anticipated Intervention Acquisition Cost*	Unit Price to Achieve $50,000 per QALY or evLY Gained	Unit Price to Achieve $100,000 per QALY or evLY Gained	Unit Price to Achieve $150,000 per QALY or evLY Gained	Unit Price to Achieve $200,000 per QALY or evLY Gained
Sonpiretigene	$875,000	$16,700	$33,800	$50,800	$67,900

Table 4.8 Abbreviations - evLYs: equal value of life years gained, QALY: quality-adjusted life year, UC: usual care
Table 4.7 Footnote - *Based on placeholder price

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 offer to share the model with the relevant manufacturer for external verification around the time of publishing this 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 both eyes; however, we used efficacy data from the RESTORE trial in which patients received treatment in only one eye. We heard from clinical experts that patients may experience treatment effects in the untreated eye, so it is possible that additional benefit could be seen if both eyes are treated. The extent of this potential impact is unclear, so no additional benefits were modeled. We believe that our sensitivity and scenario analysis to test alternative assumptions for treatment effect and durability have sufficiently addressed the potential impact of this uncertainty. If patients were treated in only one eye and therefore halving the placeholder price, the results of the incremental cost-effectiveness ratios for sonpiretigene would be reduced but would remain above commonly used cost-effectiveness thresholds.

- 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. Even under extreme assumption, results are expected to remain above commonly used cost-effectiveness thresholds.

- 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[57] 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 focus group 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 focus group 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 2.5 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 marginal gains in QALYs and a greater number of years with vision better than counting fingers compared to patients receiving usual care. At a placeholder price of $875,000 per treatment and assuming that both eyes are treated, our analysis suggests that treatment with sonpiretigene would not meet commonly used cost-effectiveness thresholds. Even when halving the placeholder price under an assumption of only one eye being treated, and with more favorable estimates for treatment durability, cost-effectiveness is improved, however 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. 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. QALY and evLY shortfalls: • Absolute shortfall: 11.8 • Proportional shortfall: 56.1% 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 healthcare 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.

6. Health Benefit Price Benchmarks

ICER does not provide health benefit price benchmarks as part of draft reports because results may change with revision following receipt of public comments. We therefore caution readers against assuming that the values provided in the Threshold Prices section of this draft report will match the health benefit price benchmarks that will be presented in the next version of this Report.

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 $875,000 and the three threshold prices (at $50,000, $100,000, and $150,000 per evLYG) for sonpiretigene in our estimates of budget impact.

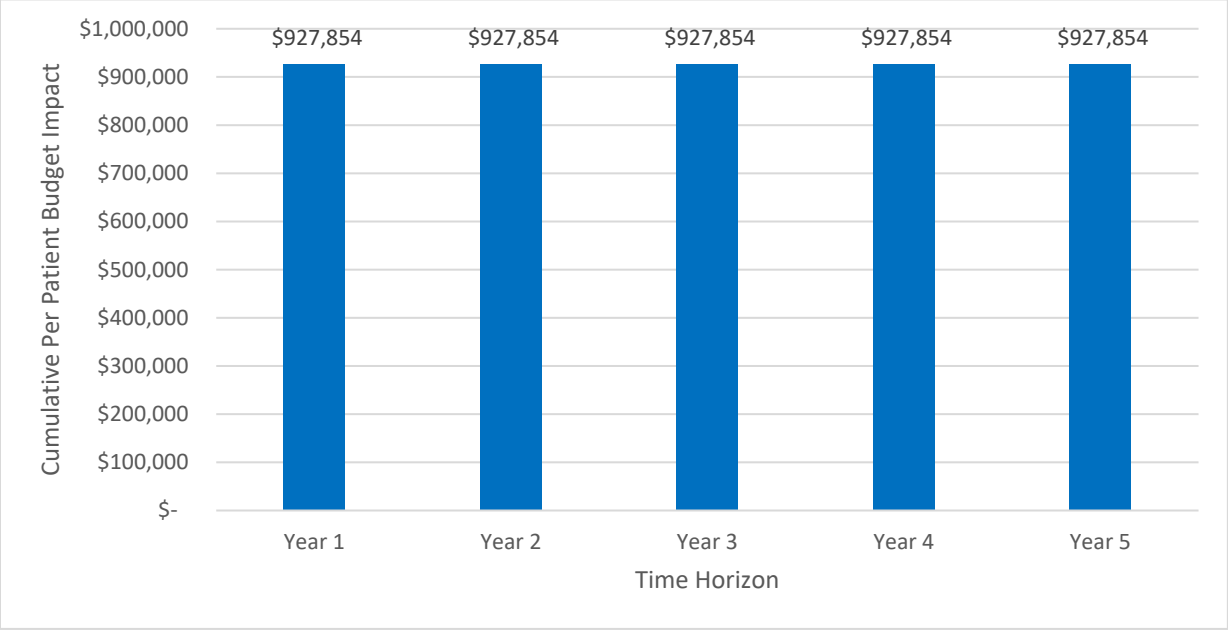
This potential budget impact analysis included the estimated number of individuals in the US who would be eligible for sonpiretigene. To estimate the size of the potential candidate populations for treatment, we used inputs for the prevalence of retinitis pigmentosa in the US (0.025%).[1] To estimate 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.[62] 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 $875,000 per treatment and assuming both eyes are treated, the average annual budget impact per patient was $927,854 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, 46% of patients could be treated over five years at the placeholder price of $875,000 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 ($16,724, $33,783 and $50,841 respectively).

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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, in advanced stages, near total blindness with the loss of central vision.[1,2]

Best Corrected Visual Acuity (BCVA): BCVA is a validated measure of visual acuity that evaluates the best vision that can be achieved 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.[63,64]

Freiberg Visual Acuity and Contrast Test (FrACT): The FrACT is a validated measure of visual acuity. This computerized tool displays optotypes, a visual aid used to determine visual acuity such as a letter, displayed at varying sizes and orientations for the individual to identify.[65,66] 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).[50]

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.[44] A LogMAR of zero corresponds to 20/20 vision with values increasing above 0 indicating worsening visual acuity and values decreasing below zero indicating improved visual acuity. In the RESTORE trial an improvement by -0.3 LogMAR, or three lines gained, is considered clinically meaningful.[34,45]

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 for each illumination level was defined by passing three times.[45] 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 for each illumination level was defined as correct identification of the shapes three different times.[45] 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.[67] 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.[68,69] 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 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 Perspectives: 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 perspectives chapter 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 this Draft Evidence Report. The third session (Session 3) is an optional discussion for participants that is scheduled to take place after the posting of the Draft Evidence Report 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.

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[70]

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

Data permitting, 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
    - Healthcare 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.[71,72] We conducted the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[73] 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 the Population, Intervention, Comparator, and Study Design elements described above. 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

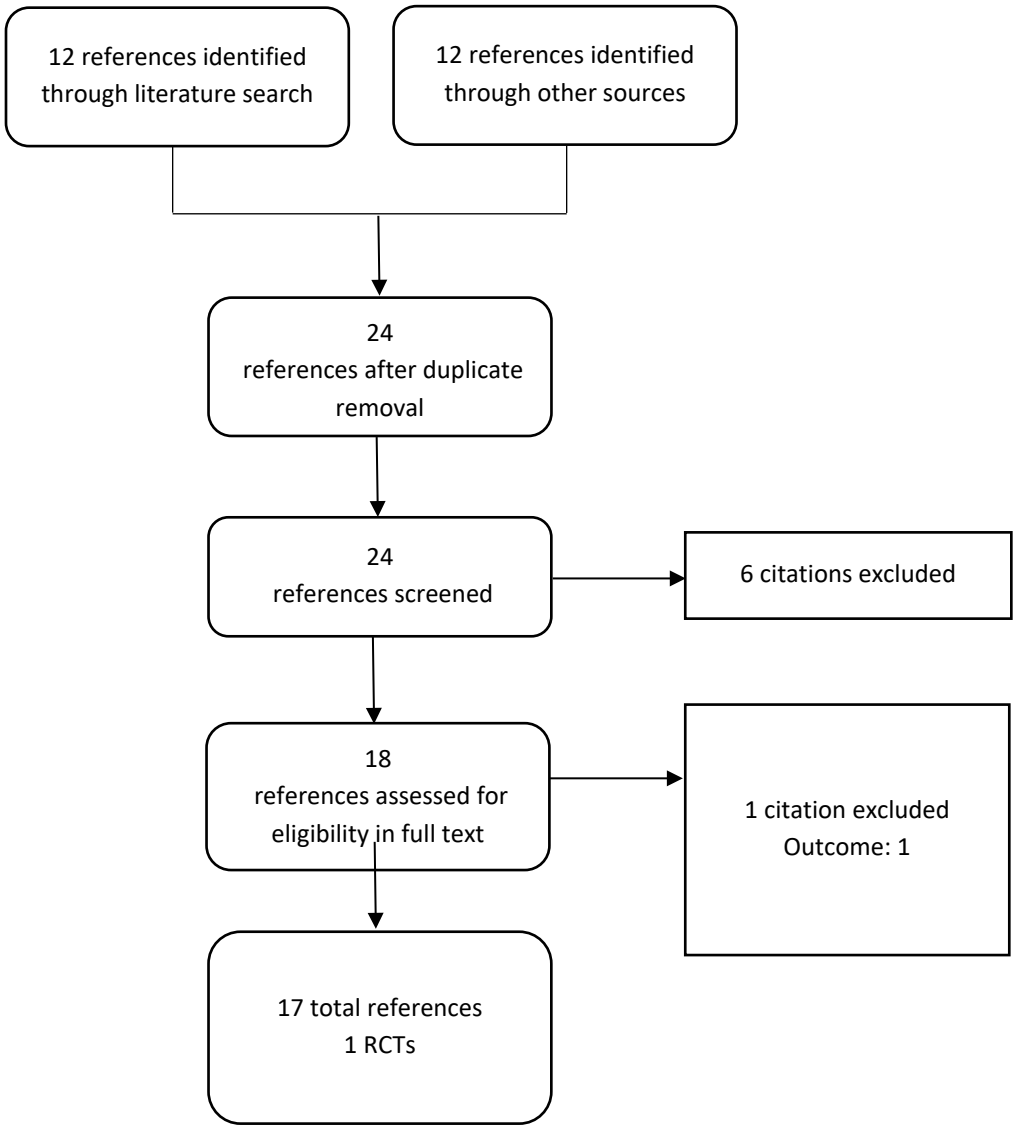
Date of search: October 2, 2024

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 search: October 2, 2024

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, 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.[72,74] 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
Frieberg Visual Acuity Test (FrACT)	Low	Some concern	Low	Some concern	Low	Some Concern
Multi-Luminance Y-Mobility Test (MLYMT)	Low	Some concern	Low	Some concern	Some concern	Some Concern
Multi-Luminance Shape Discrimination Test (MLSDT)	Low	Some concern	Low	Some concern	Some concern	Some Concern

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.[53] 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).[75,76]

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).[77]

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.[77]

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.[77]

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.[39,43]

BCVA Individual Participant Data: 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.[42]

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.[42]

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

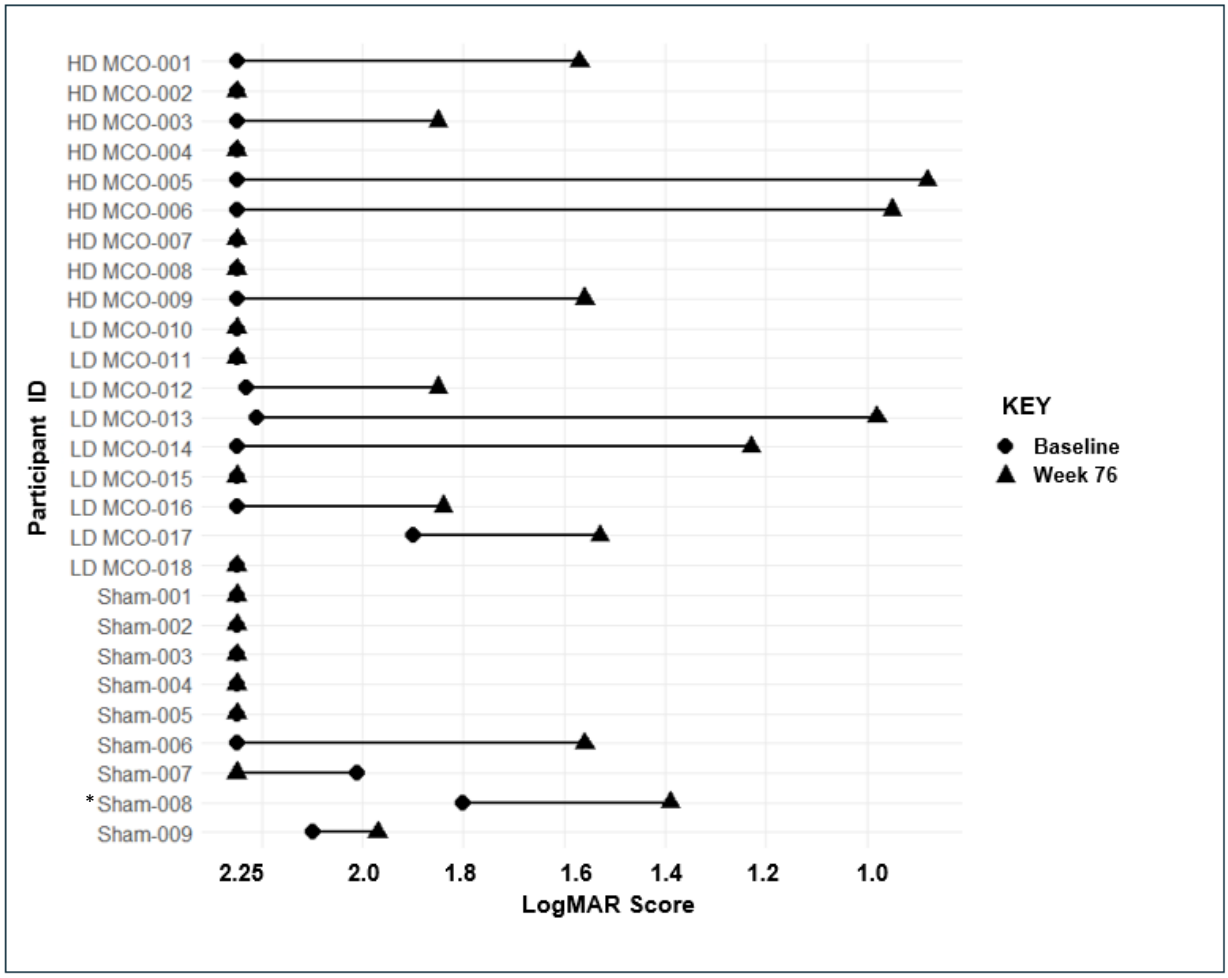


Figure D2.1 Abbreviations – HD: high-dose, LD: low-dose, LogMAR: logarithmic minimum angle of resolution, MCO: sonpiretigene isteparvovec

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

Source: Data from a presentation by Loewenstein 2024[42]

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.[35]

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.[35-37]

D3. Evidence Tables

Table D3.1. Evidence Tables[47,77]

Trial & Design	Interventions (n)	Inclusion & Exclusion Criteria	Primary Outcome
RESTORE (NCT04945772) **Phase IIb/III, randomized, double-masked, sham-controlled** **N=27** **Follow-up: 100 weeks**	**Low-Dose:** $0.9x10^{11}$ gc/eye sonpiretigene (n=9) **High-Dose:** $1.2x10^{11}$ gc/eye sonpiretigene (n=9) Sham injection (n=9)	**Inclusions:** - Age ≥ 18 years. - Diagnosed with Advanced Retinitis Pigmentosa (RP). - Best-Corrected Visual Acuity (BCVA) < 1.9 LogMAR in the study eye. - BCVA > 1.6 LogMAR in the non-study eye. **Exclusions**: - Prior participation in gene therapy program. - 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. - Active ocular inflammation, recurrent history of idiopathic or autoimmune associated uveitis - Presence of any complicating systemic diseases such as malignancies whose treatment could affect central nervous system function - 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) **Phase I/IIa, open-label, dose-escalation** **N=11** **Follow-up: 52 weeks**	**Low-Dose:** $0.6x10^{11}$ gc/eye sonpiretigene (n=3) **High-Dose:** $1.2x10^{11}$ gc/eye sonpiretigene (n=8)	**Inclusions:** - Age ≥ 18 years. - Diagnosed with Advanced Retinitis Pigmentosa (RP). - Snellen's visual acuity equivalent light-perception/no light-perception in study eye. - Visual acuity in the non-study eye of no-better-than finger counting. **Exclusions:** - Participation in investigational drug clinical trials, agent or therapy or any gene or stem cell therapy in the past six months - Pre-existing eye conditions such as glaucoma, diseases affecting the optic nerve causing significant visual field loss, active uveitis, corneal or lenticular opacities. - Ocular surgery in the study eye within three months prior to Day 0. - Presence of disorders of the ocular media which interfere with visual acuity and other ocular assessments, including OCT, during the study period. - Presence of vitreo-macular adhesion or traction, epiretinal membrane, macular pucker and macular hole, evident by ophthalmoscopy and/or by OCT examinations - Current evidence of retinal detachment significantly affecting central vision. - 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[45]

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, %		33.3	33.3	33.3	44.4
Race, n (%)	Asian	1 (11.1)	0	1 (5.6)	0
	Black and African American	NR	NR	NR	NR
	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	Redacted Data	Redacted Data	NR	Redacted Data
	Non-Syndromic Disease	Redacted Data	Redacted Data	NR	Redacted Data
	X-linked	Redacted Data	Redacted Data	NR	Redacted Data
	Autosomal recessive	Redacted Data	Redacted Data	NR	Redacted Data
	Autosomal-dominant	Redacted Data	Redacted Data	NR	Redacted Data
Baseline Visual Functioning, mean score (SE)	Best-Corrected Visual Acuity (BCVA)	NR	NR	2.229 (0.02)	2.172 (0.05)
	Visual field (e.g., degrees)	NR	NR	NR	NR
	Multi-luminance Y- Mobility Test (MLYMT)	NR	Redacted Data	1.2 (0.6)	1.0 (1.0)
	Multi-Luminance Shape Discrimination Test (MLSDT)	NR	Redacted Data	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[34,38-40,42-45]

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)	NR	NR	2.229 (0.018)	2.172 (0.045)
	52 weeks	Mean Score (SEM); p-value vs. baseline	1.823 (NR); NR	1.964 (NR); NR	1.894 (0.119); 0.0105	2.074 (0.127); 0.2952
		LSM Change from Baseline (SEM); p-value vs. sham	-0.382 (0.1244); 0.0290	-0.337 (0.829); 0.0209	-0.335 (0.494); 0.0745	-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)	NR	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 (%)	Redacted Data	Redacted Data	12 (67)	3 (33)
		Light Level Improvement	NR	NR	+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)	NR	NR	0.8333 (0.364)	1.667 (0.624)
	32 weeks	Responders, n (%)	Redacted Data	Redacted Data	Redacted Data	Redacted Data
	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 (%)	Redacted Data	Redacted Data	10 (56)	2 (22)
		Light Level Improvement	NR	NR	NR	NR
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)

Note: Italicized data has been digitized or calculated

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 D3.4. RESTORE Safety Outcomes[39-45]

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	Redacted Data	Redacted Data	Redacted Data	Redacted Data
	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)
	Serious	52 weeks	0	0	0	0
Adverse Events of Special Interest, n (%)	Asymptomatic COVID-19	52 weeks	Redacted Data	Redacted Data	Redacted Data	Redacted Data
	Hypertension	52 weeks	Redacted Data	Redacted Data	Redacted Data	Redacted Data
	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)
	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)
	≥1 ocular TEAE	100 weeks	9 (100.0)	8 (88.9)	17 (94.4)	7 (77.8)
	Eye disorders	100 weeks	9 (100.0)	8 (88.9)	17 (94.4)	7 (77.8)
	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
	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				
	Treatment with topic steroids	NR	NR	NR	2 (22.2)
	Treatment with oral steroids	NR	NR	1 (5.6)	NR

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

Table D3.5 Individual Participant Data for Key Efficacy Outcomes at Week 52[34,40,41,44]

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

*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*[35-37]

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

Note: Italicized data has been digitized or calculated

Table D3.6 Abbreviations - AEs: adverse events, BCVA: best corrected visual acuity, LogMAR: logarithmic minimum angle of resolution, n: number, SE: standard error, SEM: standard mean error, TEAEs: treatment-emergent adverse event, %: percent

*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).

D4. Ongoing Studies

Table D4.1. Ongoing Studies for Sonpiretigene Isteparvovec[48,78,79]

Title/Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Date
REMAIN **NCT06162585** **Nanoscope Therapeutics**	Observational, non-interventional, long-term safety follow-up. Estimated enrollment: N=18	**Arm 1:** $1.2x10^{11}$ gc/eye of sonpiretigene (high-dose) **Arm 2:** $0.9x10^{11}$ gc/eye of sonpiretigene (low-dose)	**Inclusions**: - Previously enrolled in study NTXMCO-002 (RESTORE) and received sonpiretigene. - 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 **NCT05921162** **Nanoscope Therapeutics**	Observational, non-interventional, long-term safety follow-up. Estimated enrollment: N=11	**Arm 1:** $1.2x10^{11}$ gc/eye of sonpiretigene **Arm 2:** $0.6 x10^{11}$ gc/eye of sonpiretigene	**Inclusion**: - 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 **NCT06048185** **Nanoscope Therapeutics**	Observational, non-interventional, long-term safety follow-up. Estimated enrollment: N=6	**Arm 1:** Sonpiretigene	**Inclusions**: - Previously enrolled in study NTXMCO-004 (STARLIGHT for Stargardt Disease) and received sonpiretigene. - 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.[80]

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

Adapted from Sanders et al[81]

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.[82]
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 3 and 4.
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.

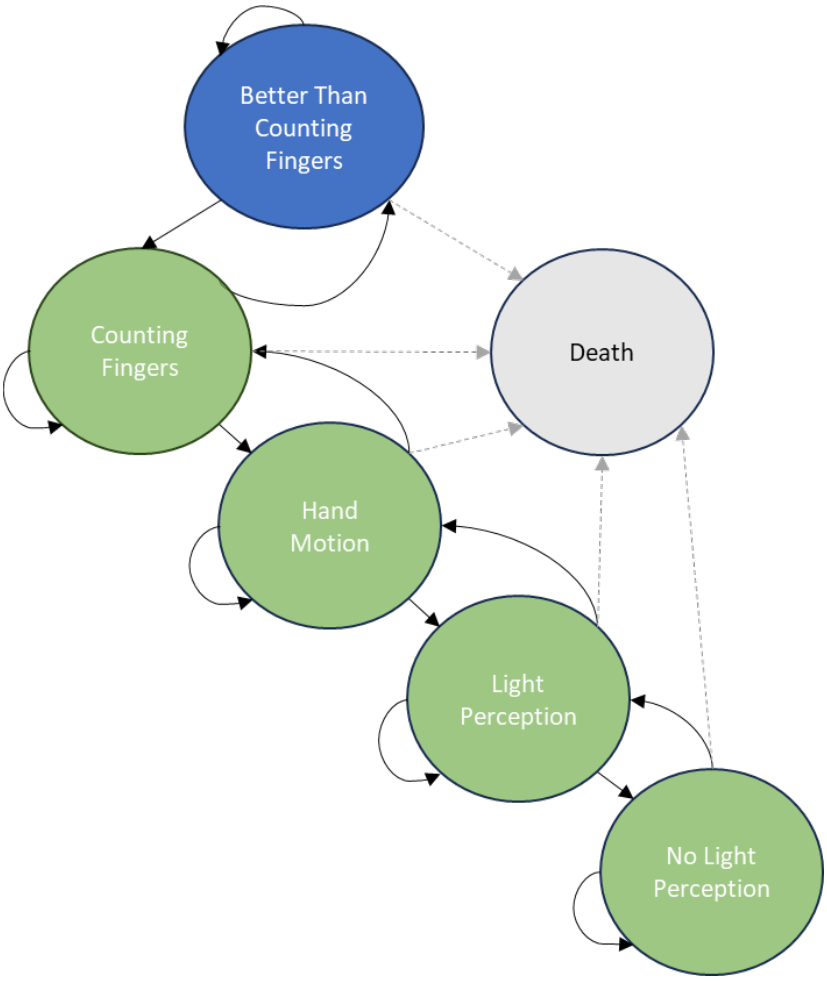
Overview and Model Structure

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 an intention-to-treat analysis, with 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 based on data from the RESTORE trial.[34]

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[45]
Female, %	37%		Boyer 2023[45]
Baseline Visual Functioning			
Baseline BCVA, LogMAR, mean (SE)	2.229 (0.018)	2.17 (0.05)	Sadda 2024[34]
MLYMT, Luminance Level, mean (SE)	1.17 (0.61)	1.0 (1.0)	Ho 2024[39]
MLSDT, Luminance Level, mean (SE)	0.83 (0.36)	1.67 (0.62)	Sadda 2024[34]

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.

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 confidential 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 both eyes.	Patients receiving sonpiretigene in the RESTORE trial received a one-time intravitreal injection in only one eye. We heard from clinical experts that patients 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 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 confidential 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.

Table E2.2. Baseline Health State Classification

Health State	Sonpiretigene Isteparvovec, %	Usual Care, %	Source and Notes
Better than Counting Fingers	0%	0%	RESTORE trial
Counting Fingers	Redacted Data	Redacted Data	Confidential Data on File[46]
Hand Motion	Redacted Data	Redacted Data	
Light Perception	Redacted Data	Redacted Data	
No Light Perception	Redacted Data	Redacted Data	

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. 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 confidential 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 (e.g., move from light perception to counting fingers), a two-health state improvement 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.

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).[49]

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	Redacted Data	Redacted Data	Redacted Data	Redacted Data	Redacted Data
Hand Motion	Redacted Data	Redacted Data	Redacted Data	Redacted Data	Redacted Data
Light Perception	Redacted Data	Redacted Data	Redacted Data	Redacted Data	Redacted Data
No Light Perception	Redacted Data	Redacted Data	Redacted Data	Redacted Data	Redacted Data
Usual Care					
Better than Counting Fingers	0%	0%	0%	0%	0%
Counting Fingers	Redacted Data	Redacted Data	Redacted Data	Redacted Data	Redacted Data
Hand Motion	Redacted Data	Redacted Data	Redacted Data	Redacted Data	Redacted Data
Light Perception	Redacted Data	Redacted Data	Redacted Data	Redacted Data	Redacted Data
No Light Perception	Redacted Data	Redacted Data	Redacted Data	Redacted Data	Redacted Data

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.[44]

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.[55] 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. The 1.75% annual rate of decline was used to create an exponential function to track visual functioning over time based on LogMAR scores. The use of an exponential function implies that patients in less severe vision loss (e.g., better than counting fingers) have a faster rate of decline compared to patients with more severe vision loss (e.g., light perception) as demonstrated in Table E2.4 below. 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[50], Lam et al 2024,[55] and calculation assuming exponential decline in LogMAR 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[50]: 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 3.75 (no light perception) and fitting an exponential function to the data (y=0.02684e-0.07980x) where y is equal to the LogMAR score in decimal form 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.[56]

Adverse Events

No patients receiving sonpiretigene in the RESTORE trial experienced a serious adverse event.[34] 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.[34] 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.[57] 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.[83,84] Because the health states collapsed the most severe levels of visual functioning (hand motion to no light perception), we used data from Brown 2001[58] 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 E2.5. 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	0.50 (0.27)	O'Brien 2023[57]
Counting Fingers	0.43 (0.28)	O'Brien 2023[57]
Hand Motion	0.38 (NA)	O'Brien 2023,[57] calculation for adjustment
Light Perception	0.33 (0.26)	O'Brien 2023[57]
No Light Perception	0.26 (0.08)	Brown 2001[58]

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 E2.6 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[34]
Manufacturer	Nanoscope Therapeutics	
Route of Administration	One-time intravitreal injection into each eye	
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 $875,000 per treatment, which is the midpoint of the range predicted by IPD Analytics ($750,000 to $1,000,000 for treatment of both eyes).[59] This estimate was based on the presumption that pricing will be similar to that of 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.[60]

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 E2.7.

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[61] 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.[61] 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.[61] 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 E2.8 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,[61], 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,[61], 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[61] (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	Years in Better than Counting Fingers	Years with Light Perception	QALYs	evLYs	Life Years
Sonpiretigene	4.32	21.36	9.71	9.71	26.19
Usual Care	1.37	20.47	9.24	9.24	26.19
Incremental	2.95	0.89	0.46	0.46	0.00

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	$875,000	$52,900	$506,000	$1,434,000
Usual Care	$0	$0	$506,000	$506,000
Incremental	$875,000	$52,900	$0	$928,000

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.

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 versus Usual Care

	Lower Incremental CE Ratio	Upper Incremental CE Ratio	Lower Input*	Upper Input*
Utility for better than counting fingers	$4,935,886	$839,005	0.43	0.80
Utility for counting fingers	$1,773,005	$4,871,925	0.26	0.61
Utility for light perception	$2,278,681	$5,170,548	0.26	0.61
Average age	$2,145,915	$4,366,967	23	83
Years of maintenance of treatment effect	$1,049,154	$3,172,397	2	20
Utility for No light perception	$2,137,819	$2,940,129	0.15	0.33
Utility for hand motion	$2,390,289	$2,985,546	0.26	0.61
Direct medical costs for better than counting fingers	$2,539,158	$2,592,192	$15,462	$23,192
Direct medical costs for counting fingers	$2,555,510	$2,575,840	$15,462	$23,192
Percent female	$2,557,214	$2,574,087	0.296	0.444

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

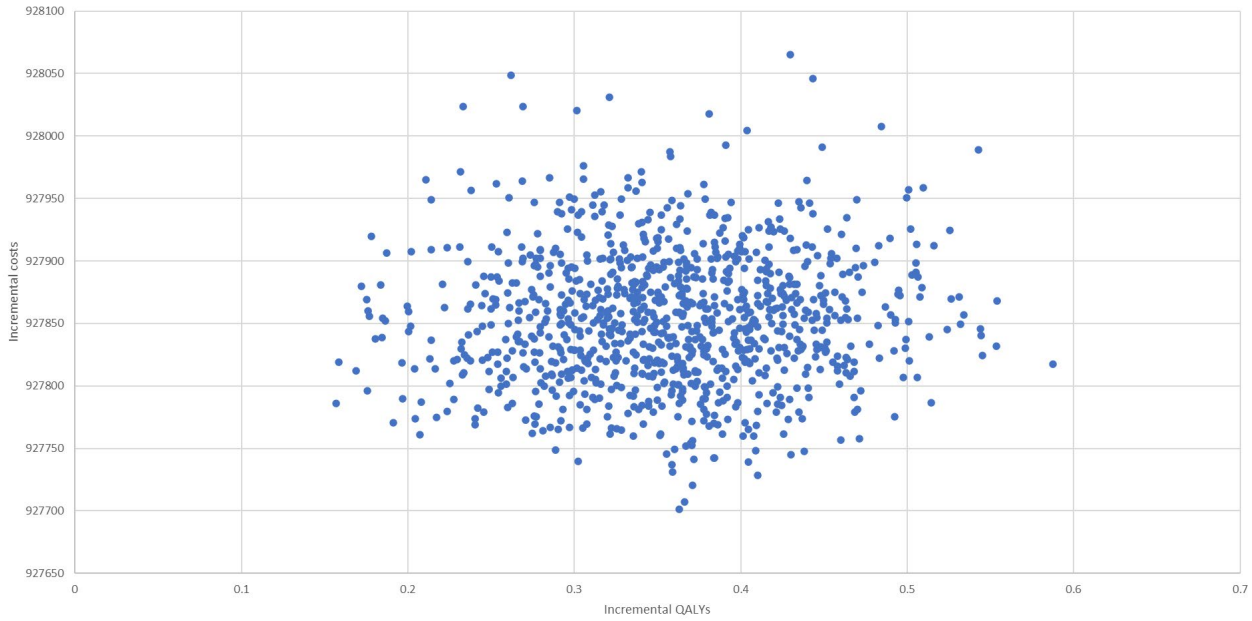


Figure E4.1 Abbreviations - QALY: quality-adjusted life year

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	$1,270,412	$342,558	$927,854
Mean QALYs	6.71 (6.33, 7.11)	6.35 (5.95, 6.81)	0.36 (0.21, 0.50)
Mean evLYs	6.71 (6.33, 7.11)	6.35 (5.95, 6.81)	0.36 (0.21, 0.50)
Incremental CE Ratio			$2,601,509

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:

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

9. 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 confidential 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.

10. 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.

11. Lifetime durability of treatment effect.

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

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

14. 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	0.50 (0.27)	0.50 (0.27)	0.65 (0.21)
Counting Fingers	0.43 (0.28)	0.43 (0.28)	0.47 (0.29)
Hand Motion	0.38 (NA)	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	Years in Better than Counting Fingers	Years with Light Perception	QALYs	evLYs	Life Years
Sonpiretigene	3.55	14.90	6.70	6.70	17.70
Usual Care	1.07	14.24	6.33	6.33	17.70
Incremental	2.48	0.66	0.36	0.36	0

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	$875,000	$52,900	$1,148,000	$2,076,000
Usual Care	$0	$0	$1,151,000	$1,151,000
Incremental	$875,000	$52,900	$(3,000)	$925,000

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	Years in Better than Counting Fingers	Years with Light Perception	QALYs	evLYs	Life Years
Sonpiretigene	4.67	15.39	6.88	6.88	17.70
Usual Care	1.07	14.24	6.33	6.33	17.70
Incremental	3.60	1.15	0.54	0.54	0.00

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	$875,000	$52,900	$342,000	$1,270,000
Usual Care	$0	$0	$342,000	$342,000
Incremental	$875,000	$52,900	$0	$928,000

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	Years in Better than Counting Fingers	Years with Light Perception	QALYs	evLYs	Life Years
Sonpiretigene	2.22	14.36	6.39	6.39	17.70
Usual Care	1.07	13.94	6.07	6.07	17.70
Incremental	1.15	0.42	0.32	0.32	0.00

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	$875,000	$52,900	$342,000	$1,270,000
Usual Care	$0	$0	$342,000	$342,000
Incremental	$875,000	$52,900	$0	$928,000

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	Years in Better than Counting Fingers	Years with Light Perception	QALYs	evLYs	Life Years
Sonpiretigene	7.65	16.72	7.37	7.37	17.70
Usual Care	1.07	14.24	6.33	6.33	17.70
Incremental	6.58	2.48	1.04	1.04	0.00

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	$875,000	$52,900	$342,000	$1,270,000
Usual Care	$0	$0	$342,000	$342,000
Incremental	$875,000	$52,900	$0	$928,000

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.

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	Years in Better than Counting Fingers	Years with Light Perception	QALYs	evLYs	Life Years
Sonpiretigene	3.55	14.90	6.55	6.55	17.70
Usual Care	1.07	14.24	6.18	6.18	17.70
Incremental	2.48	0.66	0.37	0.37	0.00

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

Table E5.12 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	$875,000	$52,900	$342,000	$1,270,000
Usual Care	$0	$0	$342,000	$342,000
Incremental	$875,000	$52,900	$0	$928,000

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

Table E5.13 Footnotes - *Based on placeholder price

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

Table E5.13 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	Years in Better than Counting Fingers	Years with Light Perception	QALYs	evLYs	Life Years
Sonpiretigene	3.55	14.90	8.37	8.37	17.70
Usual Care	1.07	14.24	7.78	7.78	17.70
Incremental	2.48	0.66	0.58	0.58	0.00

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

Table E5.14 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	$875,000	$52,900	$342,000	$1,270,000
Usual Care	$0	$0	$342,000	$342,000
Incremental	$875,000	$52,900	$0	$928,000

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

Table E5.15 Footnotes - *Based on placeholder price

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

Table E5.15 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	Years in Better than Counting Fingers	Years with Light Perception	QALYs	evLYs	Life Years
Sonpiretigene	3.10	14.87	6.65	6.65	17.70
Usual Care	1.07	14.24	6.34	6.34	17.70
Incremental	2.04	0.63	0.31	0.31	0.00

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

Table E5.16 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	$875,000	$52,900	$342,000	$1,270,000
Usual Care	$0	$0	$342,000	$342,000
Incremental	$875,000	$52,900	$0	$928,000

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.

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 Additional Year in Better Than Counting Fingers	Cost per Additional Year with Light Perception	Cost per QALY Gained*	Cost per evLY Gained*	Cost per Life Year Gained*
Base Case	$374,000	$1,410,000	$2,566,000	$2,566,000	N/A
Scenario 1: Modified Societal Perspective					
	$373,000	$1,406,000	$2,558,000	$2,558,000	N/A
Scenario 2A: Optimistic					
	$257,000	$807,000	$1,708,000	$1,708,000	N/A
Scenario 2B: Conservative Benefit					
	$806,000	$2,233,000	$2,864,000	$2,864,000	N/A
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					
	$141,000	$374,000	$895,000	$895,000	N/A
Scenario 5: Unadjusted Utility Values					
	$374,000	$1,410,000	$2,490,000	$2,490,000	N/A
Scenario 6: Alternative Utility Values					
	$374,000	$1,410,000	$1,587,000	$1,587,000	N/A
Scenario 7: Alternative Baseline Health State Classification					
	$455,000	$1,477,000	$3,021,000	$3,021,000	N/A

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 will also share the model with the relevant manufacturer for external verification around the time of publishing this draft report. Lastly, 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[25] and four additional assessments of voretigene neparvovec in other jurisdictions.[85-88] Other published economic models include assessments of artificial vision devices (e.g., the Argus II Retinal Prosthesis System) for retinitis pigmentosa.[89-91]

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. [89-91] 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 0.36 for sonpiretigene compared to usual care, other models found incremental QALYs of 2.0,[89] 2.9,[90] and 2.6 for artificial vision devices compared to usual care.[91] 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,[89,90] using higher utility values for the health states in the model,[89] modeling a younger population,[90,91] assuming a higher mortality for patients with RP,[91] and using a lower discount rate.[91] 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)[62] 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.[92,93] 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.