Sonpiretigene Isteparvovec for Advanced Retinitis Pigmentosa
Response to Public Comments on Draft Evidence Report

March 26, 2025

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<tr><td>1.</td><td>Nanoscope Therapeutics appreciates the opportunity to comment on the Institute for Clinical and Economic Review's (ICER's) draft evidence report of sonpiretigene isteparvovec for advanced retinitis pigmentosa (RP). We thank ICER for expertly modeling disease progression for advanced RP via six health states and utilizing RESTORE clinical trial data to map the health state transitions. However, Nanoscope has specific concerns regarding the clinical effectiveness and cost-effectiveness outcomes in the draft report. With respect to cost-effectiveness, the Table below addresses the impact of specific model assumptions and inputs on the incremental cost-effectiveness ratio (ICER). Each individual scenario highlighted in the Table significantly lowers the ICER, and the cumulative impact of the scenarios drive sonpiretigene cost-effectiveness to approach accepted thresholds for rare diseases. Under the detailed comments and recommendations section, we provide justification for the proposed scenarios to be incorporated as part of the base case and earnestly request ICER to adopt them.

<table>
<tr><th>Table: Scenarios</th><th>Individual Scenario ($/QALY)</th><th>Cumulative Scenarios ($/QALY)</th></tr>
<tr><td>Base Case</td><td colspan="2">$2,565,675</td></tr>
<tr><td>1. Correction of baseline health state distribution</td><td>$1,380,697</td><td>$1,380,697</td></tr>
<tr><td>2. Lifetime treatment effect</td><td>$894,642</td><td>$687,915</td></tr>
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2.	1. Incorrect assumption of duration of treatment effect and safety: In the base case analysis, ICER used a 5-year duration of treatment effect (utilizing the lowest end of the 5–7-year range provided by opinions from their clinical experts), followed by progressive waning of the treatment effect and accelerated disease progression at a rate higher than natural history over the subsequent 5 years. However, no rationale for the clinical experts' opinions was provided. As part of ongoing interactions with ICER, Nanoscope provided *sonpiretigene* durability data from animal models, long-term follow-up data from *sonpiretigene* phase 1/2a trial, and contextual information from an analogous gene therapy in support of longer treatment durability estimates, which was unfortunately not used to inform the modeling assumption of durability. ICER's draft model is sensitive to the *sonpiretigene* durability assumption, as clearly evidenced by the lifetime durability scenario results when the assumption changes from 5 years to lifetime durability (base-case *ICER* in the individual scenario drops from $2,565,675/QALY to $894,642/QALY). Below, we provide arguments to support lifetime durability for *sonpiretigene*.	ICER Response: As highlighted in response to other comments below, while promising, long-term durability is uncertain. The clinical experts we spoke with felt that the results in mice do not adequately predict durability in humans. The results of a scenario analysis assuming a lifetime durability of treatment effect remain included in the evidence report.
3.	*Preclinical evidence:* Preclinical efficacy studies in mice demonstrated sustained functional and structural benefits of the retina with *sonpiretigene* for the whole duration of 6-month study period. The biological age ratio between mice and humans is 1 mouse month to approximately greater than 3 human years. The rationale behind this is the observation that mice age approximately 36 times faster than humans, with a 2-year-old mouse being roughly equivalent to a 72-year-old human in terms of biological aging. The observed 6-month durability in mice from the preclinical studies can be carefully extrapolated to a minimum of an 18 years treatment effect in humans. Adeno-associated virus (AAV) vector delivered transgenes are known to form episome, which has been shown to last more than 9.4 years in canine retinas. Since light-sensitive multi-characteristic opsin (MCO-010) is a membrane-embedded (non-secreting) protein, it can be estimated to last greater than 65 years (equivalent to 9.4 years in canines) when delivered via AAV in humans. Persistent transduction is observed from sustained *sonpiretigene* presence in the soma and axons of matured, post-mitotic retinal bipolar cells in *sonpiretigene*-injected mice. Sustained visual function improvement is demonstrated in the treated mice model of advanced RP with improved performance in electrophysiological response and visually-guided water maze tests.	ICER Response: In the absence of longer-term clinical evidence in humans, we would consider animal studies in larger mammalians to inform our estimates of effectiveness, durability, and potential long-term toxicity. Experts we spoke felt that the visual system and immune response in mice does not adequately translate to humans.

4.	*Previous ICER reviews of gene therapies using a similar mechanism of action used a lifetime duration of effect:* AAV gene therapy of other central nervous system neurons was considered to be durable for the lifetime of patients in the spinal muscular atrophy (SMA) report. The targeted bipolar neurons, similar to spinal motor neurons in SMA, are terminally differentiated, non-dividing neurons that are stable. In addition, the MCO-010 protein is embedded in the cell membrane and does not secrete to extracellular space for light activation of bipolar neurons, unlike exosome secretion required in the case of treatment of SMA with *onasemnogene abeparvovec*.	ICER Response: We have made it clear in each gene therapy review that we do not consider durability to easily translate across models. The implications of correcting a genetic defect with gene therapy is different from the implications of inserting opsin proteins into bipolar cells.
5.	*No phototoxicity due to MCO-010 sensitization:* Unlike other optogenetic approaches that require high-intensity light, MCO-010 has an order of magnitude lower threshold for light activation (threshold: 0.01mW/mm^2) that enables vision restoration under ambient lighting conditions without requiring a light-intensifying device and associated phototoxicity. Even under chronic exposure to higher intensity light (0.1mW/mm^2, an order of magnitude higher than that required to activate MCO-010) over 4 months, there was no loss of viability of MCO-010 expressing bipolar neurons. Furthermore, *sonpiretigene* has demonstrated a favorable safety profile with no evidence of phototoxicity in any treated RP patient in phase 1/2a (NCT04919473) or phase 2b RESTORE (NCT04945772) clinical trials.	ICER Response: While promising, longer-term safety and durability is uncertain for this innovative therapy, longer-term safety data from clinical trials is preferred. In the absence of clinical trial data, evidence from larger mammals that better reflect retinal functioning and immune response is preferred over studies in mice.
6.	*Evidence of intact higher-order neurons in the retina of advanced RP patients:* ARGUS-Retinal prosthesis is an epiretinal implant designed for patients with inherited retinal diseases to convert light into transmittable electrical impulse for restoring vision. The implant replaces photoreceptor function by stimulating higher-order retinal neurons. This has shown durable vision improvement over 8 years. This implies the durability of *sonpiretigene's* optogenetic stimulation therapy utilizing the higher-order visual circuitry will not be impacted by pathophysiology of advanced RP. The *sonpiretigene's* target patient population with late-stage RP is similar to that of ARGUS-implanted older RP patient population, for whom higher-order visual circuitry was maintained over decades during the late-stage disease progression.	ICER Response: We recognize that retinal prosthesis provides a proof of concept. However, direct evidence on sonpiretigene's durability and safety is needed.
7.	2. Baseline health state distribution imbalance leading to inflated base-case *ICER* ICER used different baseline health state distributions for *sonpiretigene* and usual care. This is not a methodologically sound approach and introduces bias against *sonpiretigene*. The appropriate approach would be to apply treatment-specific transition probabilities to a common baseline	ICER Response: Thank you for your comment. We agree that the baseline health state distribution should be the same for sonpiretigene and usual care. We have revised this for the evidence report.

	population (*i.e.* a weighted average of all the patients in the trial). Correction for this potentially lowers the base case *ICER* from $2,565,675/QALY to $1,380,697/QALY (please refer to the Table on page 1). We strongly recommend that ICER construct a new distribution using the weighted average distribution across both treatment groups, where the average distribution will represent the typical baseline health state for the combined cohorts and apply differential transition probabilities for estimating the 1-year health state distribution. We are happy to provide ICER our calculations.	
8.	3. Benefit of single-eye injection modeled with cost of *sonpiretigene* for both eyes Despite patients in the clinical trial only receiving a single injection in the defined worse eye, ICER assumed patients would receive *sonpiretigene* in both eyes, multiplying the price by two while modeling the benefits of a single eye injection. This leads to a clear misalignment between the modeled treatment and associated intervention costs and the modeled benefits. The only clinical rationale for treating both eyes with *sonpiretigene*, would be to increase the benefits. Nanoscope recommends ICER adjust the base case analysis to mirror the treatments and benefits from the trial.	ICER Response: It is unclear if, in practice, sonpiretigene will be routinely used for treatment in one or both eyes and what the price will be. We have revised the placeholder price estimate that we used in the model to $437,500 (half of the placeholder price used in the draft report) to represent the price of treating only one eye. This change emphasizes that there are no data to inform the additional benefit that could be achieved if both eyes are treated. The additional cost of treating the second eye will need to be justified by its benefits, and right now there is no evidence to inform an additional payment for treating the second eye beyond the manufacturing costs associated with treatment. As such, we have now described this as an additional uncertainty in the Comparative Clinical Effectiveness section.
9.	4. Improper assignment of health utility values The health utilities used in ICER's analysis are sourced from a time trade-off (TTO) -based study conducted in the UK.[9] The mapping methodology between the visual impairment health state to health utilities drawn from the study and applied to the model is not exercised consistently. In following the linear functional relationship, the better than counting fingers (BCF) health state utility (0.5) is taken from the "profound impairment" health state. However, the trial data show a 6% probability of achieving a health state of "moderate impairment," which has a much high utility (0.78) in the study. An appropriate alternative would be to estimate the utility for the BCF health state to be a weighted average of the health states that were BCF in the original publication. This would yield a utility of 0.643 for the BCF health state. Alternatively, the model structure	ICER Response: We have added clarity to the evidence report to acknowledge the assumptions we made to apply the health state utility values from O'Brien 2023 in our model. Additionally, we adjusted the 0.5 utility for better than counting fingers to 0.54 to reflect findings from the RESTORE trial that approximately 25% of patients who reached the better than counting fingers health state achieved a level of visual functioning of "severe impairment" which was associated with a utility value of 0.65 (i.e., 0.65*25% + 0.50*75%).

	could be adjusted to include health states that capture the full range of visual acuity improvements that patients experienced in the trial up to moderate impairment.	
10.	5. Rate of visual acuity decline for usual care and *sonpiretigene* from natural history data ICER with the current modeling approach of using an exponential function (y=0.02684e-0.07980x, y=logMAR score, x = time in years, with the rate of logMAR increase decreasing with time) based upon 1.75% annual rate of visual acuity decline from the literature grossly underestimates the natural history visual acuity decline. For example, with initial logMAR of 1.4, the first year decline is 1.74%, with the rate of decline decreasing in time (for example, at 10 years, the rate of decline is only 0.77%). For an initial logMAR of 1.6, the first year rate of decline is 1.53%, well below the assumed 1.75%. In addition, the assumed exponential rate of visual acuity decline is inconsistent with the average transition times provided in Table E2.4. We kindly request ICER to use a constant 0.04 logMAR/year decrease in visual acuity across the health states based on existing literature and Nanoscope's pre-BLA submissions to the FDA (several sources including analysis of Qdata® Retinitis Pigmentosa data from Verana Health® based on the AAO IRIS® Registry support the 0.04 logMAR/year decrease in visual acuity). Without offering strong biological reasoning, ICER assumed a much greater rate of visual acuity decline for the *sonpiretigene* arm after the end of the durability period (5 years for base case) such that the visual acuity of *sonpiretigene* arm and usual care arm are the same at Year 10. Using the same rate of visual acuity decline across arms after the end of the durable treatment period has a strong material impact on the incremental cost-effectiveness ratio, as shown in the Table (base case *ICER* drops from $2,565,675/QALY to $1,656,581/QALY). It is not clinically plausible that *sonpiretigene*-treated patients would progress faster than natural history during the waning period after the full treatment effect. We recommend that patients should, at a minimum, return to the natural history progression rate after the treatment effect duration timeline. Also, this recommendation is more reasonable and avoids the plausibility of rapid decline extending past the waning period and *sonpiretigene* arm having a worse visual acuity than the usual care arm beyond the waning period.	ICER Response: We would like to clarify that to determine the average number of years to progress to the next health state, we simulated data using a 1.75% decline in visual functioning using change in LogMAR score (i.e., increase) per year starting at a LogMAR of 1.6. We converted the simulated data to decimal form and fit an exponential function to the data. This function served to derive the number of years it would take a patient to progress to the next health state and offered a more intuitive interpretation of the loss of visual functioning over time. Using this approach, the decline in visual functioning based on an increase in LogMAR is approximately 0.035 per year.
11.	6. Additional considerations: "There were secondary outcomes described in RESTORE that have not been publicly reported. Some were not fully collected, and others…Given these considerations, for	ICER Response: Thank you for this comment. We had acknowledged that some secondary outcomes were "not fully collected, and others were noted to have

	adults with advanced RP and severe vision loss, we rate treatment with sonpiretigene as promising but inconclusive ("P/I")." -Page ES2 Nanoscope Response: Advanced RP is a rare disease, and there are challenges to conducting a randomized, double-masked, sham-controlled trial with a large sample size and collecting data on endpoints. Despite these challenges, we shared with ICER the requested outcomes data from RESTORE. As expected, some outcome measures in the RESTORE protocol were exploratory endpoints, which were not the primary focus nor mandatory for assessing the clinical efficacy of *sonpiretigene*. Also, we would like to clarify that the exploratory endpoints referenced were not consistently collected across sites/patients and, therefore, not shared with ICER due to incomplete data availability and limited interpretability. In addition, the RESTORE trial results are currently under review in a peer-reviewed journal, and therefore, ICER's concerns regarding reporting bias are unwarranted. The primary and key secondary endpoints of the RESTORE trial were met, and numerous biomarkers (e.g., *sonpiretigene* expression) collected in the trial support the proposed mechanism of action (MOA). Therefore, ICER expressing skepticism about the biologic plausibility of the treatment is at odds with the existing evidence. Based on the arguments presented above, we request ICER to revise the "promising but inconclusive ("**P/I**") rating for clinical effectiveness to "**A**."	challenges with interpretation" based on prior feedback. We continue to have some concerns about the mismatch of the trial protocol and the outcomes data provided to us at the time of this report. Please note that our rating of "P/I" was informed by the totality of uncertainties described in the first paragraph on Page ES2 and in the "Uncertainty and Controversies" section, and not by the potential for reporting bias alone.
12.	"The *sonpiretigene*-treated group also had numerically greater improvements on mobility and shape discrimination tests that were not statistically significant." -Page ES1 Nanoscope Response: The statistical significance was lost due to the small sample size (not uncommon for rare diseases) as a significant number of participants' performance was at the ceiling of the assays during baseline assessment (e.g., 5/18 in the *sonpiretigene*-treatment group were at the ceiling for mobility and had no room to improve). The novel endpoints were deployed for the first time in RESTORE, and the study was powered to find a difference in visual acuity and not powered to find a difference in these novel functional vision endpoints.	ICER Response: Thank you. We now acknowledge in the Uncertainty subsection in Section 3.2 that RESTORE "may be underpowered for secondary outcomes."
13.	"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." -Page ES2	ICER Response: As addressed in prior comments, we have revised the baseline health state distributions to be equal between sonpiretigene and usual care and have revised our placeholder price to half of the estimate in our draft evidence

	Nanoscope Response: If the imbalance in baseline health states distribution between *sonpiretigene* and usual care groups is addressed with one eye only treatment and lifetime durability, the cost-effectiveness approaches commonly used cost-effectiveness thresholds and is below thresholds suggested for rare diseases (please refer Table on page 1).	report to align with the evidence from the RESTORE trial where patients were only treated in one eye. We have also reiterated in prior comments our concerns about the anticipated durability of treatment effect and have retained the potential for lifetime durability of treatment effect as a scenario analysis. Cost-effectiveness analysis results have improved and remain above commonly used cost-effectiveness thresholds.
14.	"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." -Page 32 Nanoscope Response: Based on the proposed MOA, preclinical data, and clinical evidence, lifetime durability is expected. As described in Page 2, no phototoxicity was observed in preclinical studies (having >70% transduced bipolar cells confirmed) even under chronic exposure to high-intensity light (0.1mW/mm^2, an order of magnitude higher than that required to activate MCO-010) over 4 months.	ICER Response: While promising, long-term durability is uncertain for this innovative therapy. In the absence of such evidence, this estimate was informed by input from experts and was evaluated in sensitivity and scenario analyses in the economic model, including a scenario that assumed a lifetime maintenance of treatment effect.
15.	"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." -Page 16 Nanoscope Response: Our publication shows that intravitreally-injected *sonpiretigene* is not present in the brain (and there was no transduction of cells in the brain), therefore, ICER's concern is not supported by the available evidence.	ICER Response: Thank you. We note this possibility because we do not have data on transfection in human brains.
16.	"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." -Page 16 Nanoscope Response: We have several publications on *sonpiretigene* in larger animals. In addition, we have a study completed in a non-human primate model of retinal degeneration that shows the effectiveness and safety of *sonpiretigene* in improving visual function (objectively	ICER Response: We commend Nanoscope for beginning to generate efficacy and safety data in non-human primates. At this time, the evidence is insufficient to assuage concerns about durability and safety. Longer-term trial outcomes in humans would be most helpful to clarify these uncertainties.

	measured by multifocal electroretinogram) and structural improvement (measured by optical coherence tomography) as similarly observed in the mice study.[1] This study report can be provided to ICER, upon request. Further, multiple publications on *sonpiretigene* clinical trial outcomes are in review in high-impact journals.	
17.	"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)." -Page 15 Nanoscope Response: Visual acuity is assessed in a robust manner using Freiburg Visual Acuity Test (FrACT), which avoids assay learning through repeat testing. FrACT has been successfully validated in a prospective clinical trial (NCT02198534) and by independent laboratories. FrACT demonstrates good test-retest reliability, with a variation of ~0.1 logMAR. It is standardized and reproducible, and has been recommended for clinical studies, including those for optogenetic therapies, in individuals with low vision by the International HOVER (Harmonization of Outcomes and Vision Endpoints in Vision Restoration Trials) Taskforce, which comprises eighty of the world's experts in vision restoration and low vision. It has been demonstrated that FrACT results are bias-free estimators of visual acuity over the full range of visual capacities of the *sonpiretigene* patient population. Even in the hand motion (HM) range, FrACT enables reproducible quantification of visual acuity. Therefore, the measured improvement (observed in repeated measures and visits) in LD MCO-013 from ~2.25 logMAR to ~0.5 logMAR is accurate. Theoretically, it is plausible to achieve 0.5 logMAR vision by stimulation of dense bipolar cells. Since *sonpiretigene* transduces bipolar cells and ambient light is sufficient to activate transduced cells, the achieved 0.5 logMAR (20/60) vision is within the range of vision that is achievable by the MOA of *sonpiretigene.* Finally, given the totality of our response to key clinical questions on *sonpiretigene* biological plausibility, efficacy, and safety posed by ICER, we request ICER to upgrade the evidence rating of "promising but inconclusive ("**P/I**") rating for clinical effectiveness to "**A**."	ICER Response: Thank you for this comment. We have revised this sentence to reflect inconsistency in measurements rather than implausibility of treatment benefit, which now reads: "…some of the outcomes in single patients appear internally inconsistent and may reflect measurement issues (e.g., HD MCO-003 in Figure 3.2 had minimal improvement in visual acuity but maximal improvement in mobility of 6 light levels)." Please note that the treatment effect captured in the economic model accommodates transitions of three health states (e.g., movement from light perception to better than counting fingers) to account for this degree of treatment benefit observed in some participants in RESTORE. Lastly, our rating of "promising but inconclusive" is reflective of the level of certainty in the evidence, which we summarized in the first paragraph on page ES2. This rating does not reflect the potential range of clinical effectiveness for individual patients. As shown in the ICER Evidence Rating Matrix in Figure 3.3, the clinical effectiveness of "P/I" rating can include potential for a small to substantial net benefit.

#	Comment	ICER Response
Patient Group		
Prevent Blindness		
1.	Background: The background does not provide detail as to the typical age of onset of RP, the first symptoms of which typically occurs in childhood or early adolescence, with significant vision loss occurring by age 30. This is significant as the timing of this disease will involve significant parent/caregiver costs to meet the needs of a child or young person with RP. This may also increase societal costs related to added educational accommodations, engaging experts such as Teachers for the Visually impaired, or structural modifications.	ICER Response: Thank you for this comment. We have now added this sentence to the Background: "The age of onset and rate of progression vary depending on the genetic mutation; some individuals develop significant vision loss in childhood, while others are asymptomatic until adulthood."
2.	Also, not covered are the secondary visual effects that patients with RP often encounter, including cataract and glaucoma. Some discussion as to the prevalence of concurrent conditions in patients with RP would be appropriate in this section and how the presence of other ocular conditions may contribute to the complication of the progressive nature of vision loss and related costs for those with RP.	ICER Response: Thank you for this comment. We recognized that standard of care includes managing ophthalmic complications of RP, such as cataracts and macular edema. Because this optogenetic therapy is not expected to prevent or treat these complications, we did not elaborate on this further in our Evidence Report.
3.	Chapter 2, Line 9: Should read as "progressive, central visual loss."	ICER Response: Thank you for this feedback. The sentence has been revised.
4.	Chapter 2: This section is titled "Patient and Caregiver Perspectives", though there is no indication that any caregivers were ever recruited for or participated an interview or focus group. It may be a bit presumptive to say that caregiver perspectives are included if it is only statements from research studies or patients in relation to their perceived impact on caregivers. If this is the case, please retitle this chapter to "Patient Perspectives" and restate the sentence on page 16 to "Research shows [*or* the patient participants stated that they recognize] 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."	ICER Response: Thank you for raising this concern. There were only individuals living with RP in the small group interviews and Econ Patient Pilot Project. Per your suggestion, Section 2, formerly, "Patient and Caregiver Perspectives", will be retitled to "Patient Community Insights." Additionally, we have also revised this sentence as suggested to read "Research has shown that there are considerable…"
5.	Additionally, with the discussion on the psychosocial impact of RP on caregivers being limited to a single sentence, it poorly reflects the true scope of impacts experienced by caregivers. This can be better defined in the context of the report as they experience a range of impacts- from social, work-related, family relation dynamics, economic, and other sorts of stressors due to their care of an individual with RP.	ICER Response: Thank you for this suggestion. We have now expanded this section to better define and contextualize caregiver burden in advanced RP.
6.	Chapter 2 of the report would also benefit from a broader explanation and exploration of the psychological impact of	ICER Response: Thank you for this comment. We have now further

	low vision due to RP and the need for mental health support in this area. At present, the report only briefly touches on this topic.	elaborated on this important topic. We have added that individuals express frustration and worry and that people with RP have higher rates of anxiety and depression symptoms.
7.	Chapter 2, Health Equity Considerations: There was no recognition of variations in ability to address stressors due to differences in status of Social Determinants of Health, a much broader approach to ability to access and engage in care than "socioeconomic status" alone. This would include considerations such as social support, ability to get time from work, personal beliefs, insurance coverage, financial stability, etc. Additionally, this section uses a number of terms which are not well received by the current administration (such as "equity" and "historically marginalized"). You may want to consider reframing under the SDoH framework for better positioning.	ICER Response: Thank you for this comment. We have now defined lower socioeconomic status in this section as suggested. Thank you for your comments on reframing our SDoH framework. As an independent organization that conducts evidence-based reviews of health care interventions, it is our long-standing commitment to use language that is widely understood and employed in scientific and medical literature.
8.	Supplement B1: Under "Key Data Inputs for the Model (Quality of Life)" -should read: "How would you describe changes in your quality of life, if any, if you went from being able to perceive light to being able to see hand motions?	ICER Response: For this question, we asked participants to share how their quality of life has changed as their vision changed. The question was framed from the standpoint of understanding the impact on quality of life due to progressive vision loss. The language in the report reflects how the question was presented to participants during the discussion – i.e., the impact on quality of life when moving from being able to see hand motion to only being able to perceive light.
9.	Supplement E1: The table should provide economic consideration results separately for both patients and caregivers. Combining them into one table insinuates that there is only a singular impact due to non-health care sector costs, when in reality both the patient and caregiver may EACH experience costs related to productivity, education, housing, etc. reflecting a more compounded impact of RP related costs.	ICER Response: The impact inventory presented in Supplement E1 reflects the version currently recommended by the Second Panel In Cost-Effectiveness in Health and Medicine. Although the current version of the impact inventory does not report all patient and caregiver impacts separately, it is our intent to report cases where the caregiver impacts were also captured within each associated domain. For this review, caregiver costs were included for those accrued through unpaid family and friends and have been captured under "unpaid caregiver-time costs".
10.	We also recommend providing a key for the markings used throughout the table, including the "X", the square, and NA	ICER Response: Thank you for the suggestion.

	to ensure uniform understanding of the data being presented.	We added footnotes to explain the meaning of the indicators included in the table: i.e., "Table E1.1 Notes: The "X" within the table shows that the domain was included in the analysis. The square in the table represents a potentially applicable domain that was not included in the analysis."
11.	General comments: - The report does not have a strong emphasis on the broader education of the public and those with RP about the condition which will be needed as treatments for the condition become available. Educating the RP community and care givers is essential in coping with this disease when new treatment options emerge. - In those areas of the paper which discuss access, consideration for geographical variations in availability of care should be discussed as well.. If the treatment were to be implemented as was done with Luxturna, at limited treatment centers around the country, the possibility of challenges related to geographical access will occur.	ICER Response: Thank you for these comments. In Section 2, we now included discussion of the need for better awareness of the progression of vision loss and adaptive tools and training to better help individuals cope with living with RP. Our report will be complemented by the public meeting and policy roundtable discussion which will provide additional opportunities for education on key areas pertaining to this specific treatment of advanced RP in general. Regarding geographic access, experts we spoke to expressed that the mode of injection (intravitreal) might increase availability compared to subretinal injection of Luxturna®, which requires more specialized treatment centers. We will be further exploring availability and potential challenges with access during our policy roundtable during the public meeting.