March 6, 2025

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: Scenarios	**Individual Scenario ($/QALY)**	**Cumulative Scenarios ($/QALY)**
Base Case	$2,565,675	
1. Correction of baseline health state distribution	$1,380,697	$1,380,697
2. Lifetime treatment effect	$894,642	$687,915
3. Alignment of intervention cost with treatment effects	$1,283,327	$348,593
4. Adjustment of utility value for Better than Counting Fingers to 0.643 from 0.5	$1,295,155	$197,019
5. Adjustment of natural history visual acuity progression	$1,656,581	$167,429

Detailed Comments and Recommendations:

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*.

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.[1] The biological age ratio between mice and humans is 1 mouse month to approximately greater than 3 human years.[2] 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.[2,3] 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.[4] 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.[2,4] 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.[1]

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*.

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.[1] 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.[1,5] 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.

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.[6,7] 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.[8]

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 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.

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.

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.[9] 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 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.

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[10] 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.

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 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**."

"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.

"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

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).

"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.[1,5]

"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[11] 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.

"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.[12,13] 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 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.

"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.[14] 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.[15] 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.[16] 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**."

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March 6, 2025

Institute for Clinical and Economic Review
Attention: Madeline Booth, Program Manager
Two Liberty Square Boston, MA 02109
Email: publiccomments@icer.org

RE: Draft Evidence Report for sonpiretigene isteparvovec (Nanoscope Therapeutics)

Dear Ms. Booth,

On behalf of Prevent Blindness, I appreciate the opportunity to offer comments in response to the Institute for Clinical and Economic Review's (ICER) Draft Evidence Report on for sonpiretigene isteparvovec (Nanoscope Therapeutics) for treatment of Retinitis Pigmentosa (RP). Prevent Blindness is the nation's leading eye health and safety patient advocacy organization. We promote vision awareness and action through education, advocacy, and empowerment, impacting the lives of millions of Americans each year through our mission of preventing blindness and preserving sight. We work with members of our Scientific Committee, patient advocates, and key stakeholders to guide the implementation of our mission and ensure an evidence-based approach. Based on this expertise, we offer the following recommendations on the report:

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.

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.

Chapter 2, Line 9: Should read as "progressive, **central** visual loss."

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.[33]”

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.

Chapter 2 of the report would also benefit from a broader explanation and exploration of the psychological impact of 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.

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.

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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**?

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.

We also recommend providing a key for the markings used throughout the table, including the "X", the square, and NA to ensure uniform understanding of the data being presented.

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.

On behalf of Prevent Blindness, we are pleased to be an active part of this treatment and value assessment process, elevating the role of the patient voice in this work. We look forward to continuing dialogue with ICER as this project moves forward.

Respectfully submitted,

Kira N. Baldonado, MPH
Vice President of Public Health & Policy
Prevent Blindness