REPORT AT A GLANCE: RETINITIS PIGMENTOSA

KEY FINDINGS

Intervention	Comparators	Evidence Rating	US Price	Health-Benefit Price Benchmark
sonpiretigene isteparvovec (Nanoscope Therapeutics)	Usual care, such as: • Low vision aids • Mobility training and support • Vision related rehabilitation	"P/I" promising but inconclusive	Not yet approved	$67,400 to $101,300 for treatment in one eye

"Many individuals with retinitis pigmentosa develop severe vision loss as the disease progresses and photoreceptor cells are lost. Researchers have examined the idea of inserting proteins into other cells that remain in the back of the eye to allow those cells to react to light. Sonpiretigene isteparvovec is a one-time gene therapy that codes for such proteins in remaining retinal bipolar cells. We have a number of uncertainties about the efficacy and durability of this therapy given the limited evidence to date, but the underlying scientific approach is remarkable."

– ICER's Chief Medical Officer David Rind, MD

THEMES AND RECOMMENDATIONS

- Researchers and regulators should partner with patients, clinical specialty societies, and manufacturers to validate and standardize patient-centered outcome measures for use in registries and future trials that capture the full range of perceived visual function in individuals with advanced RP with severe vision loss.
- Given that response to sonpiretigene appears to be widely variable across patients and that the durability of response is uncertain, payers that consider implementing outcomes-based contracts using best-corrected visual acuity (BCVA) should have a mechanism for judging meaningful responses that cannot be captured from BCVA. An outcomes-based contract that allows for patient and clinician reported outcomes and allows for refunds or rebates for treatment effects that are not maintained may be appropriate for a gene therapy that is expected to have a high price.
- The manufacturer should moderate launch price decisions to reflect the substantial uncertainty regarding treatment response, durability of treatment effect, and longer-term safety.
- While some payers may consider a requirement that sonpiretigene be administered by retinal specialists or at a center of excellence for retinal care, clinical experts agreed that most ophthalmologists could administer this treatment in their office given the intravitreal route of injection. Payers may consider requiring consultation with a retinal specialist to attest the diagnosis and eligibility for treatment.

Clinical Analyses

KEY CLINICAL BENEFITS STUDIED IN CLINICAL TRIALS

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). 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. RP by itself is not a lethal disease. Overall annual health care costs per person are estimated to be only $7,000 more in people with retinitis pigmentosa than the general population, but vision loss can also lead to substantial individual productivity losses, including unemployment, as well as harms to wellbeing.

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. 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. This approach may work across a wide range of RP mutations since the therapy does not directly target any particular genetic cause.

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

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

RP affects different aspects of vision (peripheral vision, light perception, color perception, acuity) over time and, as such, any single measure of benefit may be inadequate for assessing a given patient. The data in RESTORE, with only 27 participants, are sometimes difficult to interpret given the variability in treatment response across different outcomes measures. Patients may respond differently to the treatment. Floor and ceiling effects in the various outcome measure ranges contribute to this issue, and some of the outcomes in single patients appear internally inconsistent. There were secondary outcomes described in RESTORE that have not been publicly reported. Some were not fully collected, and others were noted to have challenges with interpretation. The mismatch between the protocol and data available raises some concerns about reporting bias. We necessarily have concerns about the durability

Clinical Analyses

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").

Economic Analyses

LONG-TERM COST EFFECTIVENESS

We conducted an economic analysis that modeled the long-term cost-effectiveness of sonpiretigene using a placeholder price of $437,500 assuming that treatment is only given in one eye. Short-term treatment effect (improvement at Year One) was modeled using individual patient-level data submitted by the manufacturer under ICER's academic-in-confidence policy. Patients treated with sonpiretigene had improved health outcomes (0.72 discounted incremental evLYs and QALYs) and higher costs ($464,100 incremental costs) compared to usual care.

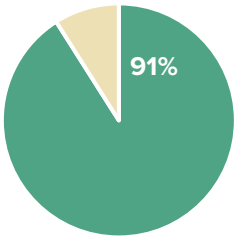
At the placeholder price, assuming that only one eye is treated, our analysis suggests that treatment with sonpiretigene would exceed commonly used cost-effectiveness thresholds. Results were primarily driven by health state utilities, durability of treatment effect, and the starting age of patients receiving treatments. Assuming a five-year durability of treatment effect, sonpiretigene would meet commonly used cost-effectiveness thresholds if priced between $67,400 and $101,300 for treatment in one eye.

The potential benefit of treating both eyes is unknown, and as such, there is no evidence to support an additional cost for treating a second eye beyond the cost of manufacturing. If sonpiretigene is shown to have a longer durability of effect, cost-effectiveness would improve. However, even when assuming a lifetime durability of treatment effect, sonpiretigene remained above commonly used cost-effectiveness thresholds.

POTENTIAL BUDGET IMPACT

Assuming a 20% uptake of sonpiretigene each year, 91% of patients could be treated over five years at the placeholder price of $437,500 before reaching the ICER potential budget impact threshold of $880 million per year.

sonpiretigene isteparvovec



Percent of eligible patients with retinitis pigmentosa that could be treated in a given year before crossing the ICER potential budget impact threshold

Public Meeting Deliberations

VOTING RESULTS

ICER's Virtual Public Meeting: Voting Results on Clinical Effectiveness and Contextual Considerations

ICER assessed, and the independent appraisal committee voted on the evidence for the net health benefit of sonpiretigene in adults with retinitis pigmentosa with severe vision loss:

- A majority of panelists (10-2) found that current evidence is **adequate** to demonstrate a net health benefit of sonpiretigene isteparvovec in comparison to usual care alone.

Panel members also weighed potential benefits and disadvantages beyond the direct health effects and weighed special ethical priorities. Voting highlighted the following as particularly important for payers and other policymakers to note:

- There is substantial unmet need despite currently available treatments.
- The treatment is likely to produce substantial improvement in caregivers' quality of life and/or ability to pursue their own education, work, and family life.
- The treatment offers a substantial opportunity to improve access to effective treatment by means of its mechanism of action or method of delivery.

ICER's Virtual Public Meeting: Voting Results on Long-Term Value for Money

Sonpiretigene has not yet been approved by the FDA for retinitis pigmentosa, and the manufacturers have not announced a US price for the therapy if approved.

ICER has calculated a health benefit price benchmark (HBPB) to be between $67,400 and $101,300 for treatment in one eye.

Consistent with ICER's process, because there was no firm estimate of a potential launch price during the public meeting, the panel did not take a vote on the treatment's long-term value for money.

About ICER

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