Sonpiretigene Isteparvovec for Advanced Retinitis Pigmentosa

Revised Background and Scope

October 16, 2024

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 1 in 4,000 individuals worldwide with an estimated 80,000-110,000 people affected in the United States (U.S.).[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] RP is not a lethal disease, although visual impairment is generally associated with greater mortality.[4-6] 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 as well as harms to wellbeing.[7-9]

RP is diagnosed by a combination of eye examinations, genetic testing, and family history.[10] Genetic testing has become increasingly important because the rate of progression and visual prognosis depends on the inheritance pattern and underlying genetic mutation.[11] Around 80 causative genes have been identified.[12] Approximately 65% of RP cases are non-syndromic, meaning that only the eyes are affected.[13] 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.[13]

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.[14] In 2017, the Food and Drug Administration (FDA) approved voretigene neparvovec, a gene therapy for *RPE65* mutation-associated retinal dystrophy.[15,16] This mutation most commonly causes a retinal disorder related to RP, but rarely causes a form of RP.

Across all forms of RP, photoreceptor degeneration progresses 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.[16] 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.[17] 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-10).[18] MCO-10 photosensitizes bipolar cells, which are neurons that connect the outer retina to the inner retina.[19] A rolling submission of a Biologics License Application (BLA) to the US FDA is anticipated to begin in the first quarter of 2025.[20]

Stakeholder Input

This revised scoping document was developed through outreach and engagement of diverse stakeholders, including patients and their families, clinicians, and the manufacturer of the agent of focus. This document incorporates feedback gathered during preliminary calls with stakeholders and open input submissions from the public. ICER looks forward to continued engagement with stakeholders throughout its review and encourages comments to refine our understanding of the clinical effectiveness and value of preventive treatments.

People living with RP experience many visual symptoms, including night blindness, loss of peripheral vision, difficulty in discriminating colors, poor light adaptation, and progressive visual loss. These visual symptoms limit important day-to-day activities, such as reading, driving, and a range of activities from playing sports to performing household chores.[21,22] They also have difficulty with relationships and participating in social events. According to national survey data, Americans with visual impairment were less likely to obtain higher education degrees and employment opportunities.[23] Nearly one-third (31%) of Americans with visual impairment had incomes below the federal poverty limit.[24]

In the most advanced stages of RP, the extent of severe vision loss was described as “devastating” such that even a slight improvement in vision may “connect them back to the world.” 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.” People with advanced RP express considerable concerns about progressing to complete blindness, how blindness would affect their personal safety, and describe considerable psychosocial and emotional distress.[21] Despite the

commonality of developing coping strategies and the resilience of individuals living with RP, there is tremendous unmet need to improve light sensitivity and restore vision in advanced RP.

We heard that vision loss progresses gradually for many years until the later stages when it becomes much more rapid. While affected individuals require considerable re-adaptation of skills, their ability to meaningfully do so is variable and often contingent on socioeconomic status given the need for visual aids, rehabilitation, training, and home modifications. A therapy that restores even slight vision would be considered extremely important to affected individuals with advanced RP. Such a therapy would provide greater certainty in decision making for the future based on regaining some basic skills and abilities. This would have potential health equity implications for those with fewer economic resources to cope with vision loss.

There are also considerable emotional, physical and financial impacts on caregivers. As a person's disease progresses, there is often an increased dependence on caregivers. Caregivers may need to reduce working hours to care for their loved one, drive them to appointments, or contribute financially to their treatments.[25]

Report Aim

This project will evaluate the health and economic outcomes of sonpiretigene isteparvovec for advanced retinitis pigmentosa. The ICER value framework includes both quantitative and qualitative comparisons across treatments to ensure that the full range of benefits and harms – including those not typically captured in the clinical evidence such as innovation, public health effects, reduction in disparities, and unmet medical needs – are considered in the judgments about the clinical and economic value of the interventions.

Applicable Framework Adaptations

We propose to assess sonpiretigene isteparvovec under an adaptation of the ICER Value Framework for treatments of serious, ultra-rare conditions because we believe they meet the following criteria:

- The eligible patient populations for the treatment indication included in the scope of the ICER review is estimated at fewer than approximately 10,000 individuals.
- There are no ongoing or planned clinical trials of the treatment for a patient population greater than approximately 10,000 individuals.

We propose to assess sonpiretigene isteparvovec under an adaptation of the ICER Value Framework for treatments of high-impact "single and short-term therapies" (SSTs), because we believe they meet the following criteria defined as:

- The therapy is delivered through a single intervention or a short-term course (less than one year) of treatment that offers a significant potential for substantial and sustained health benefits extending throughout patients' lifetimes.
- The therapy may eradicate a disease or condition, or potentially produce sustained major health gains that can halt the progression of significant illnesses.

Scope of Clinical Evidence Review

The proposed scope for this assessment is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence will be abstracted from randomized controlled trials as well as high-quality systematic reviews; high-quality comparative cohort studies will be considered, particularly for long-term outcomes and uncommon adverse events. Our evidence review will include input from patients and patient advocacy organizations, data from regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards (for more information, see ICER's grey literature policy).

All relevant evidence will be synthesized qualitatively or quantitatively. Wherever possible, we will seek out head-to-head studies of the interventions and comparators of interest. Full details regarding the literature search, screening strategy, data extraction, and evidence synthesis will be provided after the revised scope in a research protocol published on the Open Science Framework website (https://osf.io/h93ud/).

Populations

The population of interest for this review is people with advanced retinitis pigmentosa with severe vision loss.

Data permitting, we will evaluate 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 intervention of interest for this review is:

- Sonpiretigene isteparvovec (Nanoscope Therapeutics)

Comparators

Data permitting, we intend to compare sonpiretigene isteparvovec to usual care, which may include 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 and harms will be derived from studies of any duration.

Settings

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

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 would not have been considered as part of the evidence on comparative clinical effectiveness. These general elements (i.e., not specific to a given disease) are listed in the table below.

Table 1.1. Benefits Beyond Health and Special Ethical Priorities

Benefits Beyond Health and Special Ethical Priorities*
There is substantial unmet need despite currently available treatments.
This condition is of substantial relevance for people from a racial/ethnic group that have not been equitably served by the healthcare 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.
The treatment offers a substantial opportunity to improve access to effective treatment by means of its mechanism of action or method of delivery.

*Benefits beyond health and special ethical priorities shape to some extent how the value of any effective treatments for a particular condition will be judged and are meant to reflect the broader effects of a specific treatment on patients, caregivers, and society. For additional information, please see the ICER Value Assessment Framework.

ICER encourages stakeholders to provide input on these elements in their public comment submissions.

Scope of Comparative Value Analyses

A detailed economic model analysis plan with proposed methodology, model structure, model parameters, model inputs, and model assumptions will be published on December 11, 2024. This scoping document provides early thoughts about the overall model structure.

As a complement to the clinical evidence review, we will develop an economic model to assess the lifetime cost-effectiveness of sonpiretigene isteparvovec relative to usual care, which may include low vision aids, mobility training and support, and vision-related rehabilitation. The model structure will be based, in part, on a literature review of prior published models of retinitis pigmentosa and related conditions, most commonly, prior assessments of voretigene neparvovec for Biallelic *RPE65*-Mediated Retinal Disease, including a prior ICER review.[15,26] Analyses will be conducted from the health care system perspective and the modified societal perspective. The base case analysis will take a health care system perspective (i.e., focus on direct medical care costs only). Societal impacts (e.g., patient and caregiver productivity) and other indirect costs will be considered in a separate modified societal perspective analysis. This analysis will be considered as a co-base case when (a) direct data on indirect costs are available, (b) the societal costs of care are large relative to direct health care costs, and (c) the impact of treatment on these costs is substantial. This will most often occur in cases where the incremental cost-effectiveness ratio changes by greater than 20%, greater than $200,000 per QALY, and/or when the result crosses the threshold of $100,000-$150,000 per QALY gained. If direct data are lacking on patient and/or caregiver productivity, we will implement a method to capture the potential impacts of sonpiretigene isteparvovec on productivity (patient and caregiver) as well as certain other impacts (e.g., patient time in treatment).

The target population will consist of people with advanced retinitis pigmentosa with severe vision loss. The model will consist of alive health state(s) based on the degree of visual functioning and a dead state. A cohort of patients will transition between states during annual cycles over a lifetime time horizon, modeling patients from treatment initiation until death. In addition, cost-effectiveness may be estimated for shorter time horizons (e.g., five years).

Key model inputs will include condition-specific clinical measures to capture visual functioning, quality of life values, and health care costs. Probabilities, costs, and other inputs will differ to reflect varying effectiveness between interventions. Treatment effectiveness will be estimated using data from key clinical trials.

Health outcomes and costs will be dependent on time spent in each health state, clinical events, adverse events (AEs), and direct medical costs. The health outcome of each intervention will be evaluated in terms of years of blindness averted, life-years gained, quality-adjusted life years (QALYs) gained, and equal value of life years gained (evLYG). Quality of life weights will be applied to each health state, including quality of life decrements for serious adverse events. The model will include direct medical costs, including but not limited to costs related to drug administration, drug monitoring, condition-related care, and serious adverse events. In addition, patient and caregiver productivity changes and other indirect costs will be included in a separate analysis, as available data allow. Results will be expressed in terms of the marginal cost per QALY gained, cost per evLYG, cost per life-year gained, and cost per year of blindness averted.

In separate analyses, we will explore the potential health care system budgetary impact of treatment over a five-year time horizon, utilizing published or otherwise publicly-available information on the potential population eligible for treatment and results from the economic model for treatment costs and cost offsets. This budgetary impact analysis will indicate the relation between treatment prices and level of use for a given potential budget impact, and will allow assessment of any need for managing the cost of such interventions. More information on ICER's methods for estimating potential budget impact can be found here.

Identification of Low-Value Services

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 additional resources in health care budgets for higher-value innovative services (for more information, see ICER's Value Assessment Framework). These services are ones that would not be directly affected by sonpiretigene isteparvovec (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. ICER encourages all stakeholders to suggest services (including treatments and mechanisms of care) that could be reduced, eliminated, or made more efficient.

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