Voretigene Neparvovec for Biallelic RPE65-Mediated Retinal Disease: Effectiveness, Value, and Value-Based Price Benchmarks

Background and Scope
August 7, 2017

Background:

Inherited retinal diseases (IRDs) are an important cause of childhood blindness. A number of different IRDs are caused by mutations in the gene that codes for the enzyme RPE65. RPE65 (retinal pigment epithelium-specific 65 kDa protein; retinoid isomerohydrolase) is found in the retinal pigment epithelium where it plays a critical role in the regeneration of light-reacting proteins in the retina. The gene that produces RPE65 is designated RPE65, and different mutations in this gene can result in absent production (null alleles) or reduced production (hypomorphic alleles) of the protein.

Phenotypic distinctions among the RPE65-associated IRDs may reflect the amount of remaining RPE65 activity, but these may also reflect clinical difficulties in assigning correct phenotypic diagnoses. Leber congenital amaurosis type 2 (LCA2), a subset of Leber congenital amaurosis (LCA), is the most common IRD caused by mutations affecting both copies of RPE65 (biallelic mutations). The LCA2 subtype is identified when genetic testing demonstrates disease due to biallelic RPE65 mutations. Children with LCA are typically severely visually impaired or blind at birth. However, in at least some individuals with LCA2, vision deteriorates later in life; it is believed that all affected individuals are blind by young adulthood. It is estimated that approximately 3,700 individuals in the United States have LCA; of these, up to 16% are estimated to have LCA2. Thus, approximately 600 individuals with LCA2 could be candidates for gene therapy aimed at treating biallelic RPE65 mutations.

Other IRDs due to biallelic RPE65 mutations include a form of retinitis pigmentosa (RP 20) and Severe Early Childhood Onset Retinal Dystrophy (SECORD). These disorders are rare, and their exact prevalence is unknown. Preliminary estimates from the manufacturer suggest that there may be as many as 3300 individuals in the U.S. with RPE65-mediated IRDs across all diagnoses.

Effective treatments to reverse IRDs or slow their progression have generally been unavailable. Voretigene neparvovec (VN) is an investigational gene therapy for RPE65-mediated IRDs that has received an Orphan Drug Designation by the U.S. FDA for all IRDs caused by biallelic RPE65 mutations. If approved, VN would be the first approval of a gene therapy in the US. VN introduces a functioning RPE65 gene into the retina using an adeno-associated virus serotype 2 (AAV2) vector. Gene therapy with AAV2 does not repair or eliminate the defective gene, but rather introduces a normal copy of the
gene into the cell. Different promoter sequences driving gene expression have been used in different trials. Adeno-associated virus vector is believed to be safe for many different types of gene therapy as it does not cause any disease, cannot reproduce without a helper virus, is less immunogenic than other viruses, and can be manufactured to only include the genetic information of the gene being transferred for therapy.

There are distinctive and important challenges to developing gene therapies, generating evidence adequate to evaluate their safety and effectiveness, and assessing their value for patients and the health system. The spectrum of genetic and phenotypic subpopulations is often incompletely understood. Small patient populations are available for trials, creating particular challenges in generating evidence to evaluate the long-term safety and efficacy of gene therapies. Complex and evolving mechanisms for administering gene therapies raise questions about how the clinical infrastructure for delivering therapies will be organized. And, high in importance for many stakeholders, questions about the affordability of gene therapy remain prominent. The first two gene therapies approved in Europe have price tags ranging from $650K to $1 million, and some commentators anticipate similar or higher prices for the cost of VN. Key elements of an assessment of a gene therapy therefore must address how to capture all relevant aspects of the “value” of gene therapies, how to translate that understanding into considerations of value-based pricing, and how to evaluate the potential for innovative payment mechanisms to help balance long-term value with short-term affordability concerns (https://icer-review.org/wp-content/uploads/2017/03/ICER-Gene-Therapy-White-Paper-030317.pdf).

Potential major advance for a serious ultra-rare condition:

After the draft scoping document for Voretigene Neparvovec (VN) was posted, ICER posted and asked for public comment on proposed changes (https://icer-review.org/material/odaps-proposed-changes/) to its value assessment framework for treatments of certain ultra-rare conditions. While awaiting those comments, we propose now that we should assess VN using this modified framework, recognizing that public comments received and further reflection may lead to some revisions to this modified set of methods and procedures.

We propose to assess VN under modified “ultra-orphan” methods because we believe it meets the following proposed criteria:

- The treatment is envisaged for a patient population of fewer than 10,000 individuals
- There is little chance of future expansion of indication or population that would extend the size of the treated population above 20,000 individuals
- The treatment potentially offers a major gain in improved quality of life and/or length of life

The candidate population for treatment with VN may be as small as 1100 individuals and is certainly below 10,000, with no current expectations that future indications would substantially expand the population size. IRDs caused by biallelic RPE65 mutations result in blindness by young adulthood, and VN offers the possibility of substantially altering the natural history of these conditions.

The proposed modifications to our approach do not affect the early phase of assessment of a treatment or our early engagement with patient groups, the manufacturer, or other stakeholders, and so we
believe that assessing VN as a treatment under the proposed framework moving forward will accord it all the appropriate advantages that would have been expected had the framework been in place prior to the beginning of the scoping process.

**Report Aims:**

This project will evaluate the clinical and economic outcomes of gene therapy with voretigene neparvovec for vision loss associated with biallelic RPE65-mediated retinal disease. The ICER value framework includes both quantitative and qualitative comparisons to ensure that the full range of benefits and harms - including those not typically captured in the clinical evidence such as public health effects, reduction in disparities, innovation, and patient experience - are considered in the judgments about the clinical and economic value of the interventions.

**Scope of the Evidence Review Focusing on Comparative Clinical Effectiveness:**

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 collected from available randomized controlled trials as well as high-quality systematic reviews. Observational studies and case series will be considered for inclusion as well, given the limited evidence base for VN.

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 [https://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/](https://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/)).
Analytic Framework:

The general analytic framework for assessment of value of gene therapy with voretigene neparvovec for vision loss associated with biallelic \textit{RPE65}-mediated retinal disease is depicted in Figure 1.

**Figure 1. Analytic Framework: Gene therapy with voretigene neparvovec for vision loss associated with biallelic \textit{RPE65}-mediated retinal disease**

**Populations**

The population of focus for this review will include all persons with vision loss associated with biallelic \textit{RPE65}-mediated retinal disease.

We will examine the feasibility of performing subgroup analyses for patients with:

- Leber congenital amaurosis 2 (LCA2)
- Retinitis pigmentosa type 20 (RP 20)
- Severe Early Childhood Onset Retinal Dystrophy (SECORD)
Interventions
The intervention of interest will be subretinal injections of voretigene neparvovec.

Comparators
The comparator will be best supportive treatment. This may include correction of refractive error, low-vision aids, and optimal access to educational and work-related opportunities.

Outcomes
Outcome measures will include tests of the structure of the retina, such as optical coherence tomography (OCT), retinal function tests, such as visual acuity, full-field sensitivity testing (FST), and other visual field testing tools and functional tests, such as the multi-luminance mobility test (MLMT) used in the phase III trial of voretigene neparvovec.13

Discussions with patient groups highlighted certain outcomes that we will assess as the evidence allows. These include improvements in visual acuity, improvements in night vision, and a halting or slowing of disease progression. The ability to navigate obstacles in lower light settings, for example, can translate into increased mobility and independence, which can have a significant impact on a visually-impaired individual’s quality of life and productivity. We will also look for evidence on patient-reported quality of life.

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.

Simulation Models Focusing on Comparative Value:
As a complement to the evidence review, we will develop a simulation model to assess the cost-effectiveness of voretigene neparvovec versus supportive care. The model structure will be informed by previously developed economic models assessing treatments for vision impairment or vision loss and will be developed from a health system perspective.14-24 The model population will include adults and children seeking care for vision loss associated with biallelic RPE65-mediated retinal disease.

Key model inputs will likely include disease-specific measures (e.g., visual acuity), treatment-related adverse events, and health-related quality of life. If quality-of-life has not been measured directly in this patient population in clinical trials, we will use published utility data and link to trial based outcomes. Model cost inputs will include those of the treatment, costs of treating adverse events, and supportive care. If sufficient data are available, we will include productivity and other non-health care costs, along with any associated offsets, as a scenario analysis. We will create scenario analyses that seek to measure potential cost-offsets in the disability and educational systems if reasonable data or consensus estimates can be found. The primary outcome will be expressed in terms of costs per quality-adjusted life year
(QALY) gained. Additionally, we will communicate with clinical experts and other stakeholders to develop an additional cost-consequence outcome if relevant data are available.

We will also assess the potential budgetary impact of voretigene neparvovec over a five-year time horizon, utilizing modeled estimates of treatment costs and any cost offsets from reductions in use of other health care resources. Potential budget impact analyses will assume different rates of technology uptake over a five-year period in each target population based on ICER’s criteria. Finally, we will develop a “value-based price benchmark” for voretigene neparvovec reflecting prices aligned with long-term cost-effectiveness thresholds.

More information on ICER’s methods for estimating product uptake and calculating value-based price benchmarks can be found on ICER’s website.
References: