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.[1] 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.[2] 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.[3]

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.[4] 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).[5] 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.[5] It is estimated that approximately 3,700 individuals in the United States have LCA; of these, up to 16% are estimated to have LCA2.[5] 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).[5-7] 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.[8,9] 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.[10] 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.[11]

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.[12] 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:

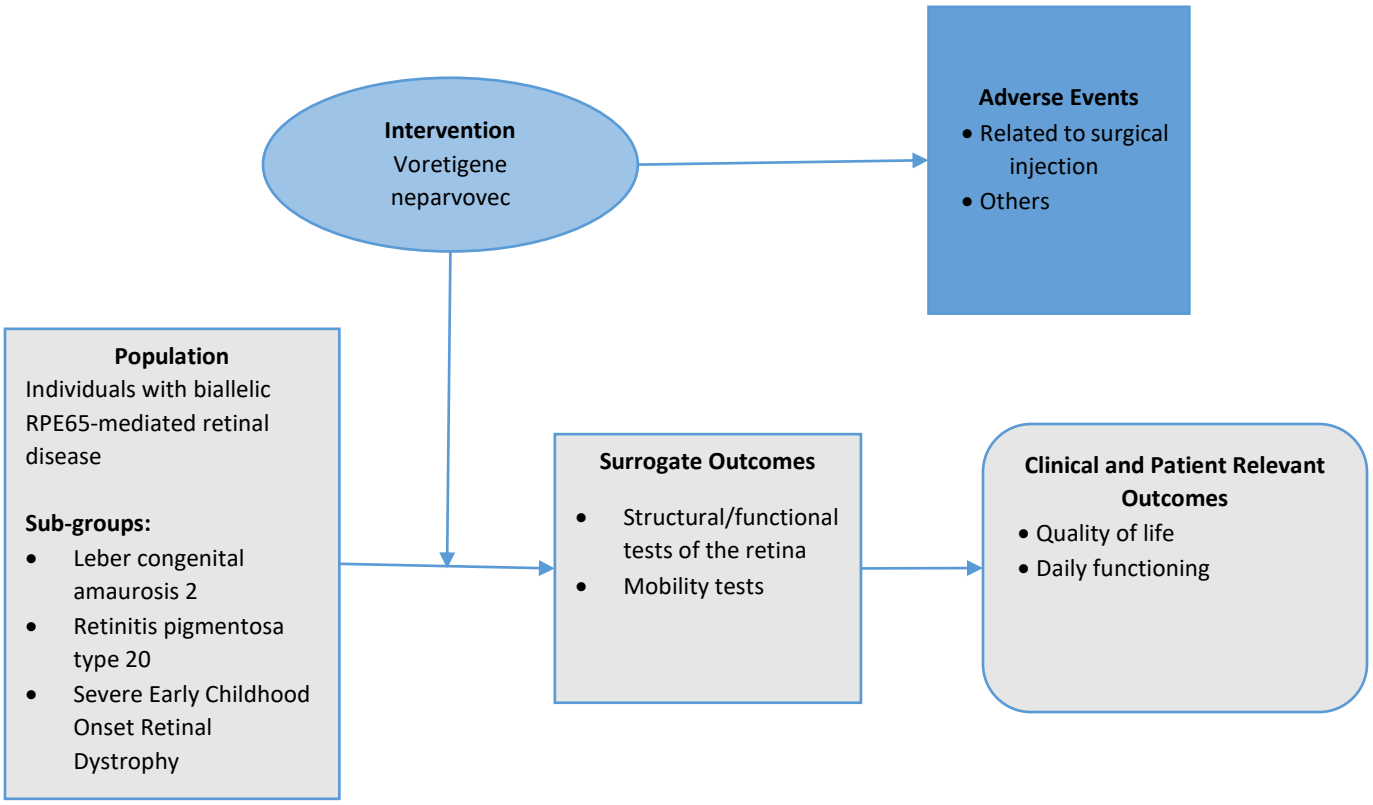
The proposed scope for this assessment is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence will be collected from available randomized controlled trials as well as high-quality systematic reviews. Observational 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/).

Analytic Framework:

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

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



<u>Populations</u>

The population of focus for this review will include all persons with vision loss associated with biallelic *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:

1. Steinkuller PG, Du L, Gilbert C, Foster A, Collins ML, Coats DK. Childhood blindness. *J AAPOS.* 1999;3(1):26-32.
2. Samardzija M, Barben M, Geiger P, Grimm C. The Consequences of Hypomorphic RPE65 for Rod and Cone Photoreceptors. *Adv Exp Med Biol.* 2016;854:341-346.
3. Morimura H, Fishman GA, Grover SA, Fulton AB, Berson EL, Dryja TP. Mutations in the RPE65 gene in patients with autosomal recessive retinitis pigmentosa or leber congenital amaurosis. *Proc Natl Acad Sci U S A.* 1998;95(6):3088-3093.
4. Chung D, Wellman J, E. L, al. e. The natural history of disease progression in patients with *RPE65*-mediated inherited retinal dystrophy. *Invest Ophthalmol Vis Sci.* 2016;57(12):6588.
5. Weleber RG, Michaelides M, Trzupek KM, Stover NB, Stone EM. The phenotype of Severe Early Childhood Onset Retinal Dystrophy (SECORD) from mutation of RPE65 and differentiation from Leber congenital amaurosis. *Invest Ophthalmol Vis Sci.* 2011;52(1):292-302.
6. Fahim AT, Daiger SP, Weleber RG. Nonsyndromic Retinitis Pigmentosa Overview. In: Pagon RA AM, Ardinger HH, et al., ed. *GeneReviews*. Seattle: University of Washington; 2017.
7. O'Neill MJF, Stumpf AM. Retinitis Pigmentosa 20; RP20. *Online Mendelian Inheritance in Man* 2017; https://www.omim.org/entry/613794. Accessed 7/6, 2017.
8. Globe Newswire. Spark Therapeutics Completes Rolling Biologics License Application Submission to FDA for Investigational Gene Therapy Voretigene Neparvovec. 2017; https://globenewswire.com/news-release/2017/05/18/987718/0/en/Spark-Therapeutics-Completes-Rolling-Biologics-License-Application-Submission-to-FDA-for-Investigational-Gene-Therapy-Voretigene-Neparvovec.html. Accessed 7/4, 2017.
9. Spark Therapeutics Inc. Spark Therapeutics Announces U.S. Orphan Drug Designation Amendment and Study Updates for Lead Investigational Gene Therapy. 2017; http://ir.sparktx.com/phoenix.zhtml?c=253900&p=irol-newsArticle&ID=2234931. Accessed 7/6, 2017.
10. Smith AJ, Bainbridge JW, Ali RR. Gene supplementation therapy for recessive forms of inherited retinal dystrophies. *Gene Ther.* 2012;19(2):154-161.
11. Naso MF, Tomkowicz B, Perry WL, 3rd, Strohl WR. Adeno-Associated Virus (AAV) as a Vector for Gene Therapy. *BioDrugs.* 2017.
12. Senior M. After Glybera's withdrawal, what's next for gene therapy? *Nat Biotechnol.* 2017;35(6):491-492.
13. Data Presented Today at the American Academy of Ophthalmology 2016 Annual Meeting Reinforce Efficacy and Durability of Voretigene Neparvovec in RPE65-Mediated Inherited Retinal Disease [press release]. 2016.
14. Dunbar JA, Hsu V., Christensen, M., Black, B., Williams, P., Beauchamp, G. . Cost-utility analysis of screening and laser treatment of retinopathy of prematurity. *Journal of AAPOS : the official publication of the American Association for Pediatric Ophthalmology and Strabismus.* 2009;13(2):186-190.
15. Earnshaw S.R. MY, Rochon S. Cost-effectiveness of pegaptanib compared to photodynamic therapy with verteporfin and to standard care in the treatment of subfoveal wet age-related macular degeneration in Canada. *Clin Ther.* 2007;29(9):2096-2106.
16. Haig J. BMFA. Cost-effectiveness of ranibizumab in the treatment of visual impairment due to diabetic macular edema. *J Med Econ.* 2016;19(7):663-671.
17. Karnon J. C-MC, Smith K., et al. A preliminary model-based assessment of the cost-utility of a screening programme for early age-related macular degeneration. *Health technology assessment (Winchester, England).* 2008;12(27):iii-iv, ix-124.

18. Mitchell P. A, L., Gallagher, M., et al. Cost-effectiveness of ranibizumab in treatment of diabetic macular oedema (DME) causing visual impairment: evidence from the RESTORE trial. *The British journal of ophthalmology.* 2012;96(5):688-693.
19. Neubauer AS HF, Sauer S, et al. . Cost-effectiveness of ranibizumab for the treatment of neovascular age-related macular degeneration in Germany: Model analysis from the perspective of Germany's statutory health insurance system. *Clin Ther.* 2010;32(7):1343-1356.
20. Rothschild MI RR, Brennan KA, et al. The Economic Model of Retinopathy of Prematurity (EcROP) Screening and Treatment: Mexico and the United States. *American journal of ophthalmology.* 2016;168:110-121.
21. Stroupe KT SJ, Tang XC, et al. . Economic evaluation of blind rehabilitation for veterans with macular diseases in the Department of Veterans Affairs. *Ophthalmic epidemiology.* 2008;15(2):84-91.
22. Taylor M SE, Ferreira A, et al. A United Kingdom-based economic evaluation of ranibizumab for patients with retinal vein occlusion (RVO). *J Med Econ.* 2014;17(6):423-434.
23. Yanagi Y FA, Barzey V, Adachi K. Cost-effectiveness of intravitreal aflibercept versus other treatments for wet age-related macular degeneration in Japan. *J Med Econ.* 2017;20(2):204-212.
24. Philippe Nordmann J LA, Berdeaux G. . Modelling the lifetime economic consequences of glaucoma in France. *J Med Econ.* 2009;12(1):9-16.