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

Background and Scope

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Background:

Inherited retinal diseases (IRDs) are a cause of childhood blindness.[1] IRDs are caused by many different mutations, and with the development and availability of genetic testing over the last decade, the responsible mutations have been identified for an increasing number of these conditions.[2-4] Effective treatments to reverse IRDs or slow their progression have generally been unavailable.

RPE65 (retinal pigment epithelium-specific 65 kDa protein; retinoid isomerohydrolase) is an enzyme found in the retinal pigment epithelium. It plays a critical role in the regeneration of light-reacting proteins in the retina, and thus is required for vision.[5] The RPE65 protein is encoded by the gene *RPE65;* mutations in *RPE65* can result in absent production (null alleles) or reduced production (hypomorphic alleles) of the protein.[6]

A number of different IRDs are caused by mutations in *RPE65*. We heard from experts that the phenotypic distinctions among the *RPE65*-associated IRDs likely reflect the amount of remaining RPE65 activity. Among IRDs caused by mutations affecting both copies of *RPE65* (biallelic mutations), Leber congenital amaurosis type 2 (LCA2), a subset of Leber congenital amaurosis (LCA), is the most common.[7] 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; all affected individuals are blind by young adulthood.[7] It is estimated that approximately 3,700 individuals in the United States have LCA; of these, up to 16% are estimated to have LCA2.[7] 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).[4,7,8] The exact prevalence of these disorders is unknown, but they appear to be rare.

Gene therapy has the potential to treat IRDs due to biallelic *RPE65* mutations. A healthy *RPE65* gene can be introduced into the retina using a viral vector. The adeno-associated virus (AAV) has proven to be a safe vector 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.[9] For IRDs, the AAV serotype 2 (AAV2) is used since it has a natural predilection for retinal cell types and can induce prolonged levels of gene expression.[10]

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.[11] The complex and evolving technology for gene therapy, the lifelong nature of genetic diseases, and the small patient populations available for trials make it difficult to establish long term safety and efficacy of gene therapy.[12,13]

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*.[14,15] If approved, VN would be the first such approval of a gene therapy in the US. The first two gene therapies approved in Europe have price tags ranging from $650K to $1 million, and it is expected that the cost of VN may be in the same price range.[13]

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:

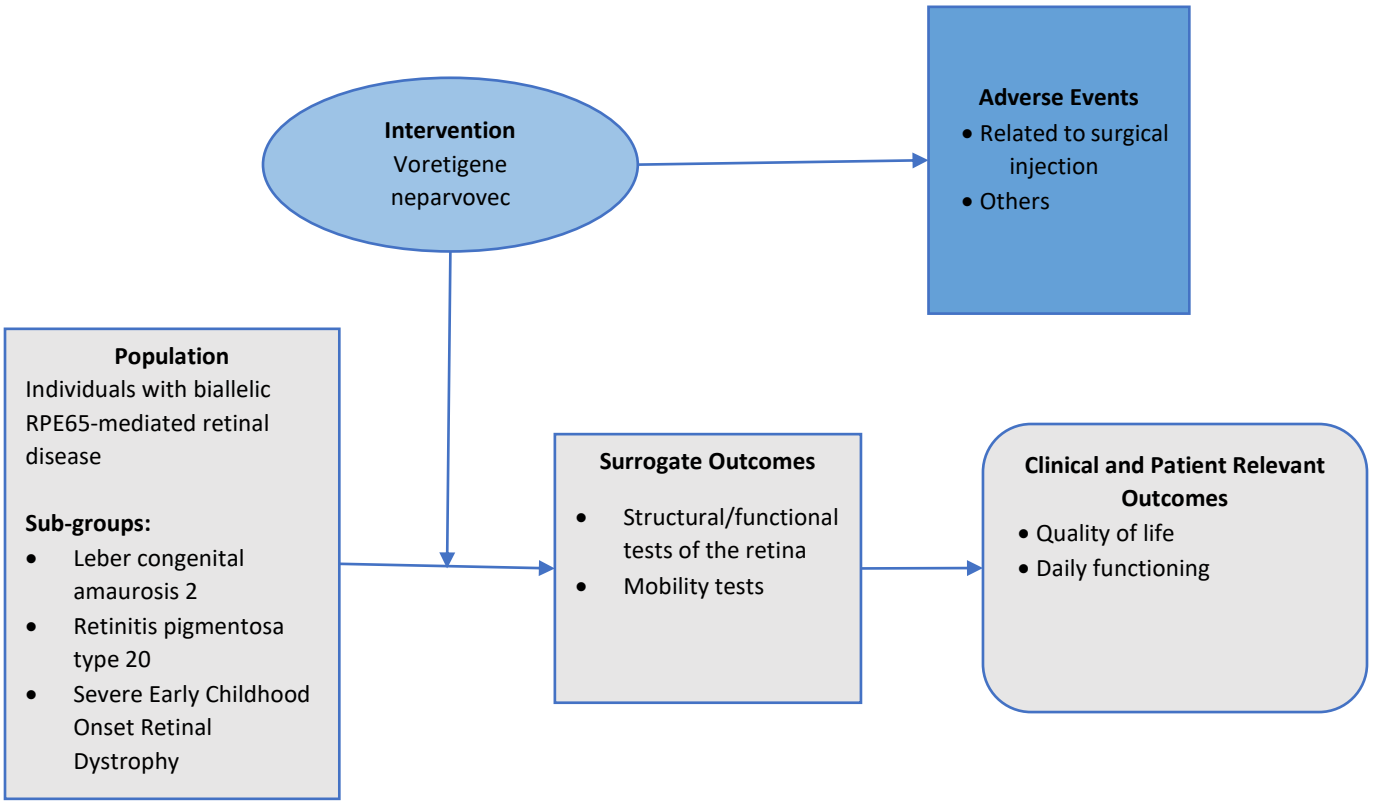
The proposed scope for this assessment is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence will be collected from available randomized controlled trials as well as high-quality systematic reviews. Observational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



Populations

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

If possible, we plan to perform 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.[16]

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.

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.[17-27] 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. 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. The primary outcome will be expressed in terms of costs per quality-adjusted life year (QALY) gained.

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. Coussa RG, Lopez Solache I, Koenekoop RK. Leber congenital amaurosis, from darkness to light: An ode to Irene Maumenee. *Ophthalmic Genet.* 2017;38(1):7-15.
3. Weleber R, Francis P, Trzupek K, Beattie C. Leber Congenital Amaurosis. In: Pagon RA AM, Ardinger HH, et al., ed. *GeneReviews*. Seattle: University of Washington; 2013.
4. 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.
5. 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.
6. 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.
7. 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.
8. 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.
9. Naso MF, Tomkowicz B, Perry WL, 3rd, Strohl WR. Adeno-Associated Virus (AAV) as a Vector for Gene Therapy. *BioDrugs.* 2017.
10. Yu-Wai-Man P. Genetic manipulation for inherited neurodegenerative diseases: myth or reality? *Br J Ophthalmol.* 2016;100(10):1322-1331.
11. Smith AJ, Bainbridge JW, Ali RR. Gene supplementation therapy for recessive forms of inherited retinal dystrophies. *Gene Ther.* 2012;19(2):154-161.
12. Marsden G, Towse A, Pearson SD, Dreitlein B, Henshall C. Gene Therapy: Understanding the Science, Assessing the Evidence, and Paying for Value - A Report from the 2016 ICER Membership Policy Summit. Boston: Institute for Clinical and Economic Review; 2017: Institute for Clinical and Economic Review. Accessed 2017-07-04.
13. Senior M. After Glybera's withdrawal, what's next for gene therapy? *Nat Biotechnol.* 2017;35(6):491-492.
14. 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.
15. 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.
16. 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.
17. 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.

18. 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.
19. 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.
20. 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.
21. 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.
22. 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.
23. 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.
24. 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.
25. 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.
26. 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.
27. Philippe Nordmann J LA, Berdeaux G. . Modelling the lifetime economic consequences of glaucoma in France. *J Med Econ.* 2009;12(1):9-16.