Spark Therapeutics (Spark) provides the following comments on the draft Background and Scope document issued by ICER on July 10, 2017 for its evaluation of the clinical and economic outcomes of gene therapy with investigational voretigene neparvovec (IVN). Spark's comments focus on the components of the Analytic Framework and the proposed Simulation Model.

I.   Comments on the Analytic Framework

Populations: Spark agrees with ICER that the appropriate population focus of the review of IVN is *all* persons with vision loss associated with biallelic *RPE65*-mediated inherited retinal disease (IRD). The proposed Analytic Framework, however, also contemplates performing subgroup analyses for patients with various clinical diagnoses. Performing subgroup analyses of patients based on clinically assigned diagnoses would likely yield unreliable and potentially misleading information because these diagnostic descriptors are not consistently applied, reflecting the similarity and fluidity of the symptoms that are used by healthcare professionals to make diagnostic distinctions. Moreover, for infrequently used diagnostic descriptors for which there are a paucity of data, the proposed analyses would be particularly difficult to perform. Subgroup analyses focusing on a few clinical diagnoses for a genetic disease that is described by numerous clinical descriptors would also reduce the sample size for an ultra-rare disease, jeopardizing the ability of an economic model to produce meaningful results for the review's targeted population; *all* persons with vision loss associated with biallelic *RPE65*-mediated IRD.

Mutations in the *RPE65* gene cause a phenotypic continuum of symptoms that are clinically grouped into various names based on different manifestations of the same etiology.[1] Clinically, this IRD was first described as Leber congenital amaurosis type 2 (LCA2) and later also as retinitis pigmentosa type 20 (RP20). Other diagnoses overlap symptomatically, some based on age of onset including early onset retinal dystrophy (EORD), early onset severe retinal dystrophy (EOSRD), severe early childhood onset retinal dystrophy (SECORD), early childhood-onset retinitis pigmentosa (ECRP), all of which eventually progress to complete blindness.[2-6] The rates of correspondence between the clinical names and the accurate molecular diagnoses are not known, but are not likely to be high considering the similarity of the symptoms used to make diagnostic distinctions.

In addition, retrospective chart reviews and a literature review indicate that distinctions in clinical diagnoses for patients with *RPE65* gene mutations are very poorly defined, and that patients might receive different diagnoses depending upon the physician. Clinical diagnoses likely reflect the training and preferences of the diagnosing physician rather than actual phenotypic differences.[4] Further, the mechanism of action, recovery of biochemical activity of the RPE65 protein, and thus the retinoid cycle, by gene augmentation, is not dependent on the clinical descriptor, but rather on the confirmed genetic diagnosis and presence of sufficient viable retinal cells. Specifically, a retrospective chart review of 70 subjects with genetically confirmed autosomal recessive mutations in the *RPE65* gene from 7 international IRD centers reported the following: over 20 distinct clinical diagnoses at initial report; 31 subjects (44%) had more than 1 clinical diagnosis over the course of their visits with an average of 3 diagnoses (range 2-7); 9 subjects (13%) had diagnoses of both LCA and RP, and another 13% had no diagnosis of either LCA or RP.[7,8]

An evaluation of the clinical and economic value of IVN must consider the natural history of biallelic *RPE65*-mediated IRD. The progressive nature of the disease is well documented with

deterioration over time in both visual field (VF) and visual acuity (VA).[2,4,7,9-13] Natural history findings also demonstrate that there is no evidence of spontaneous sustained improvement in any individual for either measurement. It is this inexorable progression toward blindness, common to all patients with IRD due to an *RPE65* gene mutation that is critical to understanding the disease rather than the disparate clinical diagnoses placed on these patients. In summary, clinical diagnoses are not reliable, are not a consistent predictor of molecular diagnosis, and do not distinguish the course of the disease for these patients, all of whom will progress toward blindness.[7,8] For these reasons, Spark does not recommend conducting a subgroup analysis based on clinical diagnoses.

Interventions: IVN is a unique gene therapy administered by subretinal injection to each eye. Results from other published gene therapy experiments treating *RPE65* gene mutations are not directly comparable to IVN or relevant to its clinical or economic evaluation.

Comparators: No regulatory-approved pharmacological treatment is available for biallelic *RPE65*-mediated IRD. The use of supportive devices for blindness such as canes, seeing eye dogs, and devices for profoundly low-vision[i] are currently used to compensate for progressive visual loss through assistive strategies; however, they do not address the underlying cause of the disease.[14,15] In clinical practice, best supportive treatment is idiosyncratic and poorly characterized in the published data.

Outcomes: All efficacy outcome measures in the IVN randomized controlled Phase 3 trial should be used in ICER's review of IVN.[2] The outcome measures assessed both functional vision and visual function. Functional vision refers to a person's ability to perform, on his/her own, visually dependent activities of daily living while visual function describes how each eye performs at the organ level.[16] In the Phase 3 IVN trial, there was clinically meaningful and highly statistically significant improvement in the primary endpoint as shown by the change in the bilateral multi-luminance mobility test (MLMT[ii]) score in the intervention group compared with controls at one year.[2] This measure of functional vision demonstrated the improved ability of subjects with biallelic *RPE65*-mediated IRD to navigate independently in low-to-moderate real-world light conditions occurring during activities of daily living. The intervention group also showed statistically significant improvements in the secondary endpoints of full-field light sensitivity threshold (FST) testing and monocular MLMT. Improvement in the third secondary endpoint of VA was not statistically significant, but improvement in VA was not necessarily expected as VA is a measure of foveal function mediated by cones and not rods, which are the primary target of IVN.

ICER proposes inclusion of optical coherence tomography (OCT) as a retinal function test. While evaluation of retinal structure measured by OCT was used as an inclusion criteria in the Phase 3 trial to determine sufficient viable retinal cells (retinal thickness >100 microns), it was not included as an efficacy outcome as it is a measure of structure, not function.[2]

As ICER is developing its framework for reviewing ultra-rare diseases, two broader classes of benefits should be considered to appropriately capture the value of an ultra-rare disease therapy

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[i] The Argus® II Retinal Prosthesis System is an implantable prosthesis available in the US on a humanitarian basis for RP patients who have no usable vision. It is not a treatment option for patients with biallelic *RPE65*-mediated IRD with viable retinal cells and therefore is not an appropriate comparator for ICER purposes.

[ii] MLMT is not currently available outside the clinical trial setting,

like IVN: 1) reduction in health disparities, taking into account that due to unknown/unclear etiology and physiopathology of rare diseases, as well as limited natural history data, there is often greater unmet need/inequity in prognosis for patients suffering from rare diseases; and 2) innovation in the pharmaceutical industry, taking into account that innovation (e.g., development of new molecular entities) has been observed to be associated with market size/profit opportunity for the innovation.[17] Given that highly innovative technologies such as gene therapies are likely to require greater research and development investment, and to face less certain market outcomes than more common technologies, decision-making around market size/profit opportunity appropriately incentivize innovation. Based on the above, ICER should elaborate how its cost-effectiveness analysis for IVN will appropriately incorporate the value of (i) equity of health outcomes and (ii) technological innovation. For instance, ICER should specify how the thresholds it has proposed (e.g., $100,000/Quality-Adjusted Life Year (QALY) and $150,000/QALY) will be adjusted. Spark will address these issues further in its response to ICER's proposed value framework for orphan drugs.

Timing: While evidence from studies of any duration may be used to inform the cost-effectiveness analysis (CEA), it should be noted that a lifetime horizon is most appropriate for the analysis, given the potential for sustained quality-of-life (QoL) differences over time between intervention and the comparator. For example, if there is uncertainty in the effectiveness beyond the duration of clinical studies, this uncertainty should be tested in sensitivity analyses over a lifetime horizon; it is not appropriate to limit the CEA time horizon to a shorter-term coinciding with duration of a clinical trial.

Settings: IVN should be surgically administered by a retinal surgeon via a procedure that consists of pars plana vitrectomy and subretinal injection administered in the surgical suite under controlled aseptic conditions. To support appropriate patient care, Spark has proposed that administration of IVN would only occur in the hospital outpatient department setting at specialized ophthalmic treatment centers. Experienced surgical staff at these centers would complete a training program provided by Spark prior to treating any patients. It is not expected that IVN would be administered in the inpatient setting, or in a physician's office.

II.   Comments on Simulations Models Focusing on Comparative Value

Without further specificity regarding the modeling approach ICER plans to use, it is difficult to offer targeted methodological comments. However, with regards to model structure, many of the cited papers in the scoping draft [citations 17-27] examine models for an age-related macular degeneration (AMD) patient population. However, the progression of AMD is based on visual acuity, which represents only one element of the progression to blindness in biallelic *RPE65*-mediated IRD. RP and similar diseases are more appropriate comparators in terms of the examined clinical endpoints, as they affect aspects of vision such as light sensitivity and VF, which are likely to significantly affect QoL (e.g., by limiting functional mobility), and the rate of impairment of these aspects of vision may differ from that of VA. In addition, without details of ICER's planned approach to completing their literature search, it is challenging to provide comments on whether the results will likely capture analogue diseases suitable for modeling biallelic *RPE65*-mediated IRD.

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Renata Szyszka, PhD   23.July.2017
Leiden, The Netherlands

Comments on the Draft Scoping Document on Voretigene Neparvovec, First Gene Therapy
Submitted for FDA Approval

It is a great privilege to be presented with an opportunity to make a brief comment on the
excellent work the entire Institute for Clinical and Economic Review (ICER) team has done up
to date towards the upcoming report on voretigene neparvovec -LUXTURNA (Spark
Therapeutics), an investigational gene therapy for *RPE65*-mediated Inherited Retinal Disorders
(IRDs), Leber's Congenital Amaurosis (LCA) type 2 usually for children with severe visual
impairment or blindness at birth.

To achieve the ultimate goal where all 600 (estimated) patients will be able to benefit from the
very best treatments at a price they can afford, it feels tempting to look into the first two gene
therapies approved in Europe which have had price tags ranging from $650K to $1 million [1].
Although the price itself might be justified if all the upfront investments to bring the therapies to
its final stage are considered, the payment schemes provide valuable lessons where
improvements can be applied.

While the EMA granted Glybera conditional market authorization with the requirement to
enlarge a post-marketing study by additional patients and to launch patient registry [2], it was not
clear if the results of the post-marketing study would confirm the company's previous claim
about it (therapy) being a one-time treatment that is effective for years. The company used that
statement in pricing negotiations with payers to finance the costly treatment.

If expected that the cost of VN may be in the same price range (from $650K to $1 million) it
might be desirable to ask whether there is already enough long-term safety and efficacy data to
support the claim for one-time treatment and the durability of the clinical benefits.

Value assessment, pricing, and payment options split over certain period, as proposed in the
report a "5-year horizon", allow the innovative therapy to blossom into its mature stage & to
prove itself a success with full range of benefits, including increase in independence and
productivity- the benefits that reach beyond the pre-determined clinical outcomes.

While there is antisense oligonucleotide technology in development for the LCA10 indication,
there are no emerging cost-competitive therapies for the LCA2 at the moment [3].

Approximately 600 individuals with LCA2 could be candidates for gene therapy aimed at
treating biallelic *RPE65* mutations. The debilitating, progressive nature of LCA2 and the young
age of patient population may carry further challenges to gathering data for the immediate
assessment of the treatment benefits. Furthermore, "if very young patients are unable to self-
report on their disease experience, it will be necessary to collect information regarding treatment
benefit indirectly from clinicians, parents, or others who have direct knowledge about patient
condition–related behavior, signs and symptoms, or functional status [4]."

Patients' awareness (including patients who are not participants of the clinical trials) about a long
term surveillance programme that might be needed to collect information on the epidemiology of
the disease is necessary at the very early phase of therapy implementation. NV is a gene therapy

product, meaning it contains genetically modified organism. Ideally, data on responses from all 600 patients might be included in the report and would be an important supplement to clinical data. The approach would highlight the importance of the patient voice in the process of marketing authorization- a considerable factor to take into account in the analyses of cost-effectiveness and risk-benefit.

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