National Institute for Health and Care Excellence

Highly Specialised Technologies (HST)

Voretigene neparvovec for treating inherited retinal dystrophies caused by RPE65 gene mutations

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	Genetic Alliance UK	Given that this treatment is expected to be licensed for only a subset of patients with inherited retinal dystrophies, an estimated ~570 individuals, it would be most appropriate for the treatment to be appraised by the HST programme, designed specifically to evaluate medicines for very small populations. As NICE is aware, the rare disease patient community have raised concerns regarding the impractical and outdated definition of 'clinically distinct' used in the topic selection criteria for the HST programme already (Genetic Alliance UK Patient Charter on NICE HST Programme). According to these criteria the medicine is technically ineligible, although exceptions have already been made for ataluren for Duchenne muscular dystrophy. **Nevertheless, we have this situation: a medicine with a likely population size of approximately 500 people is being considered for the Single Technology Appraisal (STA) programme for which the prioritisation criteria includes that a large population is impacted. In addition, the treatment meets a number of the other prioritisation**	Thank you for your comments. Following consultation, NICE proposed that this topic is evaluated through the Highly Specialised Technologies (HST) Programme. The Department of Health and Social Care have referred it as an HST evaluation.

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		criteria for the HST programme (treatment will usually be concentrated in very few centres in the NHS; the condition is chronic and severely disabling; the technology is likely to have a very high acquisition cost; the need for national commissioning of the technology is significant). The grounds for this decision are not clear and we query them.	
	NHS England	Yes although see later comments re licensing, and reservations from NHS expert clinicians.	Comments noted.
	The Royal College of Ophthalmologists	*It is important that appropriate topics are referred to NICE to ensure that NICE guidance is relevant, timely and addresses priority issues, which will help improve the health of the population. Would it be appropriate to refer this topic to NICE for appraisal?* Yes	Comments noted.
	RP Fighting Blindness	Absolutely. The condition that this technology is looking to treat is currently untreatable. This particular gene mutation (LCA) affects children and is particularly aggressive and can degenerate the retina to such an extent that sight is lost in childhood.	Comments noted.
	Spark Therapeutics	Voretigene neparvovec (VN; Luxturna™) is an innovative treatment for inherited retinal disease (IRD) caused by biallelic RPE65 gene mutations, for which no treatment is currently available. The main objective of Spark Therapeutics (Spark) is to ensure that patients in England suffering from this extremely disabling condition, which progresses to total blindness,[1,2] have access to an effective treatment as soon as possible. Spark is fully supportive of appropriate steps that will assist with ensuring such access in a timely manner.	Thank you for your comments. Following consultation, NICE proposed that this topic is evaluated through the Highly Specialised Technologies (HST) Programme. The Department of Health and Social Care have

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		As explained in more detail below this table, Spark is concerned that, by evaluating VN using the Single Technology Appraisal (STA) process, NICE may not be able to produce relevant, timely advice that will help to improve the health of the affected population. Due to the expected price for a one-time gene therapy that addresses a serious health condition (blindness) for which there is no current treatment, VN will inevitably fail an STA; any time spent conducting that exercise (instead of immediately conducting a Highly Specialised Technology (HST) appraisal) will amount to a delay in patient access, during which patients with IRD caused by RPE65 gene mutations will continue to deteriorate. Spark is confident that VN satisfies all the HST criteria as outlined below, and that the HST appraisal process is appropriate, more relevant, timely and capable of addressing priority issues.	referred it as an HST evaluation.
Wording	Genetic Alliance UK	This is the standard wording.	Comments noted.
	NHS England	*Does the wording of the remit reflect the issue(s) of clinical and cost effectiveness about this technology or technologies that NICE should consider? If not, please suggest alternative wording.* Yes	Comments noted.
	The Royal College of Ophthalmologists	*Does the wording of the remit reflect the issue(s) of clinical and cost effectiveness about this technology or technologies that NICE should consider? If not, please suggest alternative wording.* Yes	Comments noted.

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	RP Fighting Blindness	The cost of sight loss stretches far beyond the Ophthalmologist. There are secondary burdens on the NHS ranging from falls to mental health. There is also quality of life, independence and social support costs to be considered.	Comments noted. This is the standard wording for a NICE remit, please refer to the other sections of the scope for details of outcomes to be considered.
	Spark Therapeutics	The proposed labelling/indication statement for VN is under discussion with the European Medicines Agency (EMA) as the marketing authorisation application was just submitted to the EMA on July 31, 2017. Based on our current knowledge and submission to the EMA, the proposed wording of the remit reflects the issues that NICE should consider for scoping purposes. The wording of the remit should be revised to reflect the proposed indication in the marketing authorisation application. The proposed indication submitted to the EMA is as follows: "Luxturna is indicated for the treatment of patients with vision loss due to Leber congenital amaurosis or retinitis pigmentosa inherited retinal dystrophy caused by confirmed biallelic RPE65 mutations."	Comments noted. The remit has been kept broad because the marketing authorisation wording has not been confirmed. The technology will be evaluated within its marketing authorisation.
Timing Issues	Genetic Alliance UK	We understand that the marketing authorisation application was submitted to the EMA at the end of July 2017 and will receive accelerated assessment. Given the progressive nature of inherited retinal dystrophies and the lack of other treatment options, it is vital the appraisal be carried out urgently so that there is no delay to patient access following licensing.	Comments noted. NICE aim to produce draft guidance within 6 months of marketing authorisation.
	NHS England	Given that the product is yet to be licensed urgency is likely to be low at this point	Comments noted.

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	The Royal College of Ophthalmologists	Not urgent	Comments noted.
	RP Fighting Blindness	From a patient centric view-point it is imperative that when potential treatments have an opportunity to be appraised and processed as soon as is practicably possible. There are many families with children with LCA who are currently going through the trauma of watching their child lose their sight fairly quickly,	Comments noted. NICE aim to produce draft guidance within 6 months of marketing authorisation.
	Spark Therapeutics	There is an unmet need for patients with RPE65 IRD, for whom there are no current treatments,[3,4] and who will continue to progress to complete blindness.[1,2] As such, a timely review of VN is necessary so appropriate patients can be treated as soon as regulatory approval is obtained. If an appraisal is commissioned, it should be scheduled to enable NICE to issue final guidance as soon as possible after the marketing authorisation has been granted, to enable patients in need to be treated as soon as possible. Currently, a decision on the marketing authorisation is expected in [redacted].	Comments noted. NICE aim to produce draft guidance within 6 months of marketing authorisation.
Additional comments on the draft remit	RP Fighting Blindness	I cannot comment on the scientific/clinical aspects but can absolutely (on behalf of people living with these genetic mutations in their family) state that these types of treatment ned to be supported and viable treatment options brought 'to market' as soon as safely manageable.	Comments noted.
	Spark Therapeutics	Please see detailed comments towards the end of this document regarding the inappropriateness of the proposed remit under the STA process.	Comments noted. The technology will be evaluated under the HST process.

Comment 2: the draft scope

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Background information	NHS England	The background information seems appropriate.	Comments noted.
	RP Fighting Blindness	Yes to our knowledge this is correct. It is difficult to state exact prevalence of these conditions and the statistics noted are conservative.	Comments noted. The prevalence data have been updated based on other consultation comments and discussion at the scoping workshop.
	Spark Therapeutics	Certain aspects of the Background Information are inaccurate or require clarification and there is additional relevant information that should be included, as provided below. <u>Background on Genetic Mutation and Clinical Diagnosis</u> The IRD caused by mutations in the *RPE65* gene manifests a phenotypic continuum of symptoms that are clinically grouped into various names based on different manifestations of the same aetiology.[5] Clinically, this IRD was	Thank you for your comments. The background section of the scope has been updated. Please note that the scope is intended to provide a brief summary of the

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		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.[6-10] 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.[8] 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 centres 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.[1,2] Given that the evidence shows that diagnosis is not always consistent, only genetic testing can confirm the relevant patients. <u>Impact of Disease</u>	disease and how it is managed, and is not designed to be exhaustive.

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		The spectrum of *RPE65*-mediated IRD differs from the classic form of RP and its gradual progression described in the background information from NICE. *RPE65*-mediated IRD is predominantly a rod-mediated disease, although cones may be affected early in the course of the disease, as a result of accumulation of toxic by-products and structural loss of rods.[5,11] Symptoms may be temporal—the rod-mediated symptoms are usually more pronounced and earlier in both LCA2 and RP20—but the symptoms are more severe and the sequence more compressed in LCA2 patients. Due to the relative slower progression of disease in RP20 patients, the rod-mediated symptoms are more obvious before cone involvement becomes apparent.[12] Retrospective chart review showed that the progression of the disease, however, is not steady, as visual function tends to decline at a faster rate as patients reach adolescence or early adulthood, depending on the assessment used (visual field or visual acuity).[1,2] However, the high variability seen in visual function measures lends to the heterogeneity of this disease. Typically, the first symptom is the decreased ability to perceive and/or see in dim light (nyctalopia) starting in childhood, potentially associated with variable central vision impairment. Additionally, nystagmus is associated with the earliest onset form of *RPE65* disease. As the disease progresses, visual fields become even more constricted and visual acuity (central vision) declines, resulting in total blindness. Those with LCA progress more rapidly and are typically to near-total blindness as late as the 3rd decade in life.[1,6,7,13] <u>Current Treatments</u> There are no treatments that address the underlying cause of *RPE65*-mediated IRD, and the condition eventually leads to blindness. NICE notes that "Wearing sunglasses to protect the retina for ultraviolet light may help preserve vision". Although, long-term exposure to sunlight may speed-up the progression rate of the disease, and the use of sunglasses may protect the patient from this additional harmful effect of ultraviolet light, it does not	

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		address the underlying cause of the disease or its intrinsic progression rate.[14] While sunglasses may provide some theoretical longer-term protection to the retina, patients with *RPE65*-mediated IRD will inevitably progress to blindness. In addition, one of the primary symptoms of *RPE65*-mediated disease is the decreased ability to perceive and/or see in dim light (nyctalopia), and as a result, these patients consistently are in need of additional light sources (i.e., visual aid devices) to optimize their remaining, but dwindling, functional vision. Though nystagmus is less common in later stages of *RPE65* mutations, wearing sunglasses may be a social adaptation to mask the presence of nystagmus from others rather than a mechanism that protects vision. Best supportive care for IRDs in the NHS is routine monitoring on an annual basis to monitor the progression of the disease and detect the development of other complications. Currently the predominant supportive care is provided by social services. For these patients, support services comprise Personal Social Services including local authority vision impairment services, visual rehabilitation, and habilitation training / specialist educational services/ and other available support services. Many of these support services are funded by the government, or through dedicated charities. Patients also fund other necessary requirements such as home modifications. <u>Estimated Prevalence and Incidence</u> As noted above, 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.[6-10] For purposes of NICE's analysis, we vide prevalence information for estimated LCA2 and RP20 patients in England. The information below is based on the limited prevalence information available in the published literature, and Spark's own analysis, which is typical for ultra-rare diseases. It is important for NICE to understand	

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		that not all of the estimated cases outlined below are expected to be treated with VN. In addition to a positive genetic test for a RPE65 gene mutation, patients must also have sufficient retinal cell thickness to be a candidate for treatment with VN.[6] Moreover, based on conversations with physicians, a number of patients in England diagnosed with *RPE65*-mutations, have participated in clinical trials of investigational gene therapy treatments. Based on a comprehensive review and analysis of published literature, LCA is estimated to affect approximately [redacted] per [redacted] individuals[15], or approximately [redacted] individuals in England. Mutations in the *RPE65* gene are identified in 6-16% of those diagnosed with this condition,[7,8,15-34] or approximately [redacted] individuals in England, based on the total projected population in 2018 data (approximately 56.061 million).[35] The 95% CI range is approximately [redacted] to [redacted] cases. Retinitis pigmentosa (any mutation) is estimated to affect approximately [redacted] per [redacted]000 individuals.[36,37] Mutations in the *RPE65* gene were identified in [redacted]% of an enriched subset of RP patients,[7,8,16,17,20,26,38,39] which is equivalent to a frequency of [redacted]% in the entire RP population. Based on England's projected population in 2018, this represents approximately [redacted] patients with RP20. The 95% CI range is approximately [redacted] to [redacted] cases. Overall, based on the above analysis, *RPE65*-mediated IRD is extremely rare occurring in [redacted] persons per million population. The total prevalent population in England of LCA2 and RP20 expected to be [redacted] cases (95% CI [redacted] to [redacted] cases). Again, as noted above, we do not expect all of these patients to be candidates for treatment with VN. Additional research is ongoing with leading IRD experts in England to better understand the exact patient population for VN in England. Given the range of factors mentioned above, Spark anticipates a more limited number of patients being treated over the next 5 years. The range is estimated as 60-70 patients in total in England.	

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		For genetic diseases that have a normal lifespan (such as LCA or RP), incidence is equal to prevalence so we can estimate [redacted] incident cases per million births. Based on the 683,000 births in 2018 in England[40], we expect roughly [redacted] new cases (births) per year for *RPE65*-mediated LCA and RP.	
The technology/ intervention	NHS England	*Is the description of the technology or technologies accurate?* Yes	Comments noted.
	The Royal College of Ophthalmologists	*Is the description of the technology or technologies accurate?* Yes	Comments noted.
	RP Fighting Blindness	As far as our knowledge allows	Comments noted.
	Spark Therapeutics	Certain aspects of NICE's description of the technology/intervention is inaccurate or requires clarification and there is additional relevant information that should be included, which is provided below. VN is a very specific gene therapy administered by subretinal injection to each eye. There are multiple factors in the manufacture, formulation, and administration of VN that differentiate it from other investigational gene therapy products tested in clinical trials targeting the *RPE65* gene. Spark uses a chicken-β actin promoter, an optimized cytomegalovirus transcription enhancer, a bovine growth hormone poly A component, and a surfactant product in its formulation.[6,41] The surfactant product is added to minimize drug adherence to the delivery device (syringe and administration tubing, and needle).[42,43] In addition, gradient separation results in removal of nearly all "empty" capsids, i.e., viral vectors not containing active DNA product, so that the final delivered treatment contains approximately primarily "full" capsids,	Thank you for your comments. Please note that this level of detail about the technology is not normally included in NICE scopes, which are not designed to be exhaustive. Please include this information in your evidence submission.

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		with active drug product.[44] Other factors specific to VN compared to experimental procedures include the volume of the subretinal injection, the dose of genes delivered, and the pre- and post-surgical pharmacological support with corticosteroids.[6,45] Therefore, results from other published gene therapy experiments treating *RPE65* gene mutations are not directly comparable to VN or relevant to its clinical or economic evaluation. VN was submitted to the EMA for marketing authorisation on July 31, 2017; the proposed indication statement is as follows: "Luxturna is indicated for the treatment of patients with vision loss due to Leber congenital amaurosis or retinitis pigmentosa inherited retinal dystrophy caused by confirmed biallelic *RPE65* mutations." VN should be surgically administered by a retinal surgeon via a procedure that consists of pars plana vitrectomy and subretinal injection. To support appropriate patient care, Spark has proposed to the EMA that administration of VN should only occur in the hospital setting at specialised ophthalmic treatment centres. Vitreoretinal surgeons at these centres are expected to complete a training program provided by Spark prior to treating any patients with VN. Subretinal injection is not a technique commonly used by retinal surgeons for drug delivery; therefore, surgeon training is important to support appropriate patient care.	
Population	Genetic Alliance UK	We understand that the marketing authorisation application submitted to the EMA is for treatment of patients with vision loss due to Leber congenital amaurosis or retinitis pigmentosa caused by confirmed biallelic RPE65 mutations. However, based on what data from the clinical trials has been published, it appears likely that younger patients and those with less advanced disease may respond better than older patients and those with more advanced vision loss, and so should possibly be examined separately.	Comments noted. Scoping workshop attendees agreed that it would not be appropriate to evaluate subgroups separately because they are difficult to define and identify in practice, the

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			population is very heterogeneous, and the sample size of subgroups would be extremely small.
	NHS England	Lebers Congenital Amaurosis should be examined separately from Retinitis Pigmentosa.	Comments noted. Scoping workshop attendees agreed that it would not be appropriate to consider Lebers Congenital Amaurosis and Retinitis Pigmentosa separately because these subgroups are difficult to define and identify in practice. Clinical diagnoses are inconsistent between physicians and current practice focuses on genetic diagnosis.
	The Royal College of Ophthalmologists	Patients with no sight at all may not benefit, but the treatment would need to be tested in this subgroup to be sure.	Comments noted. There was no consensus at the scoping workshop about whether people with no sight at all

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			would benefit from treatment. Scoping workshop attendees agreed that it would not be appropriate to evaluate subgroups separately because they are difficult to define and identify in practice, the population is very heterogeneous, and the sample size of subgroups would be extremely small. Please note that the committee can only issue recommendations within the marketing authorisation.
	RP Fighting Blindness	yes – although this treatment maybe a pre-cursor to treating mutations on other genes that cause sight loss	Comments noted. The committee can only issue recommendations within the marketing authorisation.
	Spark Therapeutics	The population is defined appropriately in the Scoping Document; however, the text could be clarified as follows: "People with inherited retinal disease caused by biallelic RPE65 gene mutations.”	Comments noted. The technology will be evaluated within its marketing authorisation.

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			No changes to the scope required.
Comparators	NHS England	There are no comparators in established NHS clinical practice. There are a number of viral vectors in phase 2 clinical trials for RPE65. The Argus II retinal prosthesis is subject to a commissioning through evaluation scheme for suitable patients with retinitis pigmentosa.	Comments noted. No changed to the scope required.
	The Royal College of Ophthalmologists	There is no alternative at present. The visual cycle inhibitors currently in trials may have a short term effect but cannot prevent the long term degeneration.	Comments noted. No changed to the scope required.
	RP Fighting Blindness	*Is this (are these) the standard treatment(s) currently used in the NHS with which the technology should be compared? Can this (one of these) be described as 'best alternative care'?* No	Comments noted. No changed to the scope required.
	Spark Therapeutics	As noted above, currently there is no pharmacological treatments available for biallelic *RPE65*-mediated IRD. Best supportive care in the NHS is routine monitoring on an annual basis to monitor the progression of the disease and detect the development of other complications. Currently the predominant supportive care is provided by social services. For these patients, support services comprise Personal Social Services including local authority vision impairment services, visual rehabilitation, and habilitation training / specialist educational services/ and other available support services.	Comments noted. No changed to the scope required.

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		Many of these support services are funded by the government, or through dedicated charities. Patients also self-fund necessary requirements such as home modifications. For the purposes of the economic model, the relevant comparator should be the healthcare and support services available in the England for a reference group of patients experiencing the typical disease progression. In order to estimate costs of the comparator in the economic model, estimates of utilisation in the UK of resources constituting best supportive care will be sought. If such estimates are not available/sufficiently robust, estimates of resource utilisation may be sourced from the clinical literature, such as from the natural history study conducted by Reape et al. (2017).[1] Estimates of resource utilisation will be costed based on NHS reference costs.	
Outcomes	Genetic Alliance UK	While the outcomes listed describe the different individual aspects of vision loss seen in these conditions, by taking each separately the appraisal is likely to underestimate the impact of the condition, and thus possibly also the impact of the treatment. The difficulties patients with inherited retinal dystrophies experience performing essential tasks of daily living and maintaining independence come not solely from the loss of visual field or night blindness, for example, but how these and other aspects of vision loss interact and combine to cause functional visual impairment more significant than each element of vision loss taken independently might suggest. For this reason we believe that some measure of functional impairment demonstrating the real world cumulative effects of vision loss is necessary. We understand that the manufacturer have developed their own test of functional visual impairment (multi-luminance mobility testing), and believe	Thank you for your comments. Based on the discussion in the scoping workshop, no changes have been made to the list of outcomes. The list is not designed to be exhaustive; consultees are encouraged to present relevant outcomes data in their evidence submissions.

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		this and other potentially useful measures should be considered in the assessment of this treatment.	
	NHS England	The outcomes listed are appropriate but two comments are worth making. Firstly, the outcomes are not listed in order of importance. Mobility testing is clearly relevant but but tells us very little about the practical benefit to patients. A full exploration of the actual difference the therapy makes to patients' lives is crucial. Secondly, the listing of outcomes specifies no timescales for duration of benefit, and the time horizon specified in the section on economic analysis is hard to understand. Early trials of gene therapy for retinal disorders suggested that this may be limited to only a few years. It will crucial to have all available direct evidence on this point and not rely on modelled comparisons.	Thank you for your comments. The order of the outcomes listed is not intended to reflect their order of importance. Based on the discussion in the scoping workshop, no changes have been made to the list of outcomes. The outcomes list is not designed to be exhaustive; consultees are encouraged to provide information about the full impact of the disease and its treatment in their evidence submissions.
	The Royal College of Ophthalmologists	The outcome measures are appropriate. It is not so much the actual test that is important, but the fact that an endpoint proves the vector is working in the individual patient. A number of studies show that this equates to a slowing down of the retinal degeneration.	Comments noted.

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	Spark Therapeutics	All efficacy outcome measures in the VN randomized controlled Phase 3 trial should be used in NICE's review of VN.[6] To capture the most important health-related benefits of this treatment, outcomes should be selected and ordered according to their relevance to the primary disease symptoms, which reflect the pathophysiology of the disease. Specifically, the following outcomes measures should be included: Functional vision: A person's ability to perform, on his/her own, visually dependent activities of daily living as measured by the bilateral multi-luminance mobility test (MLMT). NICE should be aware that the MLMT is not currently available outside the clinical trial setting. Visual function: How each eye performs at the organ level measured by: • Full-field light sensitivity threshold (FST) testing (photosensitivity); • Visual Acuity (VA) to monitor disease progression although improvement in VA is not necessarily expected as VA is a measure of foveal function mediated exclusively by cones and not rods, which are the primary target of VN; and • Visual field. It is fully appropriate for NICE to measure the adverse event (AE) profile of VN treatment to extend the safety information Spark has collected in its clinical trials and to track AEs in clinical practice. One such AE is cataracts due to vitrectomy which are a known and expected complication post-VN administration procedure. The following outcome measures suggested in the draft Scoping Document are not appropriate and should not be included in NICE's analysis: • Contrast sensitivity: Measure of foveal function mediated by cones. Contrast sensitivity was evaluated as an exploratory endpoint in the	Thank you for your comments. Based on the discussion in the scoping workshop, no changes have been made to the list of outcomes. Clinical experts agreed that contrast sensitivity is an important outcome because it relates to a patient's central vision. The company is encouraged to submit data for this outcome. Health-related quality of life is an important outcome for patients, and important for cost-effectiveness analyses. The company is encouraged to submit data for this outcome. Please note that the outcomes list is not designed to be exhaustive; consultees are encouraged to present relevant

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		VN Phase 3 trial and there was no statistically significant difference between the intervention and control groups.[46] These results corroborate the rationale that contrast sensitivity is not an appropriate outcome measurement, since it measures cone function and not rods, which are the primary target of VN. • Health-related quality of life (HRQoL): A visual function questionnaire was tested in the VN trial, but it is not validated as a measure of improvement in functional vision nor was its intended purpose to measure patients' quality of life and therefore the results should not be included in NICE's analysis.	outcomes data in their evidence submissions.
Economic analysis	Genetic Alliance UK	This treatment has the potential to cause substantial health-related benefits unlikely to be captured in the QALY calculation. It will important to accurately calculate the full impact of the treatment on the cost of personal social services for affected individuals. However, this would still not represent the full burden of progressive vision loss due to inherited retinal dystrophies, both to individuals, their families and society. Directly and indirectly visual impairment interferes with many daily activities, including limitations accessing education, employment and recreation as well as independent living. The health-related quality of life tools NICE uses such as EQ-5D-3L capture only a tiny fraction of the physical limitations and psychosocial implications of visual impairment.	Comments noted. The company and other consultees will be able to fully describe these benefits in their evidence submissions, which will then be considered by the committee. The highly specialised technologies evaluation process considers a broader range of issues than the single technology appraisal process, the scope has been updated to reflect these.

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	NHS England	Please see comment on time horizon in previous section. There are also issues in the assessment of utility. The five dimensions of the EQ5D are unlikely to capture all the benefits of restoring functional vision to a patient who is completely or almost completely blind.	Comments noted. The highly specialised technologies evaluation process considers a broader range of issues than the single technology appraisal process, the scope has been updated to reflect these.
	The Royal College of Ophthalmologists	Gene therapy is a new treatment with great potential for a number of retinal degenerations. The concept of giving a single treatment will revolutionise the current NICE pathways of regular, life-long injections.	Comments noted.
	Spark Therapeutics	Spark intends to submit a cost-utility analysis conducted over a lifetime horizon, considering the potential for sustained quality of life differences over a lifetime between patients treated with the intervention and the comparator. In NICE's 2013 "Guide to the methods of technology appraisal"[47], it is noted that in cases where the EQ-5D may not be the most appropriate measure of quality of life, alternative health-related quality of life (HRQoL) measures may be used. In the case of visual impairment, NICE has recognized that EQ-5D may not always be the appropriate measure.[48] As such, Spark will systematically review the evidence on HRQoL in inherited retinal diseases in order to identify most suitable health-utility estimation methods. As NICE suggests, costs of relevant diagnostic procedures will be included in the base case analysis. The nature of diagnostic procedures costed in the base case may depend on NHSE's proposed commissioning for VN (i.e., the practices of expert centres where VN will be administered).	Comments noted. Please be aware of the updated Process and Methods of the Highly Specialised Technologies Programme when preparing your evidence submission: https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-highly-specialised-technologies-

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		Per NICE's guidelines, the perspective on costs will be that of the NHS and PSS. However, as shall be noted in Spark's submission, this perspective will understate other societal costs of *RPE65*-mediated IRD, such as those required for specialist education, charity support (e.g., Guide Dogs for the Blind), and faced by patients and/or their caregivers (e.g., home modifications).	guidance/HST-interim-methods-process-guide-may-17.pdf
Equality and Diversity	NHS England	We do not think there are relevant considerations under this section.	Comments noted. No action required.
	RP Fighting Blindness	*NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:* • *could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;* • *could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;* • *could have any adverse impact on people with a particular disability or disabilities.* *Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.* No	Comments noted.

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	Spark Therapeutics	Assuming that NICE proceeds to scoping on the basis that VN will be available to all suitable IRD patients, then we do not consider that the proposed remit and scope will need to be amended in order to meet NICE's equality aims. By appraising VN under the STA process rather than the HST process, NICE is setting up a process that VN will inevitably fail for cost per QALY reasons. This will prevent access to VN by people who may progress to blindness. As such, the proposed appraisal method via STA risks having an adverse impact on people with disabilities.	Comments noted. The technology will be evaluated through the Highly Specialised Technologies Programme.
Other considerations	Spark Therapeutics	VN should be stored at ≤-65°C. Once thawed, it should be used within four hours. VN is therefore best used within specialist centres that are likely to be more familiar with such storage and handling requirements.	Comments noted. No action required.
Innovation	Genetic Alliance UK	This treatment is a gene therapy, and while not the first to reach the market in the UK this is still highly innovative technology. As yet NICE has not completed an appraisal for any gene therapy, though evaluation of Strimvelis (retroviral-transduced autologous CD34+ cells) through the HST programme is currently in development. In addition this is the first treatment available for this severely debilitating form of progressive vision loss. At present the only option for patients with inherited retinal dystrophies is to learn to use aids to maximise what vision they have remaining, adapting these strategies over time as they lose more and more vision. A treatment that slows, delays or even halts vision loss in this area of substantial unmet need would truly be a stepchange.	Comment noted. The company and other consultees will be able to fully describe why they consider voretigene neparvovec to be innovative in their evidence submissions, which will then be considered by the committee.
	NHS England	The application of gene therapy to an inherited retinal disorder is innovative. However there are as yet not enough follow-up data to prove long-term	Comments noted. The innovative nature of the technology will be

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		safety and efficacy, so it is difficult to say whether this is a step change in the management of the condition.	considered by the evaluation committee.
	The Royal College of Ophthalmologists	Yes, there is no alternative treatment at present. Visual cycle inhibitors currently in trials may have a short-term effect but cannot prevent the long-term degeneration. Yes, there is no treatment for this otherwise All clinical trial data using the same vector (from Philadelphia) and not just the phase III data.	Comments noted. The company and other consultees will be able to fully describe why they consider voretigene neparvovec to be innovative in their evidence submissions, which will then be considered by the committee.
	RP Fighting Blindness	It would be worth noting that there are other competitive treatments in development that are looking at improving all elements of vision – both day light, detail as well as improving vision in dim light.	Comments noted. The evaluation will focus on the voretigene neparvovec, and compare it with current established practice for managing the condition (best supportive care).
	Spark Therapeutics	As a gene therapy, VN is highly innovative, in that it represents a one-time intervention with the potential to deliver life-long, life-changing gains in functional vision and mobility to patients. Consequently, it has the potential to make a significant and substantial impact on health-related benefits in the target population and would be a 'step change' in the management of	Comment noted. The company and other consultees will be able to fully describe why they consider voretigene neparvovec

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		inherited retinal diseases caused by *RPE65* gene mutations. Please also see our response to Question 12 from NICE below. In an emerging field of healthcare such as Cell and Gene Therapy (VN will be just the third gene therapy to receive approval in the EU), it is important that policy appropriately incentivizes innovation. In the pharmaceutical industry, the entry of new molecular entities (NMEs) has been observed to be driven by market size/profit opportunity for innovations. For example, Acemoglu and Linn (2004)[49] found that a 1% increase in market size was associated with a 4%-6% increase in NMEs.	to be innovative in their evidence submissions, which will then be considered by the committee.
Questions for consultation	Fight for Sight	**How are the services for inherited retinal dystrophies organised in the NHS? Is it expected that voretigene neparvovec would be delivered within the existing framework of services, or would new treatment centres be required?** Patients are referred to a genetic testing centre by their GP, via paediatricians or optometrists. This is a new, specialised type of treatment and appropriate training will be required to undertake the procedure. Training is already underway as a result of gene therapy trials. Our understanding is that the gene therapy would be administered as a single treatment per eye by means of a day case procedure known as a vitrectomy. There are genetic centres in Leeds, Manchester, Oxford and Moorfields in London which are able to screen for most of the known IRD genes, including RPE65. **How many people in England have inherited retinal dystrophies caused by RPE65 gene mutations? How many new cases are diagnosed each year in England?**	Thank you for your comments. The scope has been updated based on discussion at the scoping workshop (see responses to comments above). The technology will be evaluated through the Highly Specialised Technologies Programme.

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		Estimates suggest that there are approximately 100 people overall, with 5 new cases diagnosed per year. **Would voretigene neparvovec be expected to be used for both types of inherited retinal dystrophies caused by RPE65 (that is, retinitis pigmentosa and Leber's congenital amaurosis [LCA])? Should retinitis pigmentosa and LCA be examined separately?** These are similar diseases with different levels of severity. Therapeutic windows and long-term outcomes may differ between the two. **Are people with inherited retinal dystrophies in England routinely tested for genetic mutations? How are RPE65 mutations diagnosed in practice? Are the diagnostic tests routinely available in current NHS practice in England?** Limited genetic testing is currently available upon referral to a genetic testing centre. Many patients have been identified, however, through research based approaches aimed at identifying individuals for gene therapy trials. . **Is it anticipated that voretigene neparvovec would be used in neonates, babies and young children?** The trial for patients was only open to those aged 3 or above **Have all relevant comparators for voretigene neparvovec been included in the scope? Which treatments are considered to be established clinical practice in the NHS for inherited retinal dystrophies? How should best supportive care be defined?** There are no comparator treatments available for these conditions on the NHS.	

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		Are the outcomes listed appropriate? Are there any other outcomes that should be included? Are functional measures of vision, such as mobility testing (a functional test involving a maze of arrows and obstacles, to assess visual field, visual acuity, light perception and contrast sensitivity), useful in practice? These measures can provide useful information on the outcomes. However, the long–term impact will need to be assessed. **Are there any subgroups of people in whom voretigene neparvovec is expected to be more clinically effective and cost effective or other groups that should be examined separately?** We believe it likely that people with better presentation of photoreceptors would be expected to benefit more. **Where do you consider voretigene neparvovec will fit into the existing NICE pathway on retinal and macular conditions?** Many of the patients are already involved in the clinical trials. Once referred to a genetic testing centre there are annual follow-ups. This procedure could fit within this pathway. **Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.** All clinical trial data available using the same vector. **Do you consider voretigene neparvovec to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?** Yes, there is no treatment otherwise for this condition.	

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		Do you consider that the use of voretigene neparvovec can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation? The preservation of vision over a long period of time will reduce health and social care costs for those who receive this treatment. **Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.** The reduced cost of crisis intervention, including reduced incidences of falls; absence from the labour market; impact on mental health; and cost to family carers. **To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly. NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process.** Fight for Sight recognises the potential of gene therapy and that gene therapy appraisals may require changes to the process. We are pleased that NICE has established an expert panel to explore the assessment and appraisal of regenerative medicines and cell therapy products. We support their findings and recommendations. As the evidence evolves in this new field, consideration should be given to review the appraisal process to ensure a robust approach.	
	NHS England	*How are the services for inherited retinal dystrophies organised in the NHS?* There are a few key specialised centres that provide genetic services for patients with inherited retinal dystrophies- these include Moorfields Eye	Thank you for your comments. The scope has been updated

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		Hospital, Great Ormond Street Hospital, Manchester, Leeds, Oxford and Southampton. They have Consultant Ophthalmologists specialising in Genetic Eye Disease, and seeing patients in dedicated clinics. *Is it expected that voretigene neparvovec would be delivered within the existing framework of services, or would new treatment centres be required?* Most of the gene therapy trials in the UK have been undertaken at Moorfields Eye Hospital or The John Radcliffe Hospital in Oxford. These sites have the expertise to be able to deliver voretigene neparvovec. RPE65-LCA is a very rare condition, and so no new treatment centres would be required, but existing "clinical research" services would have to see if they could accommodate for the therapy. *Are people with inherited retinal dystrophies in England routinely tested for genetic mutations? How are RPE65 mutations diagnosed in practice? Are the diagnostic tests routinely available in current NHS practice in England?* Patients with inherited retinal dystrophies in England are routinely tested for genetic mutations. Patients usually have a NHS clinically accredited exome gene panel of known retinal dystrophy genes including RPE65 (or are recruited into the 100,000 genome project). Tests are routinely available. *Is it anticipated that voretigene neparvovec would be used in neonates, babies and young children?* The product is currently in trials for children aged 3 years and older, and clinicians are likely to have considerable reservations about its use in children younger than three years old.	based on discussion at the scoping workshop (see responses to comments above). The technology will be evaluated through the Highly Specialised Technologies Programme.

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	RP Fighting Blindness	Do Spark have long term data to support the preservation of cone and therefore daylight vision? Please note that our questions are raised by our patient involvement group and do not take scientific knowledge (of research we do not know about) into account.	Please see the company's comments on outcomes.
	Spark Therapeutics	1. **How are the services for inherited retinal dystrophies organised in the NHS? Is it expected that voretigene neparvovec would be delivered within the existing framework of services, or would new treatment centres be required?** **Spark Response:** In England, services for IRDs are concentrated in four specialist eye centres (Oxford, Moorfields, Manchester and Leeds). Patients are referred by general practitioners, paediatricians or optometrists to hospital ophthalmologists, who may then refer those patients to IRD specialists in tertiary centres. IRD specialists may request genetic testing to confirm diagnosis. There are currently 17 Regional Genetic Centres across England that belong to the NHS UK Genetic Testing Network (https://ukgtn.nhs.uk/), and of these, 13 centres are also NHS Genomic Medicine Centres, established under Genomics England to deliver the 100,000 Genomes Project. The 100,000 Genomes Project includes Leber Congenital Amaurosis or Early-Onset Severe Retinal Dystrophy (29272) as one of the rare diseases on the current list (List of rare diseases January 2017 https://www.genomicsengland.co.uk/information-for-gmc-staff/rare-disease-documents/). Where patients are suspected of having one of these conditions, the diagnostic test will be funded centrally by the Government through the 100,000 Genomes Project.	Thank you for your comments. The scope has been updated based on discussion at the scoping workshop (see responses to comments above). The technology will be evaluated through the Highly Specialised Technologies Programme.

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		NHS England currently commissions services for Ocular Genetic Disorders from specialist centres where there is access to multidisciplinary services, including access to electro-diagnostic testing, genetic counselling, molecular genetic testing, specialist imaging, research facilities and specialist ophthalmologists.[50] It is expected that VN would be delivered within the existing framework of services for ocular genetic disorders so no additional framework or services will be needed. **2. How many people in England have inherited retinal dystrophies caused by RPE65 gene mutations? How many new cases are diagnosed each year in England?** **Spark Response:** Please see response above under the section entitled "Background". 3. **Would voretigene neparvovec be expected to be used for both types of inherited retinal dystrophies caused by RPE65 (that is, retinitis pigmentosa and Leber congenital amaurosis [LCA])? Should retinitis pigmentosa and LCA be examined separately?** **Spark Response:** Please see response above under the section entitled "Background". In short, the appropriate population focus for VN review is all persons with vision loss associated with biallelic *RPE65*-mediated IRD. 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	

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		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. **4. Are people with inherited retinal dystrophies in England routinely tested for genetic mutations? How are RPE65 mutations diagnosed in practice? Are the diagnostic tests routinely available in current NHS practice in England?** **Spark Response:** Where there is suspicion of LCA or RP, IRD specialists often seek to identify the gene(s) responsible. Specialist ophthalmology centres provide access to both molecular genetic testing and genetic counselling services. There are 17 Regional Genetics Centres belonging to the NHS UK Genetic Testing Network (https://ukgtn.nhs.uk/). In the four tertiary centres, these tests are routinely available and funded either through Specialised Commissioning, Clinical Commissioning Groups (CCGs), local grants, the NIHR or through the 100,000 Genomes project. Based on initial primary research conducted by Spark in England, other specific genetic tests are funded locally by CCGs, and funding approval may be required prior to performing those tests. Spark is conducting further research to confirm this knowledge. There are currently 13 NHS Genomics Medicine Centres established under Genomics England that provide testing for Leber Congenital Amaurosis or Early-Onset Severe Retinal Dystrophy (29272) as one of the rare diseases on the current list for the 100,000 Genomes Project (List of rare diseases	

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		January 2017 https://www.genomicsengland.co.uk/information-for-gmc-staff/rare-disease-documents/). Tests conducted by the 100 Genomes Project are funded centrally by the Department of Health through Genomics England and therefore will not be an additional cost to the NHS for VN. **5. Is it anticipated that voretigene neparvovec would be used in neonates, babies and young children?** **Spark Response:** It is expected that VN will only be approved by regulators for patients three years of age and older. **6. Have all relevant comparators for voretigene neparvovec been included in the scope? Which treatments are considered to be established clinical practice in the NHS for inherited retinal dystrophies? How should best supportive care be defined?** **Spark Response:** Please see response above under the section entitled "Comparators." Whilst there are no pharmacological treatments available, there are many support services provided through social care services that are funded by the state. Those who are registered blind are deemed 'disabled' and consequently have access to various services funded through state provided social services (http://www.nhs.uk/Conditions/Visual-impairment/Pages/Introduction.aspx). Patients and their families are offered psychosocial support in the community, connected to local / national support organisations including local authority vision impairment services, visual rehabilitation, and habilitation training.	

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		Personal Social Services/ specialist educational services/ and other available support services, provide the current support for patients with sight loss and incur significant costs. These should therefore all be included when considering the comparative cost of care for patients with the condition. **7. Are the outcomes listed appropriate? Are there any other outcomes that should be included? Are functional measures of vision, such as mobility testing (a functional test involving a maze of arrows and obstacles, to assess visual field, visual acuity, light perception and contrast sensitivity), useful in practice?** **Spark Response:** Please see response above under the section entitled "Outcomes." **8. Are there any subgroups of people in whom voretigene neparvovec is expected to be more clinically effective and cost effective or other groups that should be examined separately?** **Spark Response:** Please see response above under the section entitled "Background" and "Population". **9. Where do you consider voretigene neparvovec will fit into the existing NICE pathway on retinal and macular conditions?** **Spark Response:** VN should be considered standard, first-line treatment for patients who meet the treatment eligibility criteria for VN, once marketing authorisation has been granted.	

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		The two procedures mentioned in the retinal and macular pathway are IPG537 (Insertion of a subretineal prostheses system for retinitis pigmentosa) and IPG519 (Insertion of an epiretineal prostheses system for retinitis pigmentosa). Neither of these products is an appropriate comparator for VN, and both are currently recommended by NICE only for use in the research setting as the evidence in both cases was found to be "limited in quality and quantity". • The subretinal prosthesis system (Argus® II) is indicated 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. • The epiretineal prostheses system for retinitis pigmentosa is also intended for people who have no useful sign and no other treatment options. It is not a treatment option for patients with biallelic *RPE65*-mediated IRD with viable retinal cells and therefore is not an appropriate comparator. Once approved, VN will significantly enhance the quality of life for those with the serious long term condition that leads to blindness, an outcome highlighted in the NHS Outcomes Framework 2016-17. **10. NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:** • **could exclude from full consideration any people protected by the equality legislation who fall within the**	

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		patient population for which voretigene neparvovec will be licensed; • **could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;** • **could have any adverse impact on people with a particular disability or disabilities.** • **Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.** **Spark Response:** Please see response above under the section entitled "Equality". **11. Do you consider voretigene neparvovec to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?** **Spark Response:** Please see response above in the section entitled "Innovation". **12. Do you consider that the use of voretigene neparvovec can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?**	

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		Spark Response: In the case of visual impairment, NICE has recognised that EQ-5D may not always be the appropriate measure.[48] As such, Spark will systematically review the evidence on HRQoL in inherited retinal diseases to identify the most suitable health-utility estimation methods to inform values used in the calculation of QALY gains. In addition, it is important that the health-related benefit modelled in the cost-utility analysis comprehensively capture the aspects of vision that may be affected by VN treatment, including visual field, light sensitivity, and visual acuity, and their combined effect on functional vision and quality of life. The combined effect of clinical outcomes (such as changes in visual field, light sensitivity, and visual acuity) on quality of life may also vary over time, as patients adapt to improved functional vision (e.g., learning to navigate themselves without assistance). Consideration should also be given to the potential for alleviation of caregiver burden associated with VN treatment. The NICE reference case specifies that the perspective on outcomes should include "all direct health effects, whether for patients or, when relevant, carers";[47] as reflected below, caregiver burden is significant for patients suffering from blindness/IRD, and therefore of relevance in the cost-utility analysis. NICE should note that the average patient age at randomisation in the clinical trial was 15 years old. We recommend that policy makers (at both NICE and NHS England) consider the indirect costs related to inherited retinal diseases, including lower educational attainment, lower productivity, and more consumption of government benefits. This burden is especially borne by children (over the age of 3 years) who would be indicated for VN given the early onset of *RPE65*-mediated inherited retinal disease. Lost educational attainment opportunities begin early in life and could be irreversible later.	

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		13. Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits ["health-related benefits that are unlikely to be included in the QALY calculation"]. **<u>Spark Response</u>:** Ophthalmologic disorders vary in terms of their pathology. Much of the literature has focused on age-related macular degeneration (ARMD), which is dissimilar to *RPE65*-mediated inherited retinal disease. ARMD involves a later age of onset, typically does not progress to later stages of blindness, affects the centre of the visual field, expanding outward as the eye progresses, and initially affects the cones of the retina, which initially lead to decreases in visual acuity. *RPE65*-mediated inherited retinal disease pathology is almost the opposite: the onset is usually among paediatric patients, it typically progresses to later stages of blindness; it tends to affect the periphery of the visual field initially, and affects the rods. At this time, we are not aware of health utility values that exist in the literature which appropriately characterize the process of *RPE65*-mediated inherited retinal disease. Spark is in the process of conducting a systematic review to identify valid benefit measures for patients with RPE-mediated IRD. The economic analysis will aim to address the limitations of standard HRQoL measures (e.g., the EQ-5D) in quantifying the burden of visual impairment, as suggested in the published literature.[48] In addition, evidence on HRQoL burden experienced by caregivers will also be incorporated into the analysis as possible based on the nature of evidence available. **14. To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.**	

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		<u>Spark Response</u>: None to our knowledge	
Additional comments on the draft scope	Fight for Sight	Fight for Sight is the leading UK charity dedicated to funding pioneering research to prevent sight loss and treat eye disease. Fight for Sight is funding research at leading universities and hospitals throughout the UK. Each year we invest over £3 million in pioneering eye research. There are currently no treatments available for people with inherited retinal diseases (IRDs). Significant investment has been made by Fight for Sight and others to support research into the understanding of IRDs and the identification of gene mutations. This has led to the commencement of trials of gene therapy as a potential treatment for certain IRDs. We believe that the publication of Phase 3 data regarding voretigene neparvovec represents the first published data of a phase 3 trial of gene therapy and the lessons learned from this will have implications for other IRDs and other diseases.	Thank you for your comments. No action required.
	Spark Therapeutics	<u>Spark Comments for NICE's Recommended Review under STA vs. HST</u> Spark suggests that the HST process rather than the STA process would be a more appropriate and efficient way to review VN, a treatment for an ultra-rare disease: • Under Regulation 7 of SI 2013/259, NICE has the power to make a technology appraisal recommendation in relation to a health technology, where directed to do so by the Secretary of State. • Under Regulation 8, NICE has a separate power to make highly specialised technology recommendations in relation to highly	Thank you for your comments. Following consultation, NICE proposed that this topic is evaluated through the Highly Specialised Technologies (HST) Programme. The Department of Health and Social Care have referred it as an HST evaluation.

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		specialised health technology, where directed to do so by the Secretary of State. • Technology appraisal recommendations and highly specialised technology recommendations are both defined in Regulation 2 of SI 2013/259. Crucially, a highly specialised technology recommendation is defined by reference to the term highly specialised health technology, which is defined as "*a health technology intended for use in the provision of services for rare and very rare conditions provided for in regulations made under section 3B(1)(d) of the 2006 Act*". • Services for rare and very rare conditions are listed in Schedule 4 to SI 2012/2996, which is made under Regulation 11 of the same SI. Regulation 11 is made under section 3B(1)(d) of the 2006 Act. Schedule 4 includes "*adult specialist ophthalmology services*". • In circumstances where NICE has been given a specific power to make highly specialised technology recommendations in relation to adult specialist ophthalmology services, NICE cannot lawfully consider a treatment that will fall within those services under an entirely separate power (namely, the power to make technology appraisal recommendations), and any direction from the Secretary of State that NICE should do so would run counter to the Regulation. In any event, given the likely pricing of VN, and the standard NICE threshold of £30,000 for non-specialised treatments, it would entirely irrational from a public law perspective for NICE to pursue a process that VN would inevitably fail.	

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		Furthermore, it is clear that it would be unreasonable and/or irrational for NICE to appraise VN under the STA process when, as explained below, VN meets the prioritisation criteria for HSTs. 1. The target patient group for the technology in its licensed indication is so small that treatment will usually be concentrated in very few centres in the NHS; Please see analysis of epidemiological numbers in the background section above, which confirm the extremely small patient numbers with *RPE65*-gene mutations in England. In addition to small expected patient numbers, VN will likely only be administered in a select number of centres in England. VN should be surgically administered by a trained 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 proposes that administration of VN would only occur at specialised ophthalmic treatment centres. Spark is in discussions with potential ophthalmic treatment centres in England and is considering potential treatment centres in the South and the North of the country to have appropriate geographic availability for patients throughout England. Experienced surgical staff at these centres would complete a training program provided by Spark prior to treating any patients. Moreover, given that Ocular Genetic Disorders are currently commissioned by NHS England from specialist centres, it is anticipated that VN would be administered at only a small number of already established specialist centres. 2. The target patient group is distinct for clinical reasons. The target patient group for administration of VN is clinically distinct and clearly defined in the proposed Statement of Product Characteristics (SMPC): "*patients with a confirmed molecular diagnosis of biallelic RPE65 mutations*	

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		and who have sufficient viable retinal cells, as estimated by optical coherence tomography (OCT) as an area of retina within the posterior pole of >100 micron thickness." Patients will be diagnosed through confirmed genetic testing, which is available through the tertiary specialist ophthalmology centres, and must have a sufficient number of viable retinal cells in order to receive VN. The treatment will not be used off-label. 3. The condition is chronic and severely disabling. The progressive nature of *RPE65*-mediated disease is well documented with deterioration over time in both visual field (VF) and visual acuity (VA). 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. Under the Equalities Act of 2010, a person who is certified as blind, severely sight impaired, sight impaired or partially sighted by a consultant ophthalmologist is deemed to have a disability.[51] The loss of sight, one of the five senses, has significant impact on a person's quality of life.[53] Independent navigation becomes severely limited, and vision-dependent activities of daily living are severely impaired. Impact on Learning: Vision impairment is a significant disability, creating unique challenges to learning that can only be addressed with specialist knowledge and understanding; many children have high levels of need.[53] Impact on Ability to Work: According to published sources:[54,55] • Ninety percent of those who lose their sight in youth will not work for more than six months in their lives;	

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		• Two-thirds of working age blind and partially sighted people are not working; and • Government research has shown that 90% of employers believe that it would be impossible or difficult to employ someone with sight loss, presenting huge barriers to finding work. Impact on Mental Health: There is evidence that the prevalence of mental health problems may be higher in young and middle-aged adults with vision loss, with 40-45% having clinically significant depressive symptomatology, and 20% exhibiting moderate to severe anxiety symptoms.[56] Impact on Quality of Life: The impact of living with sight loss is significant and multifaceted. There are currently no curative or disease modifying treatments available for IRDs, including LCA and RP.[57,58] The standard of care is progression to blindness.[59,60] Treatment options focus on visual rehabilitation, including the use of low vision aids, specialised computer software and mobility training.[61] If VN is assessed under the STA process, the outcome could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology; and could have any adverse impact on people with a particular disability or disabilities. 4. The technology is expected to be used exclusively in the context of a highly specialised service. As described above, given the very small numbers, the innovative nature of the treatment and the specific requirements for administration and delivery, VN will be expected to be used exclusively in the context of a highly specialised service. This service is likely to fall under the remit of Specialised Commissioning for Genetic Ocular disorders (D12) by NHS England.	

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		5. The technology is likely to have a very high acquisition cost. Given the one-time use of the therapy, the unique nature of the technology, as well as the low number of expected patients, the cost of VN is expected to be high, particularly compared to more traditional technologies that are reviewed under the STA process. 6. The technology has the potential for life long use. Gene augmentation therapy is employed for disorders due to loss-of-function mutations and is based on the delivery of a correct copy of the defective gene without removal of the endogenous mutant one. Retinal cell types are post-mitotic, and thus sustained long-term gene expression can be achieved. AAV have an excellent safety profile and low immunogenicity which allows for long-term expression of the therapeutic gene after a single administration.[62] Although VN is only administered once, it is intended to last for the patient's life-time, thus satisfying the life-long use requirement. It is important for NICE to consider that this HST requirement was envisioned prior to the development of one-time therapies like VN, which is not a chronic treatment that requires re-administration. 7. The need for national commissioning of the technology is significant. The need for national commission of VN is significant because the condition is very rare, complex and the procedure is best performed in specialist centres where IRD specialists have access to all the multidisciplinary services required. Centralising the service provides opportunities to increase knowledge of the nature of the condition and build expertise in the specialist techniques required for treating this rare condition.[50] NHS England currently commissions services for Ocular Genetic Disorders and VN will fall within this category as a treatment for RP caused by *RPE65* mutations.	

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		As part of the Government's Mandate to NHS England, there is a goal to embed genomic medicine and application of genomic technologies into NHS care building upon the 100,000 Genomes Project and the UK Strategy for Rare Diseases. NHS England has a mandate to develop, jointly with Genomics England, the approach to begin to embed genomics into routine care and engage other national partners including NHS Improvement, NHS Digital, Health Education England and Public Health England.[63] In the list of rare diseases from January 2017, Genomics England includes Leber Congenital Amaurosis or Early-Onset Severe Retinal Dystrophy (29272) on the current list for the 100,000 Genomes Project.[64]	
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The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

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