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SMC2228

voretigene neparvovec 5 x 10^{12} vector genomes/mL concentrate and solvent for solution for injection (Luxturna®)

Novartis

8 November 2019 *(Issued 6 December 2019)*

The Scottish Medicines Consortium (SMC) has completed its initial assessment of the evidence for the above product using the ultra-orphan framework:

Indication under review: For the treatment of adult and paediatric patients with vision loss due to inherited retinal dystrophy caused by confirmed biallelic RPE65 mutations and who have sufficient viable retinal cells.

Key points:

- Inherited retinal dystrophy due to RPE65 mutations leads to progressive blindness and there are no available treatments.
- In a clinical trial, voretigene neparvovec improved functional vision at one year compared with no treatment, measured by a multi-luminance mobility test.
- Uncontrolled follow-up data support that treatment effect is maintained at four years. Whilst it is biologically plausible that the treatment effect will continue, it is not known if effectiveness is sustained in the long term.
- A retrospectively validated visual function questionnaire showed improved activities of daily living, but there is uncertainty over how this relates to actual quality of life.
- A model-based economic evaluation projected a substantial gain in quality-adjusted life years compared to best supportive care. However, there were uncertainties particularly surrounding utility values and also how long the treatment effect lasts.
- Despite a Patient Access Scheme (PAS), the treatment's cost in relation to its health benefits remains high.

Chairman, Scottish Medicines Consortium

Indication

For the treatment of adult and paediatric patients with vision loss due to inherited retinal dystrophy caused by confirmed biallelic retinal pigment epithelium-specific 65 kDa protein (RPE65) mutations and who have sufficient viable retinal cells.[1]

Dosing Information

A single dose of 1.5 x 10^{11} vector genomes of voretigene neparvovec in each eye. Each dose will be delivered into the subretinal space in a total volume of 0.3mL. The individual administration procedure to each eye is performed on separate days within a close interval, but no fewer than 6 days apart.

Voretigene neparvovec is a single-use vial for a single administration in one eye only and is administered as a subretinal injection after vitrectomy in each eye. It should not be administered in the immediate vicinity of the fovea to maintain foveal integrity.

It must not be administered by intravitreal injection. It is a sterile concentrate solution for subretinal injection that requires thawing and dilution prior to administration. Treatment should be initiated and administered by a retinal surgeon experienced in performing macular surgery.

The administration of voretigene neparvovec should be carried out in the surgical suite under controlled aseptic conditions. Adequate anaesthesia should be given to the patient prior to the procedure. The pupil of the eye to be injected must be dilated and a broad-spectrum microbicide should be topically administered prior to the surgery according to standard medical practice.

Full details are available in the Summary of Product Characteristics (SPC) including a recommended pre- and post-operative immunomodulatory regimen for each eye.[1]

Product availability date

Anticipated January 2020

SMC ultra-orphan designation

Voretigene neparvovec has been validated as meeting SMC ultra-orphan criteria:

- The pharmacological action of voretigene neparvovec is specific to the subset of patients with RPE65-mediated inherited retinal dystrophy. This subset represents <1 in 50,000 of the population in Scotland.
- Voretigene neparvovec has EMA orphan designation for the treatment of inherited retinal dystrophy and this was maintained at the time of Marketing Authorisation (EMA/810611/2018).
- Inherited retinal dystrophy is chronic and severely disabling due to loss of vision.
- RPE65-mediated inherited retinal dystrophy is a rare genetic condition and requires highly specialised management.

Nature of condition

Inherited retinal dystrophy is a heterogeneous group of rare genetic disorders which cause loss of vision. They can be caused by mutations in more than 260 genes, including the *RPE65* gene, and have previously been identified by more than 20 different names including Leber's congenital amaurosis and retinitis pigmentosa. Voretigene neparvovec only has marketing authorisation for patients with vision loss due to inherited retinal dystrophy caused by confirmed biallelic RPE65 mutations. The RPE65 gene is responsible for the production of RPE65 protein, an enzyme which converts all-trans-retinyl to 11-cis-retinol, which subsequently forms the chromophore, 11-cis-retinal, during the visual (retinoid) cycle. These steps are critical in the biological conversion of a photon of light into an electrical signal within the retina. Mutations in the RPE65 gene result in reduced or lack of RPE65 all-trans-retinyl isomerase activity and blocking of the visual cycle. Accumulation of all-trans-retinyl leads to apoptosis of photoreceptor cells and progressive loss of vision.[1, 2]

Patients with inherited retinal dystrophy due to biallelic RPE65 mutation can present with visual impairment with initial presentation from infancy to adolescence, initially with night blindness (nyctalopia) and difficulty seeing in dim light. The condition is bilateral with similar visual loss in both eyes. Vision deteriorates with progressive loss of visual field and central vision, although the rate of progression and severity varies with progression to blindness from pre-school to the third decade of life.[2, 3]

There are no other medicines licensed for this condition and patients are generally managed by best supportive care. There is therefore a high unmet need in these patients. Clinical experts consulted by SMC considered that voretigene neparvovec fills an unmet need in this therapeutic area because there are no other treatments available.

New technology

Voretigene neparvovec is an adeno-associated viral type 2 (AAV2) gene therapy vector. It consists of a virus which carries the normal human RPE65 gene. After subretinal injection, expression of the gene will produce the enzyme, all-trans-retinyl isomerase, and allow the conversion of all-trans retinyl to 11-cis-retinol as part of the visual cycle. This provides the potential to restore the visual cycle and improved ability to detect light. Voretigene neparvovec is the first medicine to be licensed for the treatment of inherited retinal dystrophy.[1, 2]

Impact of new technology

Comparative efficacy

The efficacy of voretigene neparvovec was investigated in a randomised, open-label, phase III study (Study 301) in 31 patients with inherited retinal dystrophy and confirmed RPE65 mutations. Eligible patients were aged ≥3 years and had visual acuity of 20/60 or worse and/or visual field <20 degrees in any meridian in both eyes. They had sufficient viable retinal cells, determined by retinal thickness, fundus photography and clinical examination. They were also able to perform a multi-luminance mobility test (MLMT) within the luminance range assessed but were unable to pass the MLMT at the lowest luminance level tested (1 lux). Eligible patients were randomised in a ratio of 2:1 to receive voretigene neparvovec or control with stratification by age (<10 years and ≥10 years) and baseline mobility testing passing level (pass at ≥125 lux versus <125 lux). In the active group, a subretinal injection of 1.5 x 10^{11} vector genomes of voretigene neparvovec in a total subretinal volume of 0.3mL was administered into the first eye (worse function by visual acuity or subject preference or both) and repeated in the second eye 6 to 18 days later. Voretigene neparvovec was injected under general anaesthesia using standard vitreoretinal techniques for subretinal surgery. Patients in the voretigene neparvovec group received prednisone for 7 days, starting 3 days before the first injection and tapered until it was repeated 3 days before the second eye was injected. In the control group, patients received no treatment. One patient randomised to each group discontinued the study before any intervention.[2, 4]

The primary outcome was the mean change from baseline to one year in bilateral MLMT, an assessment tool designed to measure changes in functional vision by ability to navigate a course accurately and at a reasonable pace at different levels of lighting. The assessment used a 7 by 12 foot obstacle course with 15 varying obstacles and 12 described routes. The lighting was reduced from 400 lux (office environment) to 1 lux (moonless summer night). A pass required the patient to complete the course with less than four errors in <3 minutes, with the score determined by the lowest light level at which the patient was able to pass. The MLMT score ranged from -1 (unable to pass the course at 400 lux) and +6 (passing the course at 1 lux). Patients were adapted to the dark for 40 minutes before completing the course with each eye

and then both eyes. The test was repeated for two to seven lighting levels to determine the passing and failing light levels for each and both eyes. The course was re-configured after each attempt. Testing was recorded and assessed independently.[2, 4, 5]

Efficacy outcomes were assessed in the intention to treat (ITT) population (defined as all randomised patients; n=31) and the modified ITT (mITT) population (defined as all randomised patients except those removed from the study between randomisation and any intervention; n=29). The primary outcome, mean bilateral MLMT score, was significantly improved in the voretigene neparvovec group compared with placebo with improvements achieved by day 30 and remaining stable to one year. At one year, the maximum improvement in MLMT (pass at the lower luminance level of 1 lux) was achieved by 62% (13/21) of patients in the voretigene neparvovec group of the ITT population (65% [13/20] of patients treated with voretigene neparvovec [mITT population]). No patients in the control group achieved maximum improvements in MLMT.[2, 4] Secondary outcomes were full-field light sensitivity threshold (FST) testing using white light averaged over both eyes, MLMT for the first assigned eye and best-corrected visual acuity, using the scale adapted by Holladay. A hierarchical statistical testing strategy was followed with no formal testing of outcomes after the first non-significant outcome. Detailed results for the primary and secondary outcomes are presented in table 1.

Table 1: Results of primary and secondary outcomes in the ITT population of Study 301[2, 4]

	Voretigene neparvovec (n=21)	Control (n=10)	Difference (95% CI)
Mean (SD) change in MLMT score for both eyes from baseline	1.8 (1.1)	0.2 (1.0)	1.6 (0.72 to 2.41), p=0.0013
FST (log10[cd.s/m^2])	NR	NR	-2.11 (-3.19 to -1.04), p<0.001
Mean (SD) change in MLMT score from baseline for first assigned eye	1.9 (1.2)	0.2 (0.6)	1.7 (0.89 to 2.52), p<0.001
Mean change in BCVA for both eyes from baseline	+8.1 letters	+1.6 letters	LogMar -0.16 (-0.41 to 0.08), p=NS

CI: confidence interval; SD: standard deviation; MLMT: multi-luminance mobility test; FST: full-field light sensitivity threshold; NR: not reported; best-corrected visual acuity, measured using the scale adapted by Holladay and averaged over both eyes; NS: not significant

Visual field (Goldmann) testing was an exploratory outcome to assess changes in function of different areas of the retina. At one year, there was a 302.1 degrees improvement from baseline in the voretigene neparvovec group versus a reduction of -76.7 degrees in the control

group; difference of 378.7 degrees (95% CI: 145.5 to 612.0). These exploratory results were used in the economic analysis but are descriptive only and not inferential (no p-values reported).[2, 4]

A retrospectively validated visual function questionnaire was completed by patients or parents/guardians to assess activities of daily living relevant to visual deficits in these patients. The mean (SD) score (range 0 to 10) in the voretigene neparvovec group improved from baseline of 1.8 (1.9) to 2.6 (1.8) at one year in patient completed questionnaires and from 3.1 (2.2) to 3.9 (1.9) for parent completed questionnaires. The mean scores were generally unchanged in the control group.[4]

After one year, patients in the control group were able to crossover to receive voretigene neparvovec (Study 302). After a follow-up of three years in the original voretigene neparvovec group (n=20), there was a mean change in MLMT score of 1.8 and after a follow-up of two years post treatment in the original control group who crossed over to voretigene neparvovec (n=9), the mean change in MLMT score was 2.1. After a follow-up of 4 years in the original voretigene neparvovec group and of 3 years post-treatment in the original control group who crossed over to voretigene neparvovec, there was a mean change in MLMT score of 1.7 and 2.4 respectively.[6, 7]

Results from the open-label, uncontrolled, non-randomised phase I studies (Study 101/102) in 12 patients with inherited retinal dystrophy due to RPE65 mutations provide limited evidence of sustained treatment benefit. In Study 101, voretigene neparvovec was administered by subretinal injection at low ($1.5x10^{10}$ vector genomes), medium ($4.8x10^{10}$ vector genomes) or high ($1.5x10^{11}$ vector genomes) dose. In 11 patients, voretigene neparvovec was later administered to the second eye in study 102. The study was not designed to assess efficacy, measured by the score achieved on an in-house mobility assessment tool which was under development and patients have been followed up for 7.5 years.[2]

Comparative safety

During the controlled first year of Study 301, all patients reported an adverse event. These were considered to be related to the procedure for administering treatment in 65% (13/20) of patients treated with voretigene neparvovec. No serious adverse events related to voretigene neparvovec and no adverse immune responses were reported. The most frequently reported individual adverse events in the voretigene neparvovec (n=20) and control groups (n=9) were leuocytosis (45% and 0%), vomiting (40% and 22%), pyrexia (35% and 11%), nasopharyngitis (35% and 22%), headache (35% and 22%), oropharyngeal pain (30% and 44%), cough (30% and 11%), nausea (30% and 11%), increased intraocular pressure (20% and 0%), haematuria (15% and 11%) and cataract (15% and 0%). In the voretigene neparvovec group, adverse events were

considered to be related to the administration procedure in 65% of patients and were mainly eye disorders (40%) including cataract in 20%.

At a later follow-up, after control patients had crossed over to receive voretigene neparvovec, the most common adverse events related to treatment or the procedure in all patients (n=29) were cataract (17%), increased intraocular pressure (14%), retinal tear (10%), retinal deposit (10%), nausea (10%), eye inflammation (7%), vomiting (7%) and headache (7%) and macular hole (7%). These were related to the administration procedure, except for the retinal deposits which were considered to be probably related to voretigene neparvovec but were transient and asymptomatic and resolved with 8 weeks. There were changes in the foveal thickness for some patients after administration of voretigene neparvovec. This returned to baseline levels after one year in some patients and not in others and may have been due to a reversible disruption of the outer segments of the retina observed during the postoperative period.[2, 4]

Clinical effectiveness issues

The key strengths and uncertainties of the clinical evidence are summarised below:

Key strengths:

- In the phase III study of patients with vision loss due to inherited retinal dystrophy due to RPE65 mutations, functional vision, assessed by the bilateral MLMT, was significantly improved from baseline to one year in the voretigene neparvovec group compared with the control group. Improvement appeared to be maintained to three years. Supportive data from a phase I study suggests sustained improvement in vision for up to 7.5 years.
- The primary outcome measure was developed to assess changes in the ability of patients to perform activities in low light environments, since night blindness and difficulty seeing in dim light are key features of inherited retinal dystrophy due to RPE65 mutations. Results from the retrospectively validated visual function questionnaire suggest that voretigene neparvovec improves activities of daily living.
- The MLMT assessments were made by independent reviewers, unaware of treatment allocation, and the results of the primary outcome were generally supported by improvements in secondary outcomes: full-field light sensitivity threshold testing, MLMT for the first assigned eye and best-corrected visual acuity. Although changes in visual acuity numerically favoured voretigene neparvovec, this was not significantly different from the control group and the change was less than that considered to be meaningful.
- Clinical experts consulted by SMC viewed voretigene neparvovec as a therapeutic advancement as it addresses the underlying cause of the condition. While long-term clinical data are currently unavailable, a lifelong effect is theoretically possible.

Key uncertainties:

- The phase III study aims to follow patients for up to 15 years after treatment. The current duration of follow up is limited to 4 years and longer term efficacy and safety data for

voretigene neparvovec are awaited. The duration of treatment effect is unclear and there is no information on whether patients who may lose treatment effect would benefit from re-treatment.

- The MLMT classifies a patient as having improved, stable or worsened ability to navigate the course under low light conditions and passing the course at 1 lux results in the highest possible score of 6. This may result in a ceiling effect affecting the ability of the MLMT to detect further change over time. At year one, 65% of patients treated with voretigene neparvovec achieved maximum improvement in MLMT and the actual treatment effect may therefore be underestimated.
- The MLMT was developed by the company and there is some uncertainty over what represents a clinically relevant improvement. The key publication notes that an MLMT change score from baseline of ≥1 lux levels was considered clinically meaningful. However, the European Medicines Agency notes that patients in the control group had change in score of ±1 over 1 year and therefore any clinically relevant change with voretigene neparvovec would need to exceed this.
- Although the visual function questionnaire indicated improvements in activities of daily living, it is unclear how this relates to quality of life for patients.
- Efficacy of voretigene neparvovec was not demonstrated in all patients. Factors such as age, gender, baseline status of visual acuity or visual field or specific genetic mutation did not appear to indicate predictors of response but patient numbers are small. The only factor determining an effect was the presence of a sufficient number of viable retinal cells.
- Available evidence is based on data from a small number of heterogeneous patients only with a range of RPE65 mutations and levels of disease progression and baseline MLMT scores. The overall treatment effect may not be generalisable in terms of benefit:risk ratio in individual patients.
- Voretigene neparvovec was generally well tolerated but there are risks and complications associated with intraocular surgery required for sub-retinal injection and these could have long-term consequences.

Overall the clinical case was considered sufficiently robust in the short term when voretigene neparvovec is likely to provide important clinical benefits to patients with RPE65-mediated inherited retinal dystrophy. However, there is some uncertainty about the duration of treatment effect, the effect on quality of life of treated patients, and the long-term safety. It is unclear what factors make some patients more likely to respond to treatment.

Impact beyond direct health benefits and on specialist services

Improvement in functional vision could have a significant impact on the quality of lives of patients, family and carers. Patients could be more independent, lead a more normal life and some may be able to return to education or work. The submitting company has attempted to capture some of the effects of treatment on carers and the wider economic impact within the economic analysis, as described below.

There may be implications for the service in determining patient eligibility for treatment including genetic testing and optical coherence tomography to determine the presence of sufficient viable retinal cells, administration of voretigene neparvovec and subsequent monitoring of patients.

It was noted that the extremely high upfront acquisition cost for this single-dose treatment is likely to have significant service implications and is associated with financial risk to the service if the long-term predicted clinical benefits do not materialise.

Patient and carer involvement

The following information reflects the views of the specified Patient Groups.

- We received patient group submissions from Retina UK and Fight for Sight. Retina UK is a charitable incorporated organisation and Fight for Sight is a registered charity.

- Retina UK has received 1.7% pharmaceutical company funding in the past two years, with none from the submitting company. Fight for Sight has received less than 1% pharmaceutical company funding in the past two years, with none from the submitting company.

- Retinitis pigmentosa and Leber congenital amaurosis are progressive sight loss conditions that lead to blindness. Early-onset disease, such as that resulting from biallelic RPE65 mutations, leads to lifelong disability that has far-reaching consequences in terms of economic and social burden. People living with the condition have stated that it can affect opportunities in education, the labour market, and in day to day life that others with normal vision take for granted such as; socialising at night or driving. The inherited nature of these conditions also means that there is a ripple effect across the family, not only due to the direct consequences of supporting a loved one with a disability, but also because of the emotional toll attached to passing on or being at risk from a genetic disorder.

- There is currently no treatment available that can impact on either the progression or outcome of the condition. Voretigene neparvovec represents an important innovation that addresses an unmet need and could alleviate the burden of progressive disability.

- The clinical trial outcomes studied are highly meaningful for the day to day lives of people living with inherited retinal dystrophy. Low light is an issue in many artificially lit buildings, therefore improvements in vision and mobility in such conditions would lead to increased confidence and independence and would be expected to positively impact on education / work and social life.

- This treatment has the potential to improve quality of life and provides the possibility of patients having greater independence, hence reducing the need for care and support. Voretigene neparvovec is designed for administration early in the course of the condition including those experiencing childhood onset sight loss, where effective treatment could provide lifetime benefit in terms of educational attainment, future employment prospects, mental health and overall quality of life.

Value for money

The submitting company presented a cost-utility analysis comparing voretigene neparvovec with best supportive care (BSC) in the licensed population of adults and paediatric patients with vision loss due to inherited retinal dystrophy caused by confirmed biallelic RPE65 mutations and who have sufficient viable retinal cells.

A cohort-based state-transition Markov model was utilised to simulate lifetime costs and benefits. The model contained six health states intended to capture progressively severe levels of visual impairment (moderate, severe, profound, counting fingers, hand motion, light perception, no light perception) and death. The health states broadly align with the American Medical Association (AMA) guidelines with some differences: near-blindness is associated with the 'counting fingers' health state in the model, while total blindness is associated with 'hand movement', 'light perception' and 'no light perception' which are pooled together in the most severe health state in the model. Health state membership was determined based on the AMA guideline thresholds for visual acuity (VA) and visual field (VF).

Baseline health state distribution in the model was informed from the levels of VA and VF observed in the intention-to-treat dataset at the start of Study 301. Changes in VA and VF observed at year one in the mITT population were used to derive transition probabilities for the initial phase of the model in each treatment arm. Natural history data in individuals with RPE65-mediated inherited retinal dystrophy from a retrospective chart review were used to model long-term decline (transition probabilities) in visual function beyond year one in the BSC arm. A parametric multistate survival model was fitted to the data and the Weibull distribution was used in the base-case due to its performance in terms of statistical fit and visual inspection. In this long-term phase, individuals may only progress to a worse health state (that is, the multistate model is pre-specified as progressive only). To model the long-term effectiveness in the voretigene neparvovec arm, a relative risk reduction (RRR) was applied to the transition probabilities in the multistate model, assuming a full treatment effect maintenance for 40 years (100% RRR) followed by a linear waning of effect (down to 25% RRR) over a ten years period and a residual treatment effect (25% RRR) thereafter.

The analysis also included adverse events related to treatment and administration (cataract, eye inflammation, and increased intraocular pressure) from Study 301 which occurred in more

than one patient and were expected to be associated with an impact on quality of life and/or cost. As no death events were observed in the natural history dataset, death was not included in the multi-state model and mortality was modelled separately using general population life tables in Scotland. To reflect the potential heightened mortality risk associated to loss of vision, a state-specific hazard ratio was applied to the general population mortality as informed from a published study. The study suffered from a number of limitations in terms of its applicability to the modelled population. However, the impact on analysis results of modelling a heightened mortality risk linked to visual impairment was minimal.

Health benefits in the analysis were expressed in quality-adjusted life-years (QALYs) derived by assigning health utility scores to each health state in the model as well as health disutilities linked to the occurrence of adverse events and carer disutilities. Following a systematic literature review conducted by the submitting company, no utility values were identified in individuals with RPE65-mediated inherited retinal dystrophy and no validated preference-based instruments were applied in Study 301. A bespoke analysis was conducted by the company in which a series of vignette health states representing the five health states in the model were assessed by six retina specialists (including UK and US experts) in terms of their impact on generic health-related quality of life instruments (i.e. EQ-5D and HUI-3; the latter set was used in the baseline). The use of a proxy measure was justified by the ultra-rare nature of the condition; the submitting company considering it was not feasible to recruit a representative sample of patients such that utility data could be collected prospectively. Disutilities associated with adverse events and carers' disutilities were sourced from published sources.

A comprehensive list of resource use and costs was included in the analysis which came from appropriate sources. The cost associated with voretigene neparvovec treatment included screening (genetic testing and testing for sufficient viable retinal cells), acquisition, administration, monitoring and addressing treatment-related adverse events. Health state specific costs which varied by age category (school-age, working-age, or retirement-age) were also included: hospitalisation, low vision rehabilitation, low vision aids, depression, residential care, and community care. In an alternative scenario, a wider societal perspective was taken which also included non-healthcare costs such as productivity losses.

A patient access scheme was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. Base-case results of the analysis are summarised in table 2 at list price. Patients in the voretigene neparvovec arm of the model derive only a marginal health benefit in terms of life-years gained (0.05 incremental life-years gained) but a substantial benefit in terms of QALYs gained (7.0 incremental QALYs) given the primary impact of the treatment is on quality of life.

SMC would wish to present the with-PAS cost-effectiveness estimates that informed the SMC decision. However, owing to the commercial in confidence concerns regarding the PAS, SMC is unable to publish these results. As such, only the without-PAS figures can be presented.

Table 2. Base-case results at list prices

	Intervention		**Incremental voretigene neparvovec vs BSC**
	voretigene neparvovec	**BSC**	
Total costs (£)	£658,946	£33,970	£624,976
Total QALYs	10.6	3.6	7.0
ICER (£/QALY)	-	-	£89,871

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALYs, quality-adjusted life years.

An extensive range of scenario analyses was conducted and the most relevant ones (in which base-case ICER changed by more than 10%) are presented in table 3 below. An additional scenario was requested which combines some key and uncertain assumptions into one conservative scenario.

Table 3. Results of selected deterministic scenario analyses at list prices

	Area of uncertainty	**Base-case**	**Scenario**	**ICER at list price (£/QALY)**
1	Duration of treatment effect	40 years	20 years	£111,296
2	Duration of treatment effect	40 years	10 years	£143,444
3	Source of utility values	Acaster Lloyd (HUI-3)	Acaster Lloyd (EQ-5D)	£98,687
4	Source of utility values	Acaster Lloyd (HUI-3)	Brown et al.	£124,616
5	Multistate model distribution	Weibull	Exponential	£104,017
6	Health state definition	VA and VF	VF only	£102,790
7	Carer disutility	Included	Excluded	£98,394
8	Perspective	Healthcare system	Societal	£67,774
9	Light sensitivity utility increment	Not included	Hypothetical utility increment of 0.05 in HS1 to HS3	£77,034
10	Combined scenario with conservative but plausible assumptions: 10 years treatment effect duration with no waning-off period and			£197,971

	residual effect; log-logistic multistate model distribution; EQ-5D utility set from Acaster Lloyd.	

Deterministic univariate sensitivity analyses were also performed in which all model parameters were systematically and independently varied over a plausible range determined by either the 95% CI or +/-15% where no estimated of precision were available. A subset of ten of these analyses to which the ICER was most sensitive to are presented in table 4 below. Six of these ten most influential parameters are those describing the long-term multi-state survival model; other influential parameters include the utility values for the individual health states.

Table 4. Results of selected univariate sensitivity analyses at list prices

	Parameter	**ICER at lower value of parameter**	**ICER at upper value of parameter**
1	Multistate model, Weibull (VA+VF, average eye): Ancillary	£164,456	£59,466
2	Multistate model, Weibull (VA+VF, average eye): Constant	£163,670	£59,600
3	Acaster Lloyd (HUI-3), utility value, HS1	£122,095	£71,105
4	Multistate model, Weibull (VA+VF, average eye): HS3 to HS4	£98,001	£84,046
5	Multistate model, Weibull (VA+VF, average eye): HS4 to HS5	£97,871	£83,936
6	Acaster Lloyd (HUI-3), utility value, HS3	£83,612	£97,144
7	Acaster Lloyd (HUI-3), utility value, HS5	£85,936	£94,184
8	Acaster Lloyd (HUI-3), utility value, HS4	£86,186	£93,886
9	Multistate model, Weibull (VA+VF, average eye): HS2 to HS3	£92,710	£87,873
10	Acaster Lloyd (HUI-3), utility value, HS2	£92,131	£87,720

The key strengths and uncertainties of the economic evidence are summarised below:

Key strengths:

- The pharmaco-economic analysis presented was comprehensive and the reporting was thorough and transparent.
- The model was considered generally suitable for decision making, incorporating relevant health states and capturing fairly well the impact of disease progression on relevant costs and health outcomes important to patients.
- The methods utilised in the modelling were generally robust.
- The company presented an extensive and comprehensive list of sensitivity analyses which captured the uncertainty around the base case results reasonably well, for

example exploring various assumptions for estimating transition probabilities for the model that were not observed in the clinical data due to the small sample size.

Key uncertainties:

- **Duration of treatment effect:** The treatment effect of voretigene neparvovec on VA and VF observed at one year in Study 301 is assumed to be maintained in full over 40 years which is subject to uncertainty. Theoretically, a lifetime treatment effect might be expected given the curative nature of gene therapies. However, no long-term data are available, with only tangential evidence on potential lifetime effects from non-human studies. The duration of the treatment effect is a key driver in terms of the cost-effectiveness of the treatment. Shorter durations of 10 and 20 years resulted in substantial increases in the ICER (scenario analyses #1 and #2 in table 3).
- **Health utility:** The proxy health utility scores utilised were based on a very small sample of clinician responses and are subject to a number of limitations. The utility assigned by clinicians to the worst health state in the model using the HUI-3 instrument is worse than death, which lacks face validity. This may be due to the higher focus of the HUI-3 instrument on visual dimensions compared to EQ-5D and a potential bias of the retina specialists surveyed to place a higher value on this dimension. When the alternative EQ-5D set is used, which is generally preferred to ensure consistency in SMC assessments across treatments and disease areas, the ICER is higher (scenario #3 table 3). The ICER increased further compared to the base case when an alternative published utility value set was utilised (scenario #4 table 3). These alternative published values were derived using time trade-off methodology in a sample of patients with vision loss due to various causes, so while representing patients' rather than clinicians' judgements, they may not fully reflect the target population. To address this outstanding uncertainty in health utilities, better measures are needed: preferably derived from validated preference-based quality of life questionnaires collected prospectively in patients falling under the licence indication or through direct validation of vignette health states by a representative sample of the Scottish population using appropriate methodology.
- **Trial clinical data:** The VA and VF clinical outcomes from Study 301 used in the economic analysis were secondary and exploratory outcomes. The primary outcome (MLMT) was not used in the economic evaluation as no data were available linking this outcome to costs, utilities or mortality and no data on the long-term change in this outcome were available either. Moreover, transition probabilities in the model were derived from very small patient numbers and hence are subject to uncertainty. As no data were observed to derive some of these transitions, despite being clinically plausible, various assumptions and approaches were utilised by the submitting company to inform these transitions. This adds to the uncertainty surrounding the transition probabilities used in the model, particularly for the more severe health states, but results seem to be relatively stable across the number of approaches presented.
- **Model structure:** Because of few observations in the natural history dataset, the states of

being able to detect hand motion, light perception and detecting no light perception have been pooled together in a single health state. However, there may be substantial differences in health outcomes between these states in practice. Also, the one year cycle length used throughout the analysis may have sacrificed the granularity of the data collected during the Study 301 follow-up. The 1/12th cycle correction applied in the first year of the analysis to reflect the rapid treatment response in terms of the outcomes collected in Study 301 may overestimate the speed of the treatment response in relation to the VA outcome in which there was no immediate change. These, however, are minor issues which seemed to not affect results by much in subsequent sensitivity analyses.

The cost of voretigene neparvovec in relation to its health benefits remains high and there are outstanding uncertainties relating to the clinical data used in the model.

*Other data were also assessed but remain confidential.**

Costs to NHS and Personal Social Services

The submitting company estimated that the prevalent population eligible for treatment is nine patients and assumed that the all eligible patients would be treated uniformly across the first three years.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

*Other data were also assessed but remain confidential.**

Additional information: guidelines and protocols

No national guidelines relating to inherited retinal dystrophy were identified.

Additional information: comparators

There are no relevant comparators.

Cost of relevant comparators

Medicine	Dose Regimen	Cost per course (£)
voretigene neparvovec	**1.5 x 10^{11} vector genomes by subretinal injection in each eye**	**613,410**

Costs for voretigene neparvovec are taken from the company submission. Costs do not take any patient access schemes into consideration and do not include costs for subretinal administration.

References

1. Novartis Ltd. Voretigene neparvovec (Luxturna) summary of product characteristics. European Medicines Agency. www.europa.eu Last updated 15/04/2019.
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3. Chung DC, Bertelsen M, Lorenz B, Pennesi ME, Leroy BP, Hamel CP*, et al.* The Natural History of Inherited Retinal Dystrophy due to Biallelic Mutations in the RPE65 Gene. American Journal of Ophthalmology. 2018.
4. Russell S, Bennett J, Wellman JA, Chung DC, Yu Z-F, Tillman A*, et al.* Efficacy and safety of voretigene neparvovec (AAV2-hRPE65v2) in patients with RPE65 -mediated inherited retinal dystrophy: a randomised, controlled, open-label, phase 3 trial. The Lancet. 2017;390:849-60.
5. NCT00999609 Safety and efficacy study in subjects with Leber Congenital Amaurosis www.clinicaltrials.gov [last updated 19 March 2019].
6. Maguire AM, Bennett J, Wellman J, Chung DC, High KA, Yu Z-F*, et al.* Phase 3 trial update of voretigene neparvovec in biallelic RPE65 mutation-associated inherited retinal disease [oral presentation]. The American Academy of Ophthalmology (AAO) Annual Meeting 2017; New Orleans, LA, USA.
7. Drack AV, Bennett J, Russell S, High KA, Yu Z-F, Tillman A*, et al.*, editors. How long does gene therapy last? 4 Year follow-up of Phase 3 Voretigene Neparvovec Trial in RPE65–Associated LCA/Inherited Retinal Disease. Abstract submitted to AAPOS 45th Annual Meeting; 2019.

This assessment is based on data submitted by the applicant company up to and including 11 October 2019.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy*

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC assessment report.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When a medicine is available through the ultra-orphan pathway, a set of guidance notes on the operation of the patient access scheme will be

circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC assessment report.

Assessment report context:

No part of the assessment summary on page one may be used without the whole of the summary being quoted in full.

This assessment represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.