SMC2641

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

Novartis Pharmaceuticals UK Ltd.

07 June 2024

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

Advice: following reassessment through the ultra-orphan framework.

voretigene neparvovec (Luxturna®) is accepted for use within NHSScotland.

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.

In a phase III open-label study of patients with vision loss due to inherited retinal dystrophy due to RPE65 mutations, functional vision was significantly improved from baseline to one year in the voretigene neparvovec group compared with the control group.

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS/ list price that is equivalent or lower.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

Chair,
Scottish Medicines Consortium

1. Clinical context

1.1. Background

Voretigene neparvovec is an adeno-associated viral type 2 (AAV2) gene therapy vector. It consists of a virus which carries the normal human retinal pigment epithelium-specific 65 kilodalton protein (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]

1.2. Nature of condition

Inherited retinal dystrophies are a heterogeneous group of rare genetic diseases which cause a loss of vision and are the result of germline mutations in more than 260 different genes, including the RPE65 gene.[2, 3] 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 the progressive loss of vision.[2, 4]

The term “inherited retinal dystrophy due to biallelic RPE65 mutation” includes patients with different mutations in the RPE65 gene who were previously identified by more than 20 different names including Leber’s congenital amaurosis and retinitis pigmentosa. 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. Leber’s congenital amaurosis type 2, which has a worse prognosis but is less common than other clinical diagnoses, presents in infancy and patients deteriorate becoming blind in adolescence or young adulthood. Patients with retinitis pigmentosa present later, usually in adolescence and progress more slowly to blindness.[2, 4, 5]

There are no other medicines licensed for this condition and patients are generally managed by best supportive care. There is 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.

1.3. Category for decision-making process

Eligibility for a PACE meeting:

Voretigene neparvovec meets SMC ultra-orphan criteria.

2. Impact of new technology

Comparative efficacy

Key evidence for voretigene neparvovec for this indication is from Study 301/302.

Table 2.1 Overview of relevant study.[2, 4, 6]

Criteria	Study 301/302.
Study design	Randomised, open-label, phase III study.

Eligible patients	• Aged ≥3 years with inherited retinal dystrophy and a confirmed genetic diagnosis of biallelic RPE65 gene mutations.
	• Visual acuity of 20/60 or worse and/or visual field <20 degrees in any meridian in both eyes.
	• Sufficient viable retinal cells as determine by optical coherence tomography and/or ophthalmology as:
	  ○ retinal thickness on spectral domain (>100 microns within the posterior pole).
	  ○ ≥3 disc areas of retina without atrophy or pigmentary degeneration within the posterior pole.
	  ○ remaining visual field within 30 degrees of fixation.
	• Ability to perform a standardised multi-luminance mobility test (MLMT) within the luminance range assessed but unable to pass the MLMT at the lowest luminance level tested (1 lux).

Treatments & Randomisation	Eligible patients were randomised in a ratio of 2:1 to receive voretigene neparvovec or control. 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 prednisolone 1 mg/kg/day (maximum of 40 mg) for 7 days starting 3 days before the first injection. The prednisolone dose was tapered until it was repeated 3 days before the second eye was injected. In the control group, patients did not receive treatment. After 1 year, those in the control group who continued to meet eligibility criteria were allowed to receive voretigene neparvovec. Randomisation was stratified by age (<10 years and ≥10 years) and baseline mobility testing passing level (pass at ≥125 lux versus <125 lux).

Primary outcome	Mean change from baseline to one year in bilateral MLMT. MLMT is 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.
Secondary outcomes	• FST testing using white light averaged over both eyes. • MLMT for the first assigned eye. • Best-corrected visual acuity (BCVA), using the scale adapted by Holladay.
Statistical analysis	A hierarchical statistical testing strategy was applied for the primary outcomes and the three secondary outcomes, in the order specified above, with no formal testing of outcomes after the first non-significant outcome.

Abbreviations: FST = full-field light sensitivity threshold; MLMT = multi-luminance mobility test; RPE65 = retinal pigment epithelium-specific 65 kilodalton protein.

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). 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] Detailed results for the primary and secondary outcomes are presented in table 2.2.

Table 2.2. Results of primary and secondary outcomes in the ITT population of Study 301/302 (after one year).[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 (log_{10}[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 the 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 (Holladay scale)	+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; BCVA = best-corrected visual acuity, measured using the scale adapted by Holladay and averaged over both eyes; NS = not significant

The company also provided results of a post hoc analysis of BCVA using the scale adapted by Lange which reported a 9.0 letter improvement from baseline to 1 year in the voretigene neparvovec group versus a 1.6 letter improvement in the control group; difference of 7.4 letters (95% CI: 0.1 to 14.6) in the mITT population. Since this was a post hoc analysis, these results are descriptive only and not inferential (no p-values reported).[2] These results were used in the economic analysis.

Visual field (Goldmann) testing was an exploratory outcome to assess changes in function of different areas of the retina. At 1 year, there was a 302.1 sum total degrees improvement from baseline to 1 year in the voretigene neparvovec group versus a reduction of -76.7 sum total degrees in the control group; difference of 378.7 sum total degrees (95% CI: 145.5 to 612.0). Since this was exploratory, these results are descriptive only and not inferential (no p-values reported).[2] These results were used in the economic analysis.

After one year, the control group were given the opportunity to cross over to receive voretigene neparvovec.[2, 4] After a follow-up of 5 years in the original intervention group (n=18) and 4 years in the control/delayed intervention group (n=8), there was a mean change in MLMT score of 1.6 and 2.4 respectively. Results for FST, BCVA and visual field (Goldmann testing) also appeared to be maintained.[7, 8]

A retrospectively validated visual function questionnaire (VFQ) 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; with the improvement from baseline ranging from 1.8 (1.9) at day 30 to 2.6 (1.8) at one year in patient-completed questionnaires, and from 3.1 (2.2) at day 30 to 3.9 (1.9) at one year for parent completed questionnaires. The mean scores were generally unchanged in the control group. VFQ results over time for patient-completed surveys were provided in the company submission and suggest that the treatment effect on this outcome is maintained.[2, 4]

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.[9]

Additional evidence on reassessment

Following the initial assessment in February 2020 (SMC2228) the company had the opportunity to collect additional data to support its submission. This included information from studies as well as real-world data collection.

Longer-term follow-up from the phase III (301/302) and supportive phase I (101/102) studies have been presented which suggests that the treatment effect of voretigene neparvovec is maintained. A post hoc analysis of the study 301/302 data indicated a high correlation between the change in MLMT and the FST endpoints (Pearson correlation coefficient -0.71 at year 1 of the Phase 3 study). This correlation is clinically useful in the real-world, as FST is an ophthalmic measure that is already available and familiar.[10] FST would more likely be available in test centres administering voretigene neparvovec than MLMT, which may not be as easily reproducible in a real-world setting outside of specialist centres.

Since the original submission, data has also become available from the PERCEIVE study. This is a non-interventional, post-authorisation, multicentre, longitudinal, observational safety registry study; requested by the European Medicines Agency.[2, 11] At the third interim analysis, this study has enrolled 198 patients (from the EU and UK) who had received treatment with voretigene neparvovec in at least one eye (maximum follow-up time of 3.4 years). The primary objective was to collect long-term safety information (for 5 years after voretigene treatment) that is treatment or procedure related; however, efficacy data was also collected where possible and assessed as a secondary outcome. Available efficacy results from this study showed that for patients treated with voretigene neparvovec, there was an increase in mean retinal sensitivity over time and other assessments of visual function (that is BCVA) remained stable up to 3 years.[11, 12]

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

Comparative safety

During year 1 of study 301 the most frequently reported individual adverse events in the voretigene neparvovec (n=20) and control groups (n=9) were leukocytosis (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%).[4] 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%.[2]

At a later follow-up (05 May 2017), 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%), headache (7%) and macular hole (7%). The retinal deposits were considered to be probably related to voretigene neparvovec but were transient and asymptomatic and resolved with 8 weeks.[2] Safety data from a later follow-up (02 July 2018) showed the same rates of these adverse events.[6]

There were changes in the foveal thickness for some patients after administration of voretigene neparvovec. This returned to baseline levels after 1 year in some patients and not in others. The EMA comments that these findings may represent a reversible disruption of the outer segments of the retina observed during the post-operative period.[2]

Overall, the safety of voretigene neparvovec observed in the PERCEIVE study, with up to 3-years data, is consistent with the known safety profile of voretigene neparvovec.

Since the original submission, chorioretinal atrophy has been identified as an adverse drug reaction from post-marketing reports from EU treatment centres, including events reported within the registry study PERCEIVE. No AEs of retinal atrophy were reported in studies 301/302 or 101/102; this may be because at the time, any events of chorioretinal atrophy were assessed by the principal investigators as a result of the natural progression of the disease and therefore not reported as AEs.

In PERCEIVE, at the latest data cut-off (August 2022), events of chorioretinal atrophy were reported in some patients. Of these affected patients, the most frequently reported AEs were retinal degeneration (39/49 patients) and injection site atrophy (15/49 patients).[12]

Events of chorioretinal atrophy have not been associated with any visual impairment, and the functional benefits of voretigene do not appear to be affected in the reported cases.[13-15]

Clinical effectiveness issues

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

Key strengths:

- Voretigene neparvovec is the first licensed treatment for inherited retinal dystrophy.
- 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 at least five years. Supportive data from a phase I study suggests sustained improvement in vision for at least 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 statistically different from the control group and the change was less than that considered to be meaningful. However, this outcome measures foveal, cone-mediated function and, therefore, not the primary target of the intervention in this rod-mediated disease. It also does not capture defining characteristics of the condition including nyctalopia, reduced sensitivity and nystagmus.
- Clinical experts consulted by SMC viewed voretigene neparvovec as a therapeutic advancement since it addresses the underlying cause of the condition. Whilst there remains uncertainty about the longer-term clinical data, a lifelong treatment effect is theoretically possible.

Key uncertainties:

- The phase III study aims to follow patients for up to 15 years after treatment. Despite additional follow-up data, the duration of treatment effect remains 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, in conjunction with the Food and Drug Administration (FDA), and there is some uncertainty over what represents a clinically relevant improvement for outcomes using this assessment tool. However, as mentioned a post hoc analysis of the study 301/302 data indicated a high correlation between the change in MLMT and the FST endpoints. FST would more likely be available in test centres administering voretigene neparvovec than MLMT, which may not be as easily recruitable in a real-world setting outside of specialist centres.

- Although the visual function questionnaire indicated improvements in activities of daily living, there was no direct measure of health-related quality of life in the clinical studies; therefore, it is unclear how these results relate to quality of life for patients.
- Voretigene neparvovec was generally well tolerated but there are risks and complications associated with intraocular surgery required for subretinal injection and these could have long-term consequences.

3. 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.

4. Patient and clinician engagement (PACE)

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of **voretigene neparvovec (Luxturna®),** as an **ultra-orphan** medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- Inherited retinal dystrophy due to biallelic RPE65 mutation encompasses patients with different mutations in the RPE65 gene who were previously identified by more than 20 different names including Leber's congenital amaurosis and retinitis pigmentosa. Patients with this condition present with significant visual impairment, that can occur at any age from infancy to adolescence; however, this usually occurs from birth. The vision loss then usually progresses further, with some patients becoming blind in adolescence and young adulthood.
- The initial diagnosis of this condition can be devastating, but the knowledge that a child or adult will likely eventually become legally blind is often devastating and life-changing for parents and their families. The relentless progression of vision loss takes an immense psychological toll, with 93% of patients in a 2022 Retina UK survey report experiencing

anxiety, depression, stress and loneliness directly attributed to their inherited retinal condition; a patient with this condition described to other PACE participants their own psychological issues living with this condition prior to receiving voretigene neparvovec treatment.

- Voretigene neparvovec is the only licensed treatment for RPE65-mediated inherited dystrophy. Although very few patients with this condition are expected to be identified in Scotland, having this treatment available would fulfil the unmet need in any newly diagnosed patients. The prospect of this treatment gives hope where there has been none before and allows more options to be considered for these patients when planning for their futures, such as career and family planning.
- Evidence from clinical trials of voretigene neparvovec, as well as emerging real-world data, has shown improvement in visual function; some have even had improved reading ability. This improvement in visual function appears to be much more profound if given to younger patients, though the longevity of this improvement is yet to be fully determined. Given this treatment is licensed for those with sufficient viable cells, there is the need to maximise the treatment benefit and delay progression of this condition in younger patients when they still have relatively intact retinal function.
- A PACE clinician also highlighted their overwhelmingly positive clinical experiences of working with children who were administered voretigene neparvovec out with the UK. PACE participants, including a patient with this condition, also reported the “life-changing” impact this treatment has had on his condition.
- This medicine could add to patients’ functional and psychological wellbeing. Functionally, they would be better able to navigate the world around them, reducing their reliance on carers and improving their physical safety. Even moderate improvements in outcome could mean a patient living using sighted means as opposed to non-sighted means.
- Psychologically they would benefit due to their improved independence, as well as having a degree of hope of retaining some useful vision where there previously was none. A PACE clinician highlighted how blind children in their therapeutic specialty have often missed out on important periods of education because of lack of qualified support staff, reluctance for the education authority to purchase appropriate expensive technology and limited opportunities to pursue the same activities as their sighted peers. A patient with this condition described to PACE participants the overwhelming positive impact voretigene neparvovec had on his mental wellbeing, for example how he was able to discontinue antidepressants and engage in social activities such as watching the football.
- Treatment would require several pre- and post-operative visits to hospital, as well as two peri-operative stays (one for each eye); this would likely be a burden for the patient’s family and/or carers. However, this would likely be offset by any function improvements or

stabilisation in vision which would have significant value to the patient's family and/or carers as this could mean a reduced need for personal care and support.

- There are several service aspects (for example voretigene neparvovec requires a vitreo-retinal surgeon competent at delivering paediatric subretinal injections) and product aspects (storage, transportation, wastage disposal) to consider. However, it should be noted that despite all these requirements, two tertiary centres (Glasgow and Edinburgh) already have experience of delivering similar medicinal products in clinical trials.

Additional Patient and Carer Involvement

We received a patient group submission from the Retina UK, which is a charitable incorporated organisation. Retina UK has received 4.7% pharmaceutical company funding in the past two years, including from the submitting company. Representatives from Retina UK participated in the PACE meeting. The key points of their submission have been included in the full PACE statement considered by SMC.

5. Value for money

5.1. Economic case

The economic case is summarised in Table 5.1 below. Compared to the original submission (SMC2228), the key changes in the economic case were the updated health state utility values from a bespoke vignette study, the exclusion of genetic testing costs, and the exclusion of carer disutilities.

Table 5.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost-utility analysis.
Time horizon	Lifetime time horizon (85 years based on an assumed average starting age of 15).
Population	The submitting company requested SMC consider voretigene neparvovec 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.
Comparators	Best supportive care (BSC) comprising healthcare resource use associated with visual impairment.
Model description	A cohort-based state-transition Markov model was used. The model contained 6 health states (HS) to capture progressively worse levels of visual impairment. These were: HS1 moderate visual impairment (VI), HS2 severe VI, HS3 profound VI, HS4 counting fingers (CF), HS5 hand motion (HM), light perception (LP) to no light perception (NLP), and HS6 death. The health states broadly aligned with the American Medical Association (AMA) guidelines with some differences: near-blindness was categorised as the HS4 CF health state in the model, while total blindness was categorised as the HS5 pooled health state of HM, LP and NLP. The health state membership was determined based on the AMA guideline thresholds for visual acuity and visual field, using the worst of visual acuity and visual field in the 'average eye' (calculated by averaging the visual acuity and visual field observed in each eye at each time point). A 1-year cycle length was used, with a half cycle correction applied. A 1/12 cycle correction was applied in the first year to reflect improvement in the original intervention arm of Study 301 which was observed at approximately 1 month.
Clinical data	The baseline health state distribution in the model was informed from the levels of visual acuity and visual field observed in the intention to treat (ITT) dataset at the start of Study 301. Data on

	visual acuity and visual field from Study 301 (modified ITT) were used to inform transition probabilities from baseline to Year 1 in each of the BSC and voretigene neparvovec arms.[2, 4, 6] Natural history data in individuals with RPE65-mediated inherited retinal dystrophy from a retrospective chart review were used to model long-term transition probabilities in visual function beyond year 1. Adverse events related to treatment and administration in the original intervention arm of Study 301, occurring in greater than one patient and expected to be associated with an impact on quality of life or cost were included in the model. These were cataract (15% of patients), eye inflammation (10% of patients) and increased intraocular pressure (20% of patients). Hazard ratios linking visual impairment to mortality were sourced from literature.[16]
Extrapolation	The model comprised of initial and long-term phases. In the initial phase, from baseline to year 1, patients in the voretigene neparvovec and BSC arms transitioned between model health states at year 1 according to transition probabilities. In the long-term phase (BSC arm), a Weibull multistate survival model was fitted to the retrospective chart review data to estimate annual transition probabilities beyond year 1. The transition probabilities were progressive only, that is patients could only transition to a worse health state in the long-term phase. In the long-term phase (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-year period and a residual treatment effect (25% RRR) thereafter. As no death events were observed in the retrospective chart review, death was not included in the multistate model and mortality was modelled separately using general population life tables with state specific hazard ratios applied to capture the potential heightened mortality risk associated to loss of vision.[16, 17]
Quality of life	Health state utility values were obtained from a bespoke utility study.[18] This was a vignette study applying a time trade-off (TTO) process. Vignettes were developed following interviews with patients with retinitis pigmentosa and retinitis pigmentosa healthcare professionals in the UK, with members of the general UK public then valuing health states. Health state utility values were: 0.78 (HS1), 0.65 (HS2), 0.5 (HS3), 0.43 (HS4), and 0.33 (HS5). Adverse event disutilities were included. The base case excluded carer disutilities.
Costs and resource use	The model included treatment acquisition, administration, monitoring, testing for sufficient viable retinal cells, adverse events, and health state specific costs. Health state specific costs were dependent on age. Genetic testing costs were not included in base case following clinical feedback received by the submitting company. The base case considered healthcare system costs. A scenario considered a wider societal perspective, which included non-healthcare costs such as productivity losses.
PAS	A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a discount was offered on the list price.

5.2. Results

The base case results are shown in the table below. These results do not include the confidential PAS discount on voretigene neparvovec. The majority of incremental costs were from voretigene neparvovec acquisition. The majority of incremental quality-adjusted life year (QALY) gain was obtained in HS1.

Table 5.2: Base case results (List prices)

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
VN	654,310	17.7	615,121	0.06	5.6	110,657
BSC	39,189	12.2	-	-	-	-

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

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

5.3. Sensitivity analyses

Scenario analyses are shown in the table below. The incremental cost-effectiveness ratio (ICER) was most sensitive to the scenarios considering the perspective, discount rate, the duration of treatment effect, and the source of utility values. Again, these results do not include confidential PAS discount on voretigene neparvovec.

Table 5.3: Scenario analysis results (List prices)

	Parameter	Base case value	Scenario value	Inc. Cost (£)	Inc. QALY	ICER (£/QALY)
	Base case	-	-	615,121	**5.6**	110,657
1	Perspective	Healthcare system	Societal	434,181	5.6	78,107
2	Discount rate	3.5% both costs and outcomes	3.5% costs; 1.5% outcomes	615,121	9.5	64,564
3	Health state definition	VA and VF	VF only	614,247	5.1	121,461
4	Duration of treatment effect	40 years	20 years	617,757	4.5	137,119
5	Residual treatment effect	RRR of 25%	RRR of 0%	615,735	5.5	111,984
6	Treatment waning	10 years	0 years	615,570	5.5	111,818
7	Multistate model distribution	Weibull	Log-logistic	614,807	5.3	115,243
8	Utility values source	O'Brien.[18]	Brown et al.[19]	615,121	4.4	139,856
9		O'Brien	Acaster Lloyd (HUI3) [20]	615,121	6.3	£97,199
10		O'Brien	Acaster Lloyd (EQ-5D).[20]	615,121	5.7	107,757
11	Carer disutility	Excluded	Included	615,121	6.2	99,867

12	Light sensitivity utility increment	Not included	Hypothetical utility increment of 0.05 in HS1 to HS3 (VN arm)	615,121	6.7	91,610
13	Combined scenario	-	Combine 4, 5, 6, 7	617,978	4.0	154,537

Abbreviations: ICER = incremental cost-effectiveness ratio; Inc = incremental; QALY = quality-adjusted life year; VA = visual acuity; VF = visual field.

5.4. Key strengths:

- The cohort-based state-transition Markov model and comparator were appropriate.
- The list of resource use and costs utilised in the analysis is very comprehensive and transparently detailed.
- A comprehensive selection of variables were considered in one-way deterministic sensitivity analysis.

5.5. Key uncertainties:

- The treatment effect of voretigene neparvovec on visual acuity and visual field observed at one year in Study 301 was assumed to be maintained in full over 40 years and was subject to uncertainty. Theoretically, a lifetime treatment effect might be expected given the curative nature of gene therapies. However, no long-term lifetime data were available, with only tangential evidence on potential lifetime effects from nonhuman studies. Reducing the maintenance treatment effect to 20 years increased the ICER (See Scenario 4 in Table 5.3).
- No utility values were available from validated preference-based quality of life questionnaires collected prospectively in patients falling under the licensed indication. SMC preference is to capture utilities through the EQ-5D instrument. In the Initial Assessment for voretigene neparvovec (SMC2228), the company used utility values generated by clinicians completing standardised instruments (Scenarios 8 and 9). However, for the resubmission the company used new utility values from a bespoke vignette study applying a time trade-off process, with interviews with members of the general UK public to value health states (n=110). The updated utility values addressed some utility concerns raised in the original submission. However, the utility values for the worse health states may still have been underestimated. When using alternative utility values from Brown et al, 1999, that were derived in a sample of patients with vision loss and showed higher utility values in HS3 to HS5, the ICER increased (Scenario 8).[19]
- Transition probabilities in the model were derived from very small patient numbers and hence were 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 added to the

uncertainty surrounding the transition probabilities used in the model, particularly for the more severe health states, but results were relatively stable across the number of approaches presented.

6. Conclusions

The Committee considered the benefits of voretigene neparvovec in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that the criterion for the absence of other treatments of proven benefit was satisfied.

In addition, as voretigene neparvovec is an ultra-orphan medicine, SMC can accept greater uncertainty in the economic case. After considering all the available evidence and the output from the PACE process, the Committee accepted voretigene neparvovec for use in NHSScotland

7. Costs to NHS and Personal Social Services

The submitting company estimated there would be 9 patients eligible for treatment with voretigene neparvovec, with 1 patient (13%) receiving treatment in year 1 and fewer than 1 patients (3%) in year 5.

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. This template does not incorporate any PAS discounts associated with comparator medicines or PAS associated with medicines used in a combination regimen.

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

8. Guidelines and protocols

There are no relevant published guidelines.

9. Additional information

9.1. Product availability date

31 July 2020

Table 9.1 List price of medicine under review

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 Pharmaceuticals UK Ltd. Voretigene neparvovec concentrate and solvent for solution for injection (Luxturna®) Summary of product characteristics. Electronics Medicines Compendium www.medicines.org.uk. Last updated: 15 Nov 2023.
2. The European Medicines Agency (EMA) European Public Assessment Report. Voretigene neparvovec (Luxturna®). EMEA/H/C/004451/0000. Published 20 September 2018. Available at: www.ema.europa.eu [Accessed 21 February 2024].
3. Farrar GJ, Carrigan M, Dockery A, Millington-Ward S, Palfi A, Chadderton N*, et al.* Toward an elucidation of the molecular genetics of inherited retinal degenerations. Human molecular genetics. 2017;26(R1):R2-R11.
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. 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.
6. Maguire AM, Russell S, Chung DC, Yu ZF, Tillman A, Drack AV*, et al.* Durability of Voretigene Neparvovec for Biallelic RPE65-Mediated Inherited Retinal Disease: Phase 3 Results at 3 and 4 Years. Ophthalmology. 2021;128(10):1460-8. Epub 2021/04/03.
7. Russell S, Bennett J, High K, Drack AV, Yu Z-F, Tillman A, et al. Five-year update for the phase 3 voretigene neparvovec-rzyl study in biallelic RPE65 mutation-associated inherited retinal disease [conference abstract]. Presented at the Retina Society 53rd Annual Scientific Meeting; September 8, 2020; Virtually. Abstract Number: 221. Available from: https://www.retinasociety.org/content/documents/221.pdf [Accessed 22 February 2024].
8. Leroy BP, Fischer MD, Flannery JG, MacLaren RE, Dalkara D, Scholl HP*, et al.* Gene therapy for inherited retinal disease: Long-term durability of effect. Ophthalmic Research. 2023;66(1):179-96.
9. Chung DC, Lee K, Reape KZ, High K, Lacey S, Viriato D. Long-term effect of voretigene neparvovec on the full-field light sensitivity threshold test of patients with RPE65 mutation-associated inherited retinal dystrophy: post-hoc analysis of Phase I trial data. Abstract submitted to ARVO 2019 Annual Meeting
10. Maguire AM, Russell S, Wellman JA, Chung DC, Yu ZF, Tillman A*, et al.* Efficacy, Safety, and Durability of Voretigene Neparvovec-rzyl in RPE65 Mutation-Associated Inherited Retinal Dystrophy: Results of Phase 1 and 3 Trials. Ophthalmology. 2019;126(9):1273-85. Epub 2019/08/25.
11. The European Medicines Agency (EMA) Real World Data (RWD) catalogues. A Post-Authorization, Multicenter, Multinational, Longitudinal, Observational Safety Registry Study for Patients Treated with Voretigene Neparvovec. EU PAS number: EUPAS31153. Published 29 August 2019; last updated: 22 February 2024. Available from: https://catalogues.ema.europa.eu/node/3021/methodological-aspects [Accessed: 22 February 2024].
12. Audo I, Lorenz B, Leroy BP, Clemens A, Maier R, Fischer D. Real-world safety and effectiveness of voretigene neparvovec: Year 3 interim results from the PERCEIVE Study. Oral presentation at EURETINA 2023, October 5th-8th, Amsterdam. Abstract available at: https://euretina.softr.app/amsterdam-abstract?recordId=rec0INUyB9CycYI7D (last accessed October 2023). 2023.

13. Gange WS, Sisk RA, Besirli CG, Lee TC, Havunjian M, Schwartz H*, et al.* Perifoveal Chorioretinal Atrophy after Subretinal Voretigene Neparvovec-rzyl for RPE65-Mediated Leber Congenital Amaurosis. Ophthalmol Retina. 2022;6(1):58-64. Epub 2021/04/11.
14. Reichel FF, Seitz I, Wozar F, Dimopoulos S, Jung R, Kempf M*, et al.* Development of retinal atrophy after subretinal gene therapy with voretigene neparvovec. Br J Ophthalmol. 2022. Epub 2022/05/25.
15. Stingl K, Stingl K, Schwartz H, Reid MW, Kempf M, Dimopoulos S*, et al.* Full-field Scotopic Threshold Improvement after Voretigene Neparvovec-rzyl Treatment Correlates with Chorioretinal Atrophy. Ophthalmology. 2023;130(7):764-70. Epub 2023/02/24.
16. Christ SL, Zheng DD, Swenor BK, Lam BL, West SK, Tannenbaum SL, et al. Longitudinal Relationships Among Visual Acuity, Daily Functional Status, and Mortality: The Salisbury Eye Evaluation Study. JAMA Ophthalmology. 2014;132:1400-1406.
17. National Records of Scotland. Data Tables for Life Expectancy in Scotland, 2019-2021; 2022. Available from: https://www.nrscotland.gov.uk/statistics-and-data/statistics/statistics-by-theme/life-expectancy/life-expectancy-in-scotland/2019-2021/data-tables [Accessed: 07 March 2024].
18. O'Brien P, Enstone A, Bridge D, Wyn R, Banhazi J. Elicitation of Health State Utility Values in Retinitis Pigmentosa by Time Trade-off in the United Kingdom. Clinicoecon Outcomes Res. 2023;15:29-39.
19. Brown GC. Vision and quality-of-life. Transactions of the American Ophthalmological Society. 1999;97:473-511.
20. Lloyd A, Piglowska N, Ciulla T, Pitluck S, Johnson S, Buessing M, et al. Estimation of impact of RPE65-mediated inherited retinal disease on quality of life and the potential benefits of gene therapy. Br J Ophthalmol. 2019;103(11):1610-1614.

This assessment is based on data submitted by the applicant company up to and including 12 April 2024.

**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:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

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.