NICE National Institute for Health and Care Excellence

NICE guidance

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

Highly specialised technologies guidance
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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

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1 Recommendations

1.1 Voretigene neparvovec is recommended, within its marketing authorisation, as an option for treating RPE65-mediated inherited retinal dystrophies in people with vision loss caused by inherited retinal dystrophy from confirmed biallelic RPE65 mutations and who have sufficient viable retinal cells. It is recommended only if the company provides voretigene neparvovec according to the commercial arrangement.

Why the committee made these recommendations

RPE65-mediated inherited retinal dystrophies are rare and serious. They involve progressive loss of vision. This ultimately leads to near-total blindness, and severely affects the quality of life of people with the condition, and their families and carers. Current treatment is supportive care.

Clinical trial evidence shows that, in the short term, voretigene neparvovec improves vision and prevents the condition from getting worse. There is no long-term clinical evidence, but it is biologically plausible that the treatment effect is likely to continue for decades.

Some assumptions in the economic modelling are uncertain, particularly around the utility values and how long the treatment effect lasts. Despite the uncertainties, voretigene neparvovec is likely to provide important clinical benefits for people with RPE65-mediated inherited retinal dystrophies, and is considered an appropriate use of NHS resources within the context of a highly specialised service. It is therefore recommended for use in the NHS.

2 The condition

2.1 Inherited retinal dystrophies (IRDs) are a group of rare genetic eye diseases. They are caused by germline mutations in more than 260 genes, including that for the enzyme RPE65. This enzyme is critical for the visual cycle. It is involved in a multistep process that converts light entering the eye into electrical signals, which are transmitted to the brain. Lack of RPE65 causes severe deficiency in functional rhodopsin (a sensory protein that converts light into an electrical signal) and death of photoreceptor cells on the retina through accumulation of toxic chemical compounds. People with RPE65-mediated IRD have progressive vision loss. There is variation in the presentation and time of diagnosis of the condition. Loss of vision can begin as early as the first few months of life, or during childhood or adolescence. Initially, people have problems with peripheral vision and seeing in dim light or night blindness. These symptoms are followed by progressive deterioration in visual field (range of vision) and visual acuity (clarity of vision), and reduced sensitivity to light. Ultimately, the deterioration leads to near-total blindness.

2.2 Lack of RPE65 presents as clinical conditions such as classically termed retinitis pigmentosa (RP) and Leber's congenital amaurosis (LCA). LCA is used to describe a group of severe early infantile onset rod–cone dystrophies. It is considered to have a worse prognosis than other clinical diagnoses. RP accounts for around half of IRDs, with a prevalence of around 20 to 30 people per 100,000. LCA is less common, affecting 2 to 3 people per 100,000. Mutations in the RPE65 gene account for 2% of RP and 6% to 16% of LCA diagnoses. The exact prevalence and incidence of RPE65-mediated IRD is uncertain. The company estimated that 86 people would be eligible for treatment with voretigene neparvovec in England.

2.3 There are no licensed treatments currently available in the UK for RPE65-mediated IRD. Current management focuses on strategies to improve the use of remaining vision. This includes using low-vision aids, social and educational support, and specialised genetic counselling for people with the condition and their families. Care is provided as part of a specialised multidisciplinary service.

3 The technology

3.1 Voretigene neparvovec (Luxturna; Novartis Pharmaceuticals UK) is an adeno-associated virus vector-based gene therapy. It introduces a healthy copy of the defective RPE65 gene into the retinal cells of people with RPE65-mediated inherited retinal dystrophy (IRD), enabling patients to produce functional RPE65 protein. The aim is to improve visual function (performance of the eyes) and functional vision (the ability to carry out activities of daily living dependent on vision). Voretigene neparvovec has a marketing authorisation 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'.

3.2 Voretigene neparvovec is administered as a subretinal injection using a one-off dose of 1.5×10^{11} vector genomes to each eye on separate days (no fewer than 6 days apart). Before administration, patients have an immunomodulatory regimen that is continued for 18 to 30 days.

3.3 The adverse reactions listed as common in the summary of product characteristics include: eye inflammation (including endophthalmitis), retinal disorder, an increase in intraocular pressure and temporary visual disturbances. For full details of adverse reactions see the summary of product characteristics.

3.4 The list price of voretigene neparvovec is £613,410 per patient (excluding VAT; company submission). The company has a commercial arrangement. This makes voretigene neparvovec available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

4 Consideration of the evidence

The evaluation committee (see section 6) considered evidence submitted by Novartis, the views of people with the condition, those who represent them, clinical experts, NHS England, and a review by the evidence review group (ERG). See the committee papers for full details of the evidence. In forming the recommendations, the committee took into account the full range of factors that might affect its decision, including in particular the nature of the condition, the clinical effectiveness, value for money and the impact beyond direct health benefits.

Nature of the condition

Burden of disease

4.1 The patient experts explained the all-consuming and progressive nature of RPE65-mediated inherited retinal dystrophy (IRD), highlighting that the condition affects all aspects of their lives. They explained that the visual impairment and the deteriorating nature of the condition has a considerable effect on their independence, ability to work, social life and ability to carry out day-to-day tasks. The clinical experts described that the first symptom of RPE65-mediated IRD (night blindness) is far more than a simple inability to see clearly between dusk and dawn. It affects patients at low light levels and results in reduced mobility. They noted that many patients find themselves disorientated, confused and scared.

4.2 Clinical experts also noted that RPE65-mediated IRD can affect children's development and attainment in school because signs and symptoms usually start in children and young people. One patient expert agreed that children with a visual impairment need considerable support if they are to attend a mainstream school. The patient expert described that, as vision loss progresses and as young people transition into adulthood, they lose their independence and increasingly rely on help from family members and carers. This affects their career prospects and has a significant emotional, physical and financial effect on their lives.

4.3 The condition has a substantial effect on mental health and emotional wellbeing of the patients and their families and carers. In a survey by Retina UK of people with IRD and their carers (n=916), 92% of the respondents reported that their vision loss had an effect on their mental health. The patient expert explained that the progressive nature of the vision loss means that patients are under pressure to continually adapt and accept the slow decline in vision while having uncertainty about the future, and that this causes substantial anxiety. The condition also places a significant burden on family members because they have to provide physical and emotional care to patients while experiencing considerable psychosocial consequences of their own. Families of people with RPE65-mediated IRD often experience blame or guilt because of the hereditary nature of the condition. Patients and their families also have concerns around the reproductive risks of having a hereditary disease. Adult carers experience stress from managing the financial effects of having to reduce paid work to care for children, and to pay for adaptive aids and travel to specialist appointments. The committee acknowledged that RPE65-mediated IRD is a rare, serious and debilitating condition that severely affects the lives of patients, families and carers.

Diagnosis

4.4 The committee heard that many people with IRDs previously got a clinical diagnosis based on disease progression and the retinal cell types primarily involved in disease pathogenesis. Patients are primarily diagnosed with either retinitis pigmentosa (RP) or Leber's congenital amaurosis (LCA). The clinical experts explained that this would include an assessment of medical history and clinical symptoms, and an analysis of previous family history before a diagnosis is made. The experts noted that people with IRDs can also be assigned a molecular diagnosis via genetic testing to identify the causative gene. The committee recalled that IRDs can be caused by over 260 genes, including the RPE65 gene. The clinical experts explained that RPE65 mutations have been well studied and noted that knowledge of the condition is well established among ophthalmologist specialists. The experts stated that only 5% of patients remain undiagnosed but genetic testing would be needed to confirm eligibility for the treatment. A patient expert expressed concern about genetic testing, noting that access was not universal. NHS England stated that genetic testing is expected to be available to all patients referred, although roll out of the programme has been slightly delayed.

4.5 The committee considered the number of people who may be eligible for treatment with voretigene neparvovec. It recognised that the estimates of prevalence and incidence were uncertain, but likely to be small. The clinical experts noted that they did not expect the size of the population to grow considerably if a treatment became available or if there was an increase in genetic testing. The committee recalled that most patients are diagnosed in childhood, and believed the likelihood of underdiagnosis was small in this population. The clinical experts explained that delayed diagnosis is less of a concern for children and young people because there is often a desire to find the cause in this population. However, adults who have experienced vision loss later in life may have adapted to the condition and not sought a clinical or molecular diagnosis. The clinical experts anticipated that a limited number of additional, mainly adult, patients with RPE65-mediated IRD who are currently undiagnosed will be referred and diagnosed with the roll out of the genetic testing and the availability of treatment.

Impact of the new technology

Clinical trial evidence

4.6 The company's clinical evidence came from 2 studies:

- Study 101/102 was a phase I, open-label, dose-escalating, safety profile study in which individual patients (n=12) had 1 injection of voretigene neparvovec in 1 eye. After 1 year, study 101 ended and patients (n=11) could enter study 102, its long-term follow up (up to 15 years). In this study, the patients had 1 injection of voretigene neparvovec in the eye not treated in study 101. Data at 7.5-year follow up are available from the follow-up study.
- Study 301 was a phase III, open-label, randomised controlled trial comparing the long-term efficacy and safety of voretigene neparvovec (n=21) given in both eyes with best supportive care (BSC; n=10). After 1 year, patients who had BSC (n=9) could have voretigene neparvovec in the extension study (study 302). Data at 3- to 4-year follow up are available from study 301/302.

Generalisability of the evidence to NHS clinical practice

4.7 The marketing authorisation for voretigene neparvovec stipulates that people must have sufficient viable retinal cells. The committee judged that sufficient viable retinal cells was not fully defined in the marketing authorisation, so it would need to consider how the decision for treatment eligibility would be made in practice. The committee discussed whether study 301/302's definition of sufficient viable retinal cells would fit clinical practice in England. In this study, sufficient viable retinal cells was defined as:

- an optical coherence tomography showing more than a 100-micrometre thickness in an area of retina within the posterior pole
- 3 or more disc areas without atrophy or pigmentary degeneration within the posterior pole or
- a remaining visual field (VF) within 30? of fixation.

The clinical experts noted that the study criteria could be applied to clinical practice with the same rigour, and that they are suitable for all ophthalmologists to carry out and interpret. However, they noted that both functional and structural assessments might be used in practice. Functional assessment would review the patient's visual function and functional vision. If patients still have visual function, their eyes have the potential to respond to treatment. The committee concluded that clinical judgement incorporating both structural and functional assessment would be used in clinical practice to identify patients eligible for treatment.

4.8 The committee noted the small differences in baseline characteristics (such as age) and visual performance measures between groups in study 301/302. The ERG considered that this was inevitable because of the small sample size and was unlikely to have been a major source of bias. The clinical experts noted that the difference in baseline age was unlikely to have affected treatment effect because all eligible candidates would have had viable photoreceptor cells, so would have had a response to treatment. The company was unable to adjust outcome data for baseline visual performance because of the small sample size. The ERG noted that this added uncertainty to any estimate of true treatment effect. The clinical experts stated that they did not consider this a major concern because, while there were numerical differences, these were not clinically meaningful. The committee concluded that the baseline differences between treatment groups in study 301/302 were unlikely to have had a substantial effect on the study results.

4.9 The company's clinical studies recruited only patients with a diagnosis of LCA. The committee recalled that LCA is less common, presents earlier and has a more aggressive prognosis compared with other clinical diagnoses such as RP. It discussed whether the studies' populations would be representative of the population with RPE65-mediated IRD who would have voretigene neparvovec in clinical practice in the NHS, and whether the severity would affect disease prognosis and treatment effect. The clinical experts explained that the therapy treats the underlying cause of the condition so, biologically, the clinical diagnosis is unlikely to affect treatment effect. The clinical experts stated that the relevance of the study results to clinical practice was difficult to predict in people with the less severe types of diagnoses such as RP. This was because of the variabilities among individual patients, the small population size for a rare disease such as RPE65-meditated IRD and the limited evidence available. They noted that the over-representation of LCA in clinical studies could have been because of the earlier diagnosis of LCA compared with other diagnoses. The committee recognised the limitations of developing an evidence base for an ultra-rare disease and concluded that it had been presented with the best available evidence.

Study outcomes

4.10 Study 301/302 is ongoing: the primary endpoint was at 1 year but data up to and including a 4-year follow up are available for some (but not all) outcomes. Study 101/102 was a dose-escalating study and was not designed or powered to assess the clinical efficacy of voretigene neparvovec. The committee noted that the emphasis on clinical efficacy was given to data from study 301/302.

4.11 The committee understood that the primary outcome measure for study 301/302 was the multiluminance mobility test (MLMT) at 1 year. The MLMT is a novel outcome that measures the effect of functional vision in a quantitative and standardised way at specified light levels. The committee was aware that common outcomes used to evaluate vision, including VF, visual acuity (VA) and light sensitivity, were presented as secondary outcomes. It noted that only VF and VA were used in the economic model to define health states in people with the condition. It concluded that the MLMT was an acceptable instrument to inform efficacy in the short term, but that it would need to consider all measures presented in its decision making about clinical effectiveness.

Multiluminance mobility test

4.12 Results from study 301/302 showed that, at year 1, patients in the voretigene neparvovec arm had improved the MLMT scores compared with no improvement in the BSC arm. The difference was both statistically significant (mean difference 1.60; 95% confidence interval [CI] 0.72 to 2.40; p=0.0013) and clinically meaningful according to the criteria defined by the company (change score of 1 or more light level).

4.13 Improvements in the MLMT score seemed to remain steady until 3-year follow up. At year 3, the proportion who passed the MLMT at 1 lux (lowest light level) was 60% (12/20) in the original voretigene neparvovec arm (study 301) and 89% (8/9) in the delayed voretigene neparvovec arm (study 302). This showed a sustained improvement in functional vision for patients who had voretigene neparvovec.

4.14 The ERG highlighted that the MLMT change scores were capped at the lowest light setting, which may have underestimated the mean change. It noted that the change in the time to complete the test may have been a more compelling means of assessing functional vision.

Visual acuity

4.15 There was no statistically significant difference in changes from baseline to 1 year between voretigene neparvovec and BSC (0.16 LogMAR, 95% CI −0.41 to 0.08; p=0.17) for VA measured using the Holladay scale in study 301/302. However, a statistically significant change was seen using the Lange scale, in which there was a mean difference of −0.15 (95% CI −0.20 to 0.00; p=0.047), corresponding to a 7.5-letter improvement on the eye chart for people who had voretigene neparvovec. All changes were smaller than the company's definition of a clinically meaningful change (0.30 or more LogMAR). By year 3, little further change was seen in VA for either arm after treatment.

Visual field

4.16 VF improved for people who had voretigene neparvovec compared with people who had BSC. Improvements in VF were seen by 30 days in the voretigene neparvovec arm (assessed by Goldmann III4e at 1 year, mean difference 378.7, 95% CI 145.5 to 612.0; post-hoc p=0.0059). This difference was both statistically significant and clinically meaningful as defined by the company (20% change from baseline score). The improvement in VF seen by year 1 was sustained for 3 years.

Full-field light sensitivity

4.17 There were statistically significant improvements in full-field light sensitivity with voretigene neparvovec (mean difference −2.11 log units, 95% CI −3.91 to −1.04; p=0.0004) at 1 year. This was above the company's defined threshold of 10 dB or 1 log unit for clinical significance. The improvements were sustained for 3 years (2 years in the delayed treatment arm).

Clinical-effectiveness results

4.18 The committee was aware that the secondary endpoints of VF, VA and contrast sensitivity are often considered unreliable because of inter-test variability. It was also aware that they do not capture characteristic features of the condition such as night blindness. The clinical experts explained that the changes seen would be substantial in terms of improving mobility and functional vision. They noted that even a small change would be important for patients. The patient experts explained that new treatments offer considerable hope to patients and to their families. They noted that, even if there was no improvement, preventing vision deteriorating would be important for their quality of life. The committee concluded that the evidence showed that voretigene neparvovec had considerable benefit in terms of improving vision, and preventing vision deteriorating and disease progression.

Duration of treatment effect

4.19 The committee was aware that the assumptions about the long-term treatment effect were key drivers for the results from the economic model. It recognised that there were substantial benefits with voretigene neparvovec, as shown in study 301/302. However, it noted that voretigene neparvovec's treatment effect was expected to last for decades. It also noted that the results from study 301/302 were limited to 3 to 4 years of follow up and could not show that the condition would remain stable over a 40-year period. The committee was aware that the results of study 101/102 suggested sustained improvement in vision for up to 7.5 years. However, it noted that very few patients in the study had had the licensed dose of voretigene neparvovec (more had smaller doses), and that the eligibility criteria did not require them to have sufficient viable retinal cells in line with the marketing authorisation. The committee concluded that the clinical trial evidence showed considerable benefit in terms of improving vision. It noted that voretigene neparvovec would likely provide long-term benefits, although this was associated with substantial uncertainty.

4.20 The clinical experts explained that a long-term treatment effect with voretigene neparvovec is biologically plausible and is their expectation. They further explained that photoreceptor cells are terminally differentiated neurons that do not replicate or regenerate. Voretigene neparvovec is a gene-therapy treatment that introduces a healthy copy of the defective RPE65 gene into the retinal cells. For treatment effect, this means that, if the vector successfully delivers the RPE65 gene to a cell nucleus and RPE65 is subsequently expressed by photoreceptor cells, visual function will be restored. The clinical experts noted that there is no biological reason for the expression of the RPE65 to stop after successful insertion. The committee was aware that there is substantial uncertainty about the long-term treatment effect. However, it concluded that there is a biological rationale for the treatment effect to be maintained.

4.21 The committee recalled that a key outcome of treatment was to prevent vision deterioration and disease progression. It discussed the likelihood of deterioration in vision after treatment with voretigene neparvovec and noted that results of study 301/302 showed some fall in measures of VF and VA for patients who had voretigene neparvovec between years 3 and 4. The ERG and company highlighted that the evidence was based on a very limited number of patients and noted that improvements in VF between baseline and 4 years remained above the threshold for a clinically meaningful change. The clinical experts explained that it is possible for vision to continue to deteriorate if some photoreceptor cells outside the area of injection die. They also noted that vision deteriorates as people age, both in the general public and for those with the condition, and that this is not a reflection of treatment failure. The committee was also aware that there was a lack of direct evidence on voretigene neparvovec's effect on low-light vision. However, it acknowledged that even a small improvement in vision would be important for people with the condition.

Health-related quality of life

4.22 The company presented results from the visual function questionnaire (VFQ). The committee was aware that the questionnaire had been modified from the National Eye Institute (NEI) VFQ-25 to accommodate the poor vision associated with RPE65-mediated IRD and to include a paediatric population. However, it noted that the modification removed items related to quality of life. The results of the VFQ are considered confidential by the company so cannot be reported here. The committee was aware that patients may adapt to their surroundings over time so an improvement may be expected. However, it noted that the results were likely to be clinically meaningful. The committee was disappointed that no direct measure of health-related quality of life (HRQoL) had been used in the clinical trials and considered that the lack of patient-reported outcomes was a key limitation in the evidence.

Adverse events

4.23 The committee discussed the adverse events reported in the 2 clinical trials. It noted that, in study 301/302, 19 (66%) out of 29 patients had 62 treatment-emergent adverse events that were considered to be related to the administration procedure. Of these, 13 (65%) of the 21 patients who had the original intervention and 6 (67%) of the 9 patients who had the delayed intervention had treatment-emergent adverse events. Most of these events were mild or moderate. Across all patients who had treatment with voretigene neparvovec in both studies, there were 3 non-serious adverse events of retinal deposits in 3 (7%) of the 41 patients that were considered to be related to voretigene neparvovec. All 3 events were transient and resolved without complication. No deaths were reported, and no patients withdrew from any trials because of adverse events. The clinical experts explained that the number of adverse events is likely to be reduced as the procedure is done more frequently. The company confirmed that, as part of the implementation period, all healthcare professionals (including pharmacists) have mandatory training. This includes several simulated procedures to ensure that the procedure and storage of the technology is carried out to a required standard. The committee concluded that additional real-world data on adverse events would be informative. However, based on what it had heard from the experts, and the evidence from study 301/302 and study 101/102, it concluded that voretigene neparvovec has an acceptable safety profile.

Cost to the NHS and value for money

Economic model

4.24 The company presented an economic model comparing voretigene neparvovec with BSC. This was based on a Markov state transition model that included 5 alive health states and an absorbing death state. Health states were based on the worst of either VA or VF, and were intended to capture progressively severe levels of visual impairment. The MLMT was the primary endpoint in study 301/302 and was intended to give a practical sense of the visual impairment. However, it was not used in the economic model. The company explained that the MLMT is an objective measure of functional vision that incorporates light sensitivity, VA and VF. However, it further explained that no data were available linking this outcome to costs, utilities or mortality, and no data were available on this outcome beyond the duration of study 301/301. The committee discussed whether the model fully captured outcomes of importance for people living with RPE65-mediated IRD. It heard from the patient experts that all outcomes are approximations and it is not possible to objectively understand all aspects of the experience of someone with vision loss. It noted that results from visual function tests may have variations in the short term, which can cause confusion and fear in patients if they believe their vision is deteriorating. The clinical experts explained that the modelled health states captured important points in deteriorating vision. They noted that improvements in visual function do not always directly result in an improvement in functional vision, so using most clinical outcomes would be imperfect. However, they stated that stopping deterioration and stabilising vision would be captured by the model and was of vital importance to patients. The committee recalled 1 of the patient expert's explanation of the cycle of visual decline and adaptation. Both the clinical and patient experts emphasised that small changes in vision can make a big difference to the HRQoL of people living with the condition. The committee recognised that it would be challenging to accurately model RPE65-mediated IRD using the MLMT because of limited data, and that the company's rationale for using secondary endpoints was logical. It concluded that the model could be considered for decision making.

4.25 The committee considered the thresholds for VF and VA in the economic model. It was aware that the company used American Medical Association (AMA) guidelines rather than the Royal National Institute of Blind People (RNIB) guidelines. This was because the AMA guidelines provide clear numerical cut-offs, so avoiding ambiguity. The committee noted that all patients in health-state 2 (severe visual impairment) onwards would be classified as blind according to the RNIB. The clinical experts stated that the health states were consistent with clinically meaningful changes in visual function. The committee concluded that the definitions used to categorise vision in the model were appropriate for decision making.

Transition between health states

4.26 The committee considered the population included in the company's economic model. The distribution of patients within each of the modelled health states at baseline was based on the intention-to-treat population of study 301/302. The committee noted the ERG's concern about the small sample size and was aware that, in the ERG's preferred base case, the population was pooled with the population from the RPE65 NHx study. This was a retrospective chart review of 70 patients with RPE65-mediated IRD who would be eligible to have voretigene neparvovec. The ERG commented that RPE65 NHx comprised a less severe population and expected it to align more closely to the patient population seen in clinical practice. The committee concluded that using the larger sample size was more likely to be reflective of clinical practice in the UK. However, it noted that this made minimal difference to the cost-effectiveness estimates.

4.27 The company's model included 2 phases, an initial phase (from baseline to year 1) and a long-term phase (from year 1 onwards). In the initial phase, the company used data from study 301 to inform the transition probabilities between baseline and year 1 in each treatment arm. The committee was aware that the ERG's preferred base case used data from the original and delayed intervention arms (studies 301 and 302), which increased the sample size and informed more transitions. The committee discussed whether using the data from the delayed arm would introduce bias into the modelling. The clinical experts explained that the delay in administering treatment was unlikely to alter the treatment effect because all patients who had sufficient retinal cells would benefit from treatment. The committee concluded that increasing the sample size by using the crossover data that informed more transitions was preferred.

4.28 Transitions after year 1 (during the long-term phase of the model) were based on a parametric multistate model (MSM). In this, a parametric function determined the probability of transition to the next health state and the assumptions on duration of treatment effect of voretigene neparvovec (see section 4.19). For the voretigene neparvovec arm, the company assumed: a 40-year treatment effect (during which there was a 100% reduction in risk of transition suggested by the MSM, and patients remained in the same health state); a 10-year treatment waning period; and a 25% residual treatment effect beyond 50 years. For the BSC arm, the company fitted data from the RPE65 NHx natural history study to the MSM. The model was progressive only, meaning that patients could either stay in their current health state or progress to a worse health state during each cycle, but not move to an improved health state. The Weibull model was selected for the company's base case based on visual inspection and statistical fit. The ERG had concerns that the MSM was overly complex. It suggested that the MSM may have 'over fitted' data because there was a limited number of patients to inform the number of parameters in the model (that is, 68 patients for 11 parameters). The ERG also noted that the model predictions of time in each health state appeared to contradict the company's statements on long-term natural history outcomes in RPE65 NHx in terms of the predicted age for people progressing to 'near-total blindness'. The clinical experts explained that the phrase 'near-total blindness' could have included several of the company's health states. They noted that vision loss among RPE65-mediated IRD is heterogeneous, with some people maintaining functional vision for decades. Because of the rarity of the condition, there are limited long-term data on disease progression. However, the experts noted that patients generally experience deterioration in vision that could mirror the company's model. The committee concluded that the company's method of modelling long-term health-state transitions introduced uncertainty into the cost-effectiveness estimates. It further concluded that this would especially be the case for the extrapolation period, for which limited long-term data exist. However, the committee concluded that, overall, the company's method was suitable for decision making.

Duration of treatment effect in the model

4.29 The committee recognised that the duration of treatment effect was one of the most influential factors affecting the model results. It was aware that the company had assumed a 40-year treatment effect in its base-case analysis. This was meant to represent a reasonable midpoint between the absolute minimum (7.5 years of follow-up data with no loss of efficacy) and the potential maximum (a lifetime treatment effect of around 70 years; see section 4.28). The committee noted that the ERG conducted a threshold analysis varying the duration of treatment effect. This was to ascertain the relationship between the treatment effect duration for voretigene neparvovec and the incremental cost-effectiveness ratio (ICER). The committee agreed that the results were likely to have been substantially different had the minimum treatment duration been lower than 20 years. It concluded that, in the absence of any long-term evidence but given the biological plausibility for long-term treatment effect (see section 4.20), it considered that assuming a long-term treatment effect of 40 years' duration was uncertain but reasonable.

4.30 The committee then considered the other assumptions made by the company, including a 10-year treatment waning period from 100% to 25%, and a 25% residual treatment effect. The committee agreed that these assumptions were not based on any biological rationale and agreed that they should not be included in the modelling.

Mortality

4.31 Transitions to 'dead' were not captured by the MSM. Instead, mortality in the company's model was based on general population life tables for England and Wales from the Office for National Statistics. The company also applied mortality multipliers (hazard ratios) to health states in the model from a longitudinal study by Christ et al. (2014). The committee was aware that this study was based on a population aged 65 to 84 years (substantially different from the scope of this evaluation), and that it was done between 1993 and 2003. The ERG highlighted that no deaths occurred in any study of voretigene neparvovec included in the evidence base. The clinical experts explained that loss of functional vision could increase mortality in an older population but was not reflective of the population who would be treated with voretigene neparvovec. The committee agreed that the hazard ratios were highly uncertain. It concluded that excluding additional mortality risks better reflected the risk of death in the population included in the evaluation.

Utility values

4.32 The committee recalled that no data were collected about patient or carer HRQoL. It was also aware that no mapping function was available to elicit utility values based on the questionnaire administered within the study. Instead, the utility values for the company's base case were derived from a utility study commissioned by the company. This involved the development of vignettes for each health state using clinician and patient input. The company then asked 6 clinicians to complete 2 proxy generic HRQoL questionnaires (HUI3 and EQ-5D) for each of the health states in the economic model. The company preferred to use HUI3 values. This was because HUI3 contains a vision component while EQ-5D is known to have poor convergent validity in visual disorders. The committee discussed the results from the company's elicitation study and noted that it would generally prefer to include values directly collected in trials. It noted that the utility value using HUI3 for the lowest health state was −0.04, which indicated that the health state was worse than death. The ERG highlighted that the lowest utility values for vision loss in previous NICE submissions have been between 0.260 and 0.548. It also stated that the values given did not match patient experiences described by its clinical advisers. The patient experts agreed that losing their vision would not be considered worse than death and noted that patients are able to adapt to deteriorating vision. The committee noted that the company's methods had several serious methodological limitations, including:

- only a small number of clinicians took part
- specialist ophthalmologists may focus on issues related to vision loss rather than on the effect on all areas of a patient's life, which may have led to underestimating quality of life.

The committee concluded that the company's HUI3 values lacked face validity. It acknowledged the rationale for the use of HUI3 values considered that the EQ-5D values were more appropriate because of the potential focus on vision by the clinicians.

4.33 The committee were aware that the ERG's preferred utilities were from Rentz et al. (2014). This was a general public time-trade-off study (n=607) that looked at 8 health states with varying degrees of vision problems defined by 6 items of a disease-specific HRQoL questionnaire (NEI VFQ-25). The ERG compared the health-state descriptions given by the company with those used in Rentz et al. and assumed health-state 5 to be equivalent to the worst health state. The ERG acknowledged the results were imperfect but noted that the health states were described using functional vision problems, not just linked to VA or VF, a limitation of some of the other sources identified by the ERG. The committee discussed whether this time-trade-off study was more suitable. It noted that the health-state vignettes developed by the company were indirectly matched by the ERG to health states from Rentz et al. The committee agreed that asking clinicians to match health-state vignettes to health-state descriptions provided by the HUI3 and EQ-5D questionnaires, although not ideal, may have been more appropriate than the ERG's methodology. It also noted that the company's EQ-5D values were similar to the ERG's preferred utility values based on Rentz et al. The committee noted important weaknesses in both the company's and the ERG's utility values, which gave rise to additional uncertainty. However, the committee felt that, between them, the utility values provided sufficient information for decision making. It recalled comments from the patient and clinical experts that patients' quality of life was severely affected by loss of vision. The committee considered that neither source of data was sufficiently robust. However, it concluded that, in the absence of further evidence, it would consider that the utility values of health states in the model fell between the ERG's preferred base case (valuation based on the total population from Rentz et al.) and the EQ-5D values presented by the company.

4.34 The company included adverse event disutilities for cataract (−0.14 for 1.0 month), eye inflammation (−0.30 for 3.6 months) and increased intraocular pressure (−0.10 for 1.0 month). These were applied as a one-off quality-adjusted life year (QALY) loss at the time of voretigene neparvovec treatment. The committee recalled its conclusion that voretigene neparvovec appeared to have an acceptable safety profile. However, it noted that the disutilities of adverse events used by the company were likely to overestimate the effect in a population who already had significant visual impairment. The committee acknowledged that applying adverse event disutilities had a small effect on the cost-effectiveness results. It concluded the company's application of adverse event disutilities was suitable for decision making.

4.35 The company included disutility values for carers of both children and adults in health-states 2 to 5 in the economic model. The committee was satisfied with the principle of including these disutility values but discussed the ERG's concern that disutilities should not be applied to carers of adults. The ERG preferred to use an alternative source (Al-Janabi et al. 2016) for carer disutilities of children but to multiply this value for the mean number of parents in a household. The committee noted that there was little difference between the company's and ERG's values. It concluded that the ERG's scenario of excluding disutility values for carers of adults but including disutility for children in all heath states was more appropriate and would use it for decision making.

Resource use in the model

4.36 Costs were included in the model in 2 phases. One-off costs implemented during the first model cycle (year 1) included the administration of voretigene neparvovec (drug price, surgery, immunomodulatory regimen and monitoring costs), eligibility tests and adverse events. Longer-term resource use for managing severe visual impairment and blindness was calculated based on age, health state and medical resource use by patients who are blind according to RNIB guidelines. Long-term costs were halved for patients in the highest health state because it is not known what proportion are unlikely to be considered blind. All management costs were applied across both treatment arms over the entire modelled time horizon. The ERG corrected some costs in the model and noted that many of the estimates were based on assumptions. It amended the costs by health state. It noted that, in the absence of evidence, adjustments should not be included within the model. It also removed the costs associated with depression. The ERG noted that the depression costs in the model were based on vision loss in later life rather than lifelong vision loss. The patient expert disagreed that depression costs should not have been included in the model, pointing out the considerable effect vision loss can have on a patient's mental health. The committee agreed that, in the absence of evidence, the ERG's preference for removing health-state adjustments was preferred by the committee. However, it concluded that the additional depression costs should have been included in the model.

Discount rate

4.37 The committee was aware that NICE's guide to the methods of technology appraisal (2013) and NICE's interim process and methods of the highly specialised technologies programme (2017) specify that the reference case discount rate is 3.5%. However, it also states that a non-reference-case rate of 1.5% may be used when treatment restores people to full or near-full health when they would otherwise die or have severely impaired lives, if it is highly likely that there will be long-term benefits, and if the treatment does not commit the NHS to significant irrecoverable costs. The committee noted that the company used a 3.5% discount rate in its base case but that it provided a scenario analysis for a 1.5% discount rate. The committee considered that it was likely that the alternative 1.5% discount rate was intended to cover situations similar to this – that is, when costs are incurred upfront, but benefits are accrued over a longer period. The committee acknowledged that the technology could be transformative for people who, without treatment, would lose their ability to see. However, it recalled the clinical experts' explanation that people who have successful treatment may not regain full vision if photoreceptor cells have already been damaged. The experts also explained that people may have further visual deterioration if the treatment is not applied to 100% of photoreceptor cells (that is, people given voretigene neparvovec may still have lifelong visual impairments). The committee was highly uncertain about whether people who had voretigene neparvovec would be considered to have 'normal or near-normal health'. It also recognised that there were large uncertainties about whether the long-term benefits of treatment would be achieved because of the limited evidence. The committee concluded that it would consider both discount rates during its decision making. However, it preferred the use of 3.5% because it was uncertain about whether voretigene neparvovec fully met the criteria for using a discount rate of 1.5%.

Cost-effectiveness analysis results

4.38 The committee considered the results of the economic analysis, taking into account the company's base case, the ERG's preferred base case and exploratory scenario analyses. The committee noted that, in the company's base case, voretigene neparvovec was associated with an ICER of £86,635 per QALY gained. All ICERs presented here are associated with the company's list price. This is because the results of the economic analysis incorporating the company's commercial offer have been deemed commercial in confidence. The committee recalled that the ERG made several changes to the company's base case. These were:

- ERG-calculated pooled baseline characteristics from study 301 and the RPE65 NHx study (see section 4.26)
- ERG-calculated transition probabilities using data from patients in both the original and delayed intervention arm (see section 4.27)
- assuming a fixed duration of treatment effect with no period of waning or residual effect (see sections 4.29 and 4.30)
- assuming no additional mortality risks (see section 4.31)
- assuming utility values based on the total population from Rentz et al. (2014; see section 4.33)
- amending the company's one-time costs and that all patients have equal resource use over time regardless of health state and no depression costs (see section 4.36)
- applying carer disutility to children in all health states for the mean number of carers per household (see section 4.35).

The committee noted that applying all of the ERG's changes increased the ICERs, at a discount rate of 3.5% for voretigene neparvovec, to £155,750 per QALY gained. The committee recalled that its preferred scenario was based on the following amendments of the ERG's base case:

- considering both the ERG's utility values derived from Rentz et al. (2014) and the EQ-5D utility values from the company's elicitation study (see section 4.32)
- applying depression costs to long-term resource use (see section 4.36)

Applying QALY weighting

4.39 The committee understood that NICE's interim process and methods of the highly specialised technologies programme (2017) specifies that a most plausible ICER of below £100,000 per QALY gained for a highly specialised technology is normally considered an effective use of NHS resources. For a most plausible ICER above £100,000 per QALY gained, judgements about the acceptability of the highly specialised technology as an effective use of NHS resources must take account of the magnitude of the incremental therapeutic improvement, as revealed through the number of additional QALYs gained and by applying a 'QALY weight'. It understood that a weight between 1 and 3 can be applied when the QALY gain is between 10 and 30 QALYs. The committee discussed the QALY gains associated with voretigene neparvovec. It noted that, in the scenarios considered most plausible, the QALY gain was between 12.1 and 17.7. The committee noted that the difference in QALY gains was associated with the use of alternative utility values. It recalled the considerable uncertainty around these values and the duration of treatment effect. The committee therefore concluded that voretigene neparvovec met the criteria for a QALY weight of 1.2. The committee was satisfied that voretigene neparvovec would offer significant QALY gains, and therefore applied this weighting in its consideration of its value for money.

Impact of the technology beyond direct health benefits and on the delivery of the specialised service

4.40 The committee discussed the impact of voretigene neparvovec beyond its direct health benefits. It understood from patient and clinical experts that all aspects of the lives of patients are affected by the condition. It was aware of the very large emotional effect of RPE65-mediated IRD on families and carers. It noted that there is a substantial financial impact on families, in that parents have to give up work to provide care and because of the costs of home adaptation. The patient experts explained that treatment with voretigene neparvovec could completely change the course of a person's life with RPE65-mediated IRD. This was because, with sustained vision, children would be able to attend mainstream school, retain their independence, take part in social activities and achieve their full potential.

4.41 The committee also noted comments that treatment with voretigene neparvovec would reduce the expenditure incurred by non-NHS government departments that provide support for families affected by vision loss. The committee recognised that voretigene neparvovec has an effect beyond health benefits, but noted that the impact of that on the magnitude of the ICER would be small. The committee considered these benefits in its decision making.

Other factors

4.42 The committee noted the potential equality issue raised by clinical experts and the company, and recognised that specific mutations were more common in some ethnic groups in the UK. It also considered whether a population with a protected characteristic of disability under the Equality Act 2010 had been disadvantaged by the processes and methods of the evaluation, and whether any further adjustment should have been made. The committee concluded that its recommendations applied equally regardless of ethnicity, so a difference in disease prevalence in different ethnic groups did not in itself represent an equality issue, and no additional amendments would be made. It also considered that the methodology employed did not disadvantage people with RPE65-mediated IRD.

4.43 The committee noted that the population for which voretigene neparvovec is indicated includes children and young people. It was aware that RPE65-mediated IRD is a devastating condition that can begin in infancy, and that people with the condition, and their families and carers, are affected in all aspects of life. The committee recalled that there were considerable uncaptured benefits related to sustaining vision in children, and that these had been considered qualitatively in its decision making.

4.44 The committee discussed the innovative nature of voretigene neparvovec, noting that it is the first licensed gene therapy for vision loss. The company considers voretigene neparvovec to represent a step change in the management of RPE65-mediated IRD. It also noted that this is the first gene therapy to be assessed for a rare disease in a randomised controlled trial. It therefore noted that the methodology and results from this trial will provide support for gene-based approaches for other rare genetic diseases and advance the broader field of gene therapy. The committee concluded that there was a high unmet need in people with RPE65-mediated IRD, and that voretigene neparvovec is a step change in the treatment of this condition.

Conclusion

4.45 The committee acknowledged that RPE65-mediated IRD is a rare and debilitating condition that severely affects the lives of people with the condition, as well as their families and carers. The committee was aware that there is a high unmet need in this population because there are no current specific treatments available for this condition. It recognised that the results of clinical trials were uncertain because of the small sample size and limited follow up. However, it considered that the evidence showed that voretigene neparvovec improved visual performance and was likely to prevent disease progression, which would be a considerable benefit to patients. The committee considered that the company's assumptions in the model, especially around duration of treatment effect and the utility values, were uncertain. It noted that voretigene neparvovec met the criteria for a QALY weighting to be applied. It also acknowledged the uncertainties and took into account other benefits of voretigene neparvovec that were not captured in the analysis (see sections 4.40 and 4.41). The committee concluded, overall, that voretigene neparvovec can be considered an appropriate use of NHS resources for highly specialised technologies. It therefore recommended voretigene neparvovec as an option for treating IRDs caused by RPE65 gene mutations.

5 Implementation

5.1 Section 8(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 3 months of its date of publication.

5.2 The Welsh Ministers have issued directions to the NHS in Wales on implementing NICE highly specialised technologies guidance. When a NICE highly specialised technologies guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final evaluation document.

5.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraph above. This means that, if a patient has inherited retinal dystrophies caused by RPE65 gene mutations and the doctor responsible for their care thinks that voretigene neparvovec is the right treatment, it should be available for use, in line with NICE's recommendations.

6 Evaluation committee members and NICE project team

Evaluation committee members

The highly specialised technologies evaluation committee is a standing advisory committee of NICE.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered that there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each highly specialised technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

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