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ORIGINAL RESEARCH

# An Economic Evaluation of Voretigene Neparvovec for the Treatment of Biallelic *RPE65*-Mediated Inherited Retinal Dystrophies in the UK

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## ABSTRACT

***Introduction***: Voretigene neparvovec (VN) is a gene therapy and the first approved pharmacological treatment for biallelic *RPE65*-mediated inherited retinal dystrophies (IRD), a rare condition that starts in early life and causes vision to progressively deteriorate towards complete blindness. In a phase III trial, treatment with VN significantly improved functional vision and visual function, and in October 2019 the National Institute for Health and Care Excellence (NICE) Highly Specialised Technologies (HST) process recommended VN for patients in England and Wales. We assessed the cost-effectiveness of VN compared with best supportive care (BSC) in individuals with biallelic *RPE65*-mediated IRD in the UK.

***Methods***: A Markov model was developed to estimate the incremental cost per quality-adjusted life-year (QALY) gained for VN compared with BSC, from the perspective of the UK National Health Service and Personal Social Services. Phase III trial data were used to inform transition probabilities up to year 1, after which the treatment effect was assumed to be maintained for 40 years, followed by a decline in vision. A bespoke elicitation exercise involving clinical experts, patients and carers was conducted to estimate utility values for each model health state.

***Results***: At list price, VN is associated with incremental costs of £612,404 and incremental QALYs of 6.4, resulting in an incremental cost-effectiveness ratio (ICER) of £95,072 per QALY gained. Voretigene neparvovec is associated with a significant undiscounted QALY gain (20.5) and is therefore eligible for additional QALY weighting under the NICE HST process; an ICER of up to £205,000 per QALY gained could be considered cost-effective under this framework.

***Conclusion***: The results of the model show VN to be a cost-effective use of healthcare resources in the UK at list price. The availability of a commercial discount in the UK (as considered in the NICE appraisal) means that in reality the ICER will be even lower.

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***Plain Language Summary***: Plain language summary available for this article.

**Keywords:** Blindness; Cost-effectiveness; Economic evaluation; Inherited retinal dystrophy; One-time gene therapy; Ophthalmology; *RPE65*; Visual impairment

**Key Summary Points**

**Why carry out this study?**

Voretigene neparvovec (VN) is a gene therapy treatment for biallelic *RPE65*-mediated inherited retinal dystrophies, an extremely rare and previously untreatable condition that leads to complete blindness in almost all patients. The condition has a profound impact on patients' quality of life, and visual impairment is associated with economic burden at the individual and societal levels.

The aim of the study was to determine if VN can be considered a cost-effective use of National Health Service (NHS) resources in the UK, by modelling the costs incurred and benefits gained from treatment, compared with the current standard of care.

**What was learned from the study?**

The cost-effectiveness model determined the incremental cost-effectiveness ratio (a measure of cost per unit benefit gained) to be £95,072 per quality-adjusted life-year gained.

This is lower than typical thresholds below which technologies for rare diseases are generally considered to be cost-effective in the UK, and so VN is expected to be a cost-effective use of NHS resources.

## PLAIN LANGUAGE SUMMARY

Biallelic *RPE65*-mediated inherited retinal dystrophies (IRD) are rare genetic disorders affecting the retina (the light-sensitive membrane at the back of the eye). Patients often experience the first symptoms of not being able to see in the dark from birth, with vision worsening in childhood and eventually leading towards complete blindness. Voretigene neparvovec (VN) is a gene therapy medicine and the first drug treatment for biallelic *RPE65*-mediated IRD. It works by delivering a healthy copy of the faulty *RPE65* gene into the retina. In several clinical trials, patients experienced significant improvements in their vision following treatment with VN, and side effects were generally mild.

In some countries, once a new treatment is shown to be safe and effective, it is automatically available to patients. However, in the UK, consideration is also given to the value for money the treatment represents. With limited healthcare budgets, it is important that the benefits come at a reasonable cost. Value for money can be calculated by performing cost-effectiveness analyses; these are used by the National Institute for Health and Care Excellence (NICE) in the UK to decide whether new treatments should be made available on the National Health Service (NHS). In this article we present the results of a cost-effectiveness analysis of VN for the treatment of biallelic *RPE65*-mediated IRD.

An economic model was built to calculate the net clinical benefit of VN (using results from the clinical trial) and the net costs compared with current clinical practice. The ratio of the two provides a measure of the cost of the treatment per unit of health gained. Model results show that for VN this ratio falls below the threshold specified by NICE, demonstrating that VN is likely to be a cost-effective use of NHS resources.

## INTRODUCTION

### Disease Background

Inherited retinal dystrophies (IRD) are a heterogenous group of rare genetic diseases characterised by progressive vision loss, leading to complete blindness in almost all patients

[1, 2]. They can be caused by mutations in > 260 genes, including the *RPE65* gene. Biallelic *RPE65*-mediated IRD is very rare, with an estimated prevalence of 180 people in England [3].

Visual impairment in individuals with biallelic *RPE65*-mediated IRD can present at a range of ages, from infancy to adolescence. The first symptom is typically nyctalopia (night blindness), which causes difficulty seeing in dim light, such as at dusk or at night. This is followed by progressive visual field (VF) loss, and eventually peripheral blind spots merge to produce tunnel vision. Loss of central vision in the advanced stages of the disease leads to complete blindness [4–6].

The effects of the inexorable progression towards complete blindness are life-changing and lifelong [2]. Children affected by visual impairment are more likely to experience social and economic disadvantage [7], and the impacts of reduced mobility and independence become an increasing problem as young adults progress into further and higher education. Severe visual impairment is associated with an increased risk of depression, anxiety and sleep disorders [8–13], and studies have also reported an increased risk of depression among caregivers of those with visual impairment [14, 15]. It is estimated that the full lifetime cost of blindness in individuals with biallelic *RPE65*-mediated IRD in the UK is between £1.6 and £1.8 million. Approximately 70% of lifetime costs are associated with lost productivity, with 20% of costs incurred by the healthcare system [16].

## Voretigene Neparvovec

Voretigene neparvovec (VN) is an adeno-associated virus vector-based gene augmentation therapy approved by both the US Food and Drug Administration and the European Medicines Agency for the treatment of patients with confirmed biallelic *RPE65*-mediated IRD and sufficient viable retinal cells [17, 18]. It is administered once per eye, with the aim of restoring the visual cycle and arresting or reversing the decline in visual function.

Prior to the approval of VN, no pharmacological treatments were available for patients with biallelic *RPE65*-mediated IRD, with support limited to measures allowing the management of the disease such as low-vision aids. Retinal prostheses are available in some countries (for adults aged ≥ 25 with severe visual impairment), but not the UK (where they are recommended for research purposes only). However, these do not alter the disease process and the inevitable decline in retinal function.

## Clinical Trials

In a phase III trial, patients experienced significant improvements in visual function (the performance of the eyes) and functional vision (the ability to perform activities of daily living that are dependent on vision) following treatment with VN [2]. Following treatment, significant improvements were observed in the ability of patients to navigate independently in low-to-moderate light conditions, in light sensitivity and in VF, and a numerical improvement was observed in mean visual acuity (VA). These improvements manifested rapidly (within the first 30 days after subretinal delivery) and were maintained through to the most recent published follow-up time points (year 4 [19]).

In earlier phase I trials, improvements in vision following treatment were maintained through to the latest published follow-up time points (7.5 and 4 years), providing supporting evidence on the durability of the treatment effect [20, 21].

## Cost-Effectiveness Analysis

To make decisions about the best use of finite budgets, healthcare decision makers often rely on cost-effectiveness analyses. The primary outcome of cost-effectiveness analyses is the incremental cost-effectiveness ratio (ICER), calculated as the incremental costs associated with a new treatment divided by the incremental benefits. The latter can be expressed using quality-adjusted life years (QALYs; a product of quality and quantity of life) [22].

Some decision-making bodies have specific cost-effectiveness thresholds, below which treatments are usually considered cost-effective.

Voretigene neparvovec meets the criteria for the National Institute for Health and Care Excellence's (NICE's) Highly Specialised Technologies (HST) process, used for evaluating therapies for very rare conditions, which has a baseline cost-effectiveness threshold of £100,000 per QALY gained. However, for treatments that offer a substantial increase to quality/quantity of life (> 10 undiscounted QALYs), additional QALY weighting applies so that the threshold can effectively be between £100,000 and £300,000 depending on the extent of the benefit [23]. Voretigene neparvovec has been recommended by NICE for commissioning in England and Wales [3].

### Objective

The objective of this analysis is to present an estimate of the cost-effectiveness of VN at list price compared with best supportive care (BSC) for the treatment of individuals with biallelic *RPE65*-mediated IRD in the UK.

## METHODS

### Decision Problem

A cost-effectiveness analysis was conducted comparing VN with BSC in individuals with biallelic *RPE65*-mediated IRD who have sufficient viable retinal cells. The lack of treatment options prior to the development of VN means that BSC is limited to measures supporting the management of the disease, such as low-vision aids and genetic counselling.

The primary outcome of interest was the ICER expressed as the cost per QALY gained. Costs were considered from the perspective of the National Health Service (NHS) and Personal Social Services in England and Wales, with costs falling outside of the healthcare system included in scenario analyses; the perspective on outcomes included direct health effects for both patients and carers. A lifetime time horizon was considered, and costs and outcomes were discounted at an annual rate of 3.5% in line with current NICE guidance [24]. A scenario is considered assuming discount rates of 1.5%, in line with NICE guidance on treatments with substantial long-term treatment effects [24].

This article does not contain any new studies with human or animal subjects performed by any of the authors. The economic model uses data from a published phase III trial [2].

### Model Structure

A Markov state transition model was constructed, with five alive health states determined based on the worst of VA and VF (i.e., whichever of VA or VF would assign the patient to a more severe health state) and death (Fig. 1); health state cut points were derived using American Medical Association guidelines (see supplementary materials for further details). The average VA and VF across both eyes were assumed, with a scenario considering health states defined based on VA and VF in the best-seeing eye.

Health states could not be defined based on the multi-luminance mobility test (MLMT) (the primary outcome of Study 301) because no data are available linking this outcome to costs, utilities or mortality, and no data are available on the long-term change in this outcome. However, the MLMT is a functional endpoint that captures clinical changes in each of VA, VF and full-field light sensitivity threshold (FST; a measure of light sensitivity), and so health states defined by a combination of VA and VF are expected to capture some changes in MLMT associated with VN; the inability to capture changes in light sensitivity is expected to result in conservative estimates of cost-effectiveness for VN.

A cycle length of 1 year was used, and half-cycle correction was implemented.

The model consists of an initial phase and a long-term phase. In the initial phase, data from Study 301 were used to inform the transition probabilities between baseline and year 1 in each of the BSC and VN arms; in this phase, it was assumed that individuals may move to either better or worse health states. In the long-term phase, the year 1 distribution of VN patients was assumed to be maintained for

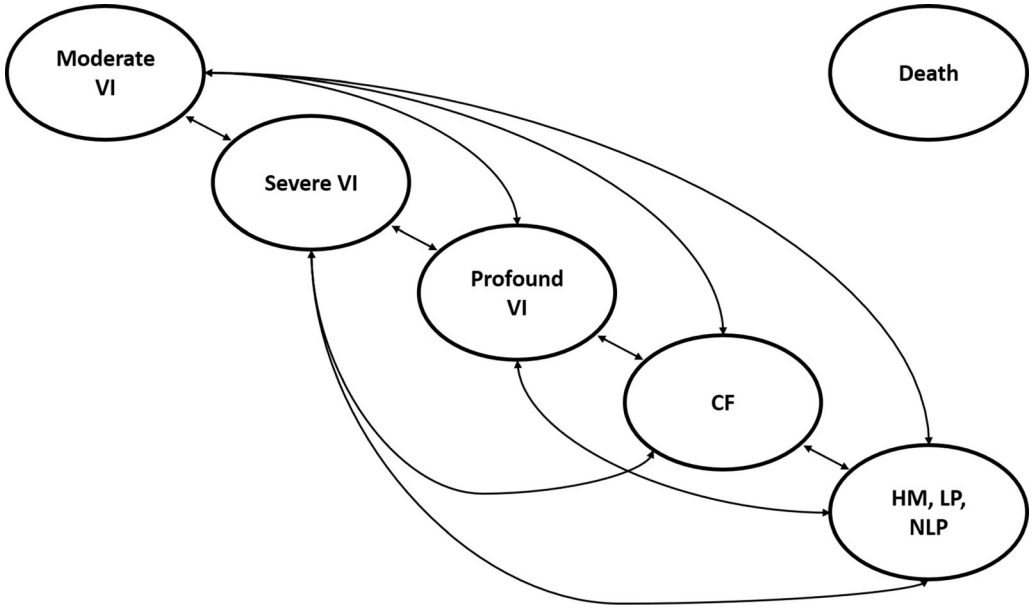


**Fig. 1** Model schematic. *CF* counting fingers, *HM* hand motion, *NLP* no light perception, *VI* visual impairment

40 years, after which natural history data in individuals with biallelic *RPE65*-mediated IRD were used to model the long-term decline in visual function in this population. A 40-year duration of treatment effect was assumed to represent a reasonable midpoint between the absolute minimum (7.5 years of follow-up with no loss of efficacy [20]) and potential maximum based on preclinical data and clinical expert opinion (lifetime treatment effect of approximately 70 years). Patients receiving BSC were assumed to progress as per the natural history data immediately following year 1. In the long-term phase, it was assumed that individuals may only progress to a worse state. Patients were exposed to the risk of mortality from all health states.

## Clinical Data

The baseline health state distribution and transition probability matrices for the first year of the model were derived from Study 301 (Tables 1, 2, 3; see supplementary materials for further details). Scenarios are considered in which the baseline health state distribution is taken from the natural history study, and data from delayed intervention patients in the extension phase of Study 301 are included when calculating first-year transition probability matrices. The baseline age in the model is 15 years, reflecting the average age of patients enrolled in Study 301. Following the treatment of existing patients who are eligible for treatment with VN, treatment of incident patients may be expected to occur at a younger age; however, subgroup analyses based on age were not considered feasible given the low number of patients enrolled in Study 301.

Patient-level data from a retrospective chart review study designed to describe the

**Table 1** Baseline health state distribution

| Health state | Proportion at baseline (%) |
|---|---|
| HS1: moderate VI | 23 |
| HS2: severe VI | 32 |
| HS3: profound VI | 23 |
| HS4: CF | 19 |
| HS5: HM, LP, NLP | 3 |

*CF* counting fingers, *HM* hand motion, *HS* health state, *LP* light perception, *NLP* no light perception, *VI* visual impairment

**Table 2** Transition probability matrix for initial phase—BSC arm

| | Health state at 1 year | | | | |
|---|---|---|---|---|---|
| | **HS1 (%)** | **HS2 (%)** | **HS3 (%)** | **HS4 (%)** | **HS5 (%)** |
| Health state at baseline | | | | | |
| HS1 | 100 | 0 | 0 | 0 | 0 |
| HS2 | 25 | 50 | 0 | 25 | 0 |
| HS3 | 0 | 0 | 100 | 0 | 0 |
| HS4 | 0 | 0 | 100 | 0 | 0 |
| HS5 | 0 | 0 | 0 | 100 | 0 |

Key: HS1, moderate visual impairment; HS2, severe visual impairment; HS3, profound visual impairment; HS4, counting fingers; HS5, hand motion, light perception to no light perception

**Table 3** Transition probability matrix for initial phase—VN arm

| | Health state at 1 year | | | | |
|---|---|---|---|---|---|
| | **HS1 (%)** | **HS2 (%)** | **HS3 (%)** | **HS4 (%)** | **HS5 (%)** |
| Health state at baseline | | | | | |
| HS1 | 100 | 0 | 0 | 0 | 0 |
| HS2 | 83 | 17 | 0 | 0 | 0 |
| HS3 | 50 | 50 | 0 | 0 | 0 |
| HS4 | 50 | 0 | 25 | 25 | 0 |
| HS5 | 0 | 50 | 0 | 25 | 25 |

Key: HS1, moderate visual impairment; HS2, severe visual impairment; HS3, profound visual impairment; HS4, counting fingers; HS5, hand motion, light perception to no light perception

natural history of biallelic *RPE65*-mediated IRD (*RPE65* NHx) informed the long-term natural history of the disease under standard of care [25]. All patients with confirmed *RPE65* mutations, from seven international centres, were enrolled in this study and their charts were collected, following redaction of protected health information. Longitudinal ocular history and visual function testing data were abstracted from the collected charts and analysed.

A multistate survival model using data from the natural history study was developed using methods detailed by Crowther and Lambert [26] to inform the transitions between the five 'alive' health states. Six parametric distributions were tested: exponential, generalised gamma, Gompertz, log-logistic, log-normal and Weibull. These models were compared using the Akaike and Bayesian information criterion (AIC and BIC, respectively) and analysis of the Cox Snell residuals. The Weibull model was selected on the basis of AIC and BIC; further details are available in the supplementary materials.

Modelled adverse events included all those considered to be related to either the treatment or the administration procedure in the VN arm of Study 301, occurring in greater than one patient, and expected to be associated with an impact on quality of life and/or cost [2]. Adverse events meeting these criteria were cataract, eye inflammation and increased intraocular pressure (IOP).

Background mortality was modelled using general population life tables for England and Wales [27]. This approach is expected to be conservative, given that visual limitations have been shown to be associated with an increased risk of death [28].

## Utility Data

A systematic literature review was conducted to identify utility values in individuals with biallelic *RPE65*-mediated IRD; however, no utility data were identified in this population. Given the ultra-rare nature of the condition, it was not considered feasible to recruit a representative sample of patients such that utility data could be collected prospectively. A bespoke utility study was therefore conducted to estimate utility values associated with each of the model health states [29], wherein bespoke vignettes were developed and assessed by clinicians in terms of their impact on standard generic health-related quality of life instruments (EQ-5D-5L and HUI3). This approach has been taken previously in rare conditions [30, 31].

Health state descriptions (vignettes) were developed through a process that combined

information gathered from five patient/caregiver testimonials, expert advisory board feedback from 12 general specialists from leading ophthalmology centres in the US and interviews with six rehabilitation experts and three caregivers. The resulting five vignettes described different levels of visual function in biallelic *RPE65*-mediated IRD, corresponding to each of the health states in the model.

Six retina specialists, all with experience in IRD, completed each of the EQ-5D-5L and the HUI3 for the five vignettes. The EQ-5D-5L was scored using the van Hout et al. algorithm [32], and the HUI3 was scored in line with developer instructions. The resulting utility values are presented in Table 4; full details of the methods and results of the bespoke utility study have been published previously [29].

The EQ-5D-5L scores ranged between 0.71 and 0.15; the HUI3 scores for each health state were found to be lower than the corresponding EQ-5D-5L score, with a range from 0.52 to − 0.04. Despite the relatively small sample size of six clinicians, the standard deviation around the utility estimates are relatively low, indicating a high level of agreement between the clinical experts.

Utility values derived from the EQ-5D-5L were selected for the model base case on the basis that the EQ-5D is the preferred measure of health-related quality of life for UK health technology assessment bodies [24, 33]. However, the HUI3 contains a vision component and so may be expected to better capture changes in quality of life corresponding to changes in vision. A scenario was therefore considered using utility values based on the HUI3.

The utility decrements and durations of event for cataracts and eye inflammation were sourced from NICE guidelines on age-related macular degeneration [34]. In the absence of other data, the utility decrement for increased IOP was conservatively assumed to be the same as that for uncontrolled/severe glaucoma [35]. The duration of increased IOP was assumed to be 1 month, given that all increased IOP events observed in Study 301 were fully resolved within 1 month [2].

The disutility associated with caring for a child with biallelic *RPE65*-mediated IRD was taken from Al-Janabi et al. and applied to the mean number of carers per child as reported by the Office for National Statistics [36, 37]. In the absence of other data, it is assumed that the disutility for carers of adults with biallelic *RPE65*-mediated IRD is half that of carers of children with biallelic *RPE65*-mediated IRD.

### Resource Use and Cost Data

Initial costs associated with VN were those for acquisition (list price), administration, monitoring, eligibility testing and adverse events (see supplementary materials for further details).

Ongoing healthcare costs associated with disease management were assumed to vary by age group and health state (see supplementary materials for further details); scenarios were considered in which broader societal costs were included.

All costs were valued in 2019 UK pounds; where necessary, costs were inflated using healthcare-specific inflation indices [38].

### Sensitivity Analysis

Parameter uncertainty was explored using univariate sensitivity analysis and probabilistic

**Table 4** Health state utility values

| HRQoL instrument | Utility value, mean (SD) | | | | |
|---|---|---|---|---|---|
| | HS1 | HS2 | HS3 | HS4 | HS5 |
| EQ-5D-5L | 0.71 (0.09) | 0.62 (0.04) | 0.52 (0.07) | 0.35 (0.06) | 0.15 (0.11) |
| HUI3 | 0.52 (0.16) | 0.36 (0.11) | 0.22 (0.10) | 0.14 (0.09) | − 0.04 (0.07) |

Key: HS1, moderate visual impairment; HS2, severe visual impairment; HS3, profound visual impairment; HS4, counting fingers; HS5, hand motion, light perception to no light perception
*HRQoL* health-related quality of life, *SD* standard deviation

sensitivity analysis (PSA). In univariate sensitivity analysis, all model parameters were systematically and independently varied over a plausible range determined by either the 95% confidence interval or ± 15% where no estimates of precision were available. The ICER was recorded at the upper and lower values to produce a tornado diagram. In PSA, all model parameters were assigned distributions and varied jointly; 10,000 Monte Carlo simulations were recorded, and the cost-effectiveness plane (CEP) and cost-effectiveness acceptability curve (CEAC) were generated.

Structural uncertainty was testing using scenario analyses, in which key assumptions were varied and ICERs were reported (Table 5).

**Table 5** Scenario analyses

| Area of uncertainty | Base case | Scenarios |
|---|---|---|
| Perspective | Healthcare system | UK government |
| | | Societal |
| Discount rate | 3.5% for costs and outcomes | 1.5% for costs and outcomes |
| Health state definition | Average eye | Best-seeing eye |
| Source of baseline characteristics | Phase III trial | Natural history data |
| Transition probability matrices in initial phase | Crossover data excluded | Crossover data included |
| Duration of treatment effect | 40 years | 20 years |
| | | 30 years |
| | | Lifetime |
| Multistate survival model distribution | Weibull | Exponential |
| | | Gompertz |
| | | Log-logistic |
| | | Log-normal |
| Utility values | EQ-5D-5L | HUI3 |

# RESULTS

## Base Case Results

VN is associated with incremental costs of £612,404 and incremental QALYs of 6.4, resulting in an ICER of £95,072 per QALY gained (Table 6). Although the acquisition cost of VN leads to a net incremental cost in the VN arm, modest cost offsets are achieved by reduced expenditure on healthcare resource use.

The cost-effectiveness threshold for the NICE HST programme is a most plausible ICER of £100,000 per QALY gained. If > 10 additional QALYs are gained, a QALY weighting between 1 and 3 may be applied, using equal increments. Voretigene neparvovec is associated with 20.5 additional undiscounted QALYs compared with BSC; the additional QALY weighting applied to treatments offering > 10 additional QALYs means that an ICER of up to £205,000 per QALY gained could be considered cost-effective under this framework.

**Table 6** Base case results

| | BSC | VN | Incremental |
|---|---|---|---|
| VN acquisition[a], administration and monitoring costs | £0 | £617,873 | £617,873 |
| Eligibility testing costs | £0 | £142 | £142 |
| Adverse event costs | £0 | £165 | £165 |
| Healthcare resource use costs | £57,050 | £51,274 | − £5776 |
| Total costs | £57,050 | £669,454 | £612,404 |
| Total QALYs | 9.8 | 16.3 | 6.4 |
| ICER | – | – | £95,072 |

*BSC* best supportive care, *CF* counting fingers, *HM* hand motion, *ICER* incremental cost-effectiveness ratio, *QALY* quality-adjusted life-year, *VI* visual impairment, *VN* voretigene neparvovec

[a] List price—note that in the UK a confidential discount to the list price is available

### Univariate Sensitivity Analysis

Results for the ten most influential parameters identified by univariate sensitivity analysis are presented in Fig. 2. Six of the ten most influential parameters are those describing the long-term multistate survival model (i.e., the ancillary and constant terms for the Weibull model and the coefficients for four of the ten health state transitions); however, this result should be treated with caution given that highly correlated parameters (i.e., the regression coefficients) are being varied as if they are independent from one another. Other influential parameters include the health state utility values.

### Probabilistic Sensitivity Analysis

The results of 10,000 PSA simulations were plotted on the CEP (Fig. 3) and a CEAC was generated (Fig. 4). The average incremental costs over the simulated results were £611,203 and the average incremental QALYs were 6.4, giving a probabilistic ICER of £95,813; this is highly congruent with deterministic changes in costs and QALYs of £612,404 and 6.4, respectively. The proportion of simulations considered cost-effective when accounting for the additional QALY weighting for treatments with significant QALY gains (i.e., > 10) was 71%.

### Scenario Analysis

Scenario analyses are presented in Fig. 5. Scenarios associated with increases to the ICER of > 10% include assuming a duration of treatment effect of 20 or 30 years and assuming the log-normal or exponential distribution for the multistate survival model. Scenarios in which a societal perspective is considered, discount rates of 1.5% are applied, or a lifetime treatment effect is assumed were associated with substantial decreases in the ICER.

## DISCUSSION

At list price, VN is associated with an ICER of £95,072 per QALY gained versus BSC. The model predicts a significant QALY gain of 20.5 QALYs (undiscounted), so an ICER of up to £205,000 per QALY gained could be considered cost-effective under the NICE HST framework because of additional QALY weighting; VN is therefore considered cost-effective at list price.

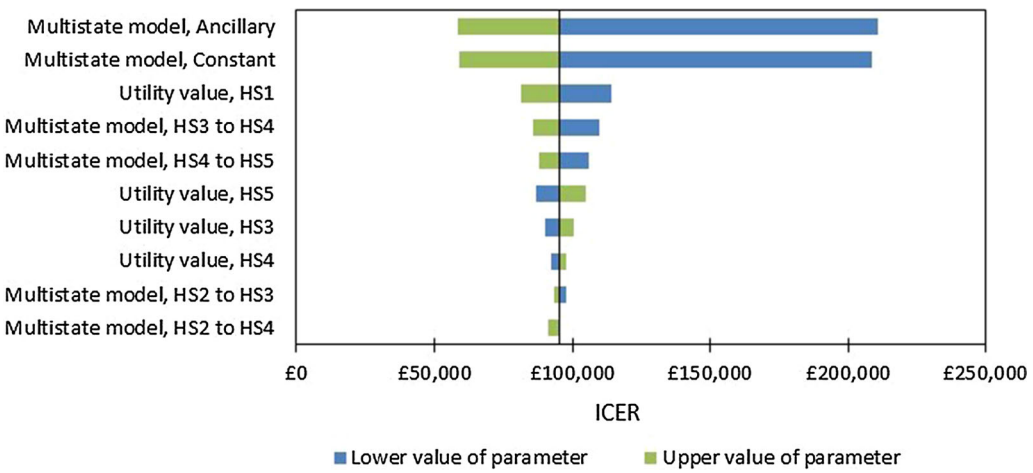


**Fig. 2** Results of univariate sensitivity analysis (tornado diagram). Key: HS1, moderate visual impairment; HS2, severe visual impairment; HS3, profound visual impairment; HS4, counting fingers; HS5, hand motion, light perception to no light perception. In a tornado diagram, the *Y*-axis is centred on the base case ICER; for each parameter, the ICERs at the upper and lower values of the parameter are recorded and presented in green and blue, respectively, for the ten most influential parameters. *ICER* incremental cost-effectiveness ratio

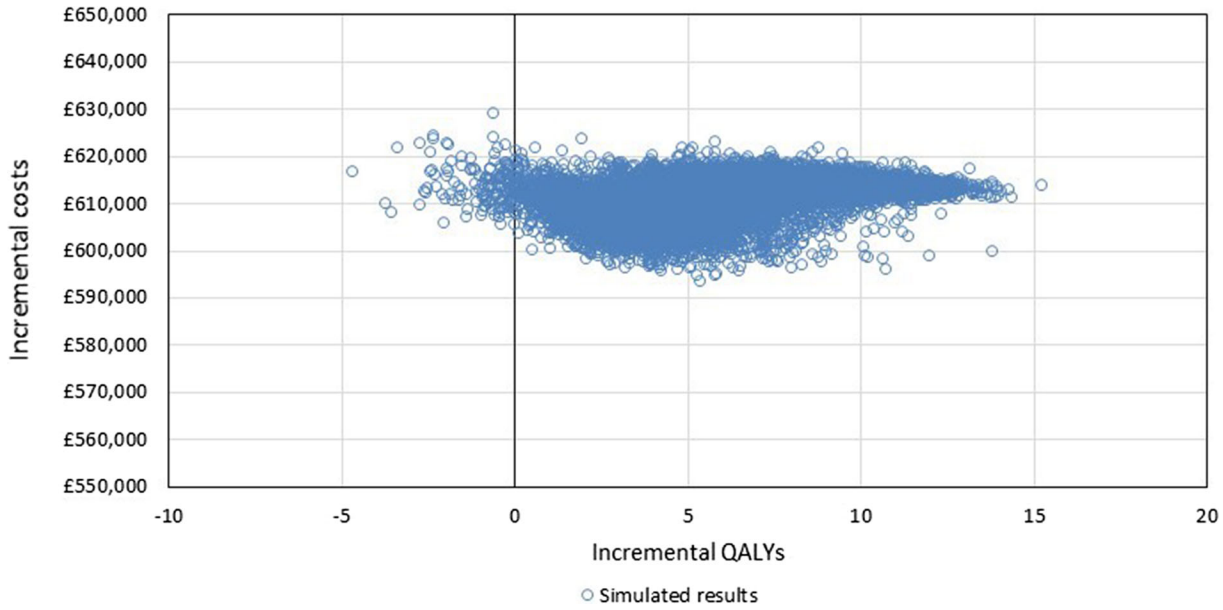


**Fig. 3** Cost-effectiveness plane. *QALY* quality-adjusted life-year

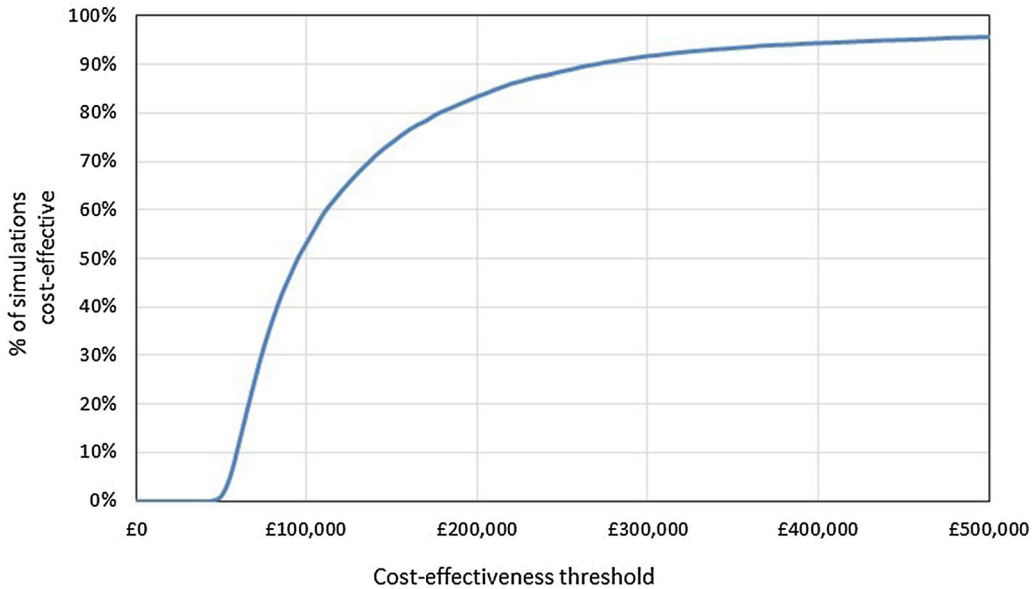


**Fig. 4** Cost-effectiveness acceptability curve. A PSA simulation is considered to be cost-effective at a specific cost-effectiveness threshold if the ICER for the simulation falls below that threshold. For example, in 52% of simulations, VN was associated with an ICER of < £100,000 per QALY. *ICER* incremental cost-effectiveness ratio, *PSA* probabilistic sensitivity analysis, *QALY* quality-adjusted life year, *VN* voretigene neparvovec

A confidential discount to the list price (i.e., a patient access scheme) for VN has been agreed with the Department of Health, so in practice the true ICER will be lower.

The results of the analysis were most sensitive to parameters defining the long-term multistate survival model, the health state utility values and the duration of treatment effect.

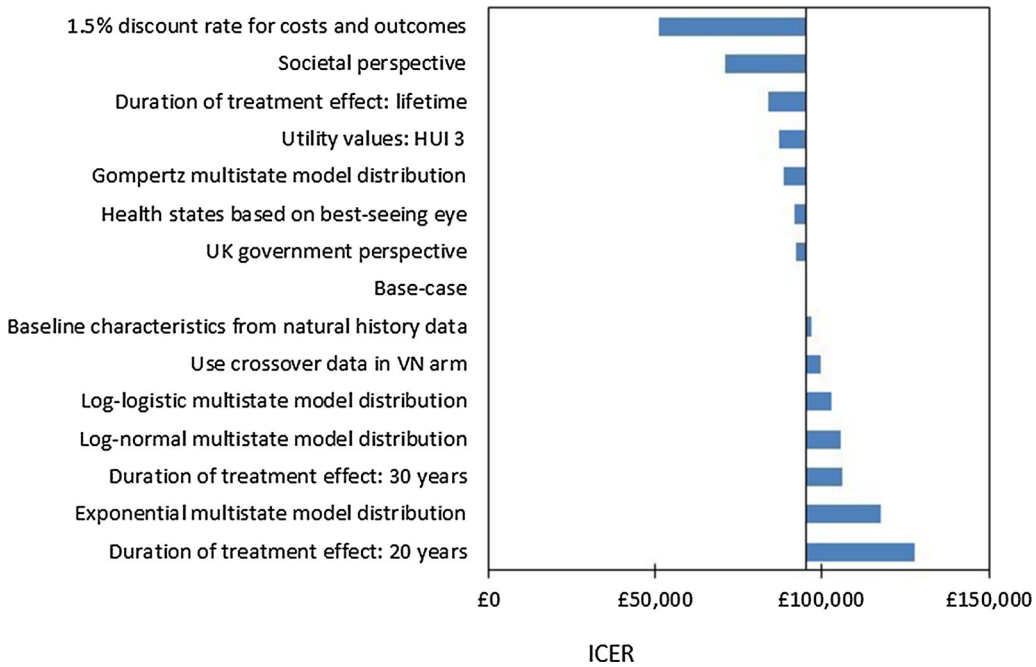


**Fig. 5** Results of scenario analyses. *ICER* incremental cost-effectiveness ratio, *VN* voretigene neparvovec

Seventy-one per cent of simulations would be considered cost-effective assuming the effective NICE HST weighted threshold given the additional QALY weighting.

A key strength of the analysis was the use of a bespoke study in which utility values in patients with biallelic *RPE65*-mediated IRD were estimated. The study made use of input from six retinal experts with experience in IRD, and vignettes were developed with input from an expert advisory board, patients and carers, and interviews with clinicians [29]; in the context of an ultra-orphan condition, this level of input from patients, carers and healthcare professionals is substantial. Previous analyses have relied on health-related quality of life data from older populations with different vision conditions [39].

Although improvements in VA and VF associated with VN were captured in the model, it was not possible to capture improvements in either MLMT (the primary trial endpoint) or light sensitivity, as no long-term data are available for these endpoints. Given that VN is associated with benefits beyond those captured by VA and VF, the modelled benefit of VN is expected to be underestimated, resulting in a conservative estimate of cost-effectiveness.

A range of scenarios were considered, and the results were found to be relatively robust to alternative assumptions. All scenario analysis results are in the range of £51,241–£127,800 per QALY.

An inevitable limitation of rare disease trials is small sample sizes. The study upon which this model was built included 31 patients, of which 29 were treated. In the model, health state transitions in both the initial and long-term phase were based on low patient numbers ($n$ = 29 and $n$ = 68, respectively), increasing the level of uncertainty in model outcomes.

In the absence of long-term data, there was also uncertainty around the long-term treatment effect associated with VN. To date, there is no evidence of loss of treatment effect over time—improvements in light sensitivity (measured by FST, which is correlated with MLMT [40]) in Study 101/102 and improvements in MLMT and FST in Study 301 were maintained through to the latest published time points [19, 20].

Furthermore, it is anticipated that the *RPE65* gene will remain active during the lifetime of

retinal pigment epithelium cells, which, in a normal state, do not undergo mitosis on a regular basis like gastrointestinal or skin epithelial cells; they form early in development and subsequently remain dormant, undergoing minimal proliferation throughout life. Additionally, vector delivery, surgical techniques and dosing in the VN trials were optimised based on lessons learned from other gene therapy trials, and VN was developed with an improved understanding of vector design and manufacturing [41].

Cost-effectiveness analyses have also been performed by the Institute for Clinical and Economic Review (Zimmermann et al. [39]) and by Johnson et al. [42], both conducted from a US perspective. The key differences among the three analyses are the duration of treatment effect, the health state utility values and the approach to modelling long-term changes in VA and VF. The analysis conducted by Zimmermann assumed a 10-year treatment effect with a 10-year waning period, utility values derived from patients with diabetic retinopathy and changes in VA and VF over time based on simple functions fit to digitised natural history data. Compared with the Zimmermann analysis, our analysis and the one by Johnson et al. benefit from access to patient-level data and a bespoke utility study specific to patients with IRD. Additionally, our assumptions may be considered to be relatively conservative compared with the study by Johnson et al., particularly regarding the duration of treatment effect (40 years in our analysis versus lifetime in Johnson et al.) and the exclusion of societal costs in our base case. Scenarios presented by Johnson et al. in which societal costs are excluded and the treatment effect of VN is reduced by either 10% or 50% after 3 years are relatively congruent with our analysis ($87,209 and $136,452 per QALY, respectively, compared with £95,072 per QALY).

The estimates presented in this analysis are consistent with a 2019 study, in which the lifetime QALY gain associated with gene therapy in individuals with retinal dystrophies was found to be 14.3 (compared with 20.5 QALYs in our study) [41].

## CONCLUSIONS

Voretigene neparvovec is a cost-effective use of NHS resources in the UK at list price, and in practice cost-effectiveness is further improved with the application of the confidential discount agreed with the Department of Health. This study demonstrates the possibility for innovative and novel gene therapies to be cost-effective despite high upfront costs because of the potential for substantial lifelong benefits.

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***Compliance with Ethics Guidelines.*** This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors. The economic model uses data from a previously published phase III trial [2].

***Data Availability.*** All shareable data generated or analysed during this study are included in this published article/as supplementary information files.



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