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Economic Evaluation

Cost Utility of Voretigene Neparvovec for Biallelic *RPE65*-Mediated Inherited Retinal Disease

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ABSTRACT

Objective: The gene therapy voretigene neparvovec (VN) is the first Food and Drug Administration–approved treatment for vision loss owing to the ultra-rare *RPE65*-mediated inherited retinal disorders. We modeled the cost-utility of VN compared with standard of care (SoC). **Study Design:** A 2-state Markov model, alive and dead, with a lifetime horizon. **Methods:** Visual acuity (VA) and visual field (VF) were tracked to model quality-adjusted life-years (QALYs). VN led to an improvement in VA and VF that we assumed was maintained for 10 years followed by a 10-year waning period. The cost of VN was $850 000, and other direct medical costs for depression and trauma were included for a US healthcare system perspective. A modified societal perspective also included direct nonmedical costs and indirect costs. **Results:** VN provided an additional 1.3 QALYs over the remaining lifetime of an individual. The average total lifetime direct medical cost for individuals treated with VN was $1 039 000 compared with $213 400 for SoC, leading to an incremental cost-effectiveness ratio (ICER) of $643 800/QALY from the US healthcare system perspective. Direct nonmedical costs totalled $1 070 900 for VN and $1 203 300 for SoC, and indirect costs totalled $405 400 for VN and $482 900 for SoC, leading to an ICER of $480 100/QALY from the modified societal perspective. **Conclusions:** At the current price, VN was unlikely to reach traditional cost-effectiveness standards compared with SoC. VN has important implications for both development and pricing of future gene therapies; therefore clinical and economic analyses must be carefully considered.

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Introduction

RPE65-mediated inherited retinal disease (IRD) comprises a group of ultra-rare conditions, affecting a total of between 1000 and 3000 people in the United States, though exact prevalence is unknown.[1] Mutations that affect both copies of the gene *RPE65* (biallelic mutations) cause Leber congenital amaurosis type 2, early onset severe retinal dystrophy, severe early childhood-onset retinal dystrophy, retinitis pigmentosa type 20, and other IRD phenotypes.[2-5] The disease affects the rod photoceptors first, decreasing peripheral and night vision, and progresses to the cone photoceptors that affect visual acuity and color vision.[1,6] The physiological mechanisms and natural history are not well understood because of the rare and heterogeneous nature of the disease.

Voretigene neparvovec (VN) was approved in 2017 as the first treatment for vision loss associated with *RPE65*-mediated IRD. VN was the first FDA-approved gene therapy that targets a disease caused by mutations in a specific gene. A viral vector delivers a functioning copy of *RPE65* to cells in the retinal pigment epithelium. This approval has the potential to set a precedent for breakthrough gene therapy treatments for many serious and rare conditions. The FDA has announced work to establish a policy framework for future gene therapies, with plans to issue disease-specific guidance on gene therapy development in 2018.[7]

Four clinical trials of VN have been conducted, one of which was a randomized controlled trial that provided the best evidence on VN to date.[8-20] In the randomized controlled trial, participants were randomized 2:1 to VN or control. Participants had a mean age of 15 years, confirmed biallelic *RPE65* mutation, visual acuity equal to or worse than 20/60, or visual field less than 20 degrees. The trial used a novel primary endpoint, change in the bilateral multi-luminance mobility test (MLMT), and full-field light sensitivity and visual acuity (VA) as secondary endpoints. The MLMT measures the time and ability to navigate an obstacle course at varying

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levels of light, with an improvement of one light level representing a clinically meaningful improvement. The study found that 1 year after treatment with VN, patients had an improvement of 1.8 light levels in the MLMT compared with 0.2 in the control group, indicating that they were able to see better in lower light.[1,12] Two-year data showed a 1.9 light-level difference in MLMT between the intervention and control group.[11] The intervention group also saw a significant improvement in full-field light sensitivity compared with the control group, and an improvement, though not statistically significant, in average VA.[12]

These data show a clear improvement in visual ability related to night vision after VN treatment; however, visual acuity was not improved. Furthermore, there was substantial heterogeneity observed in the treatment response, the period of observation was limited to 1 year (3 years with follow-up data), and the use of a novel primary endpoint coupled with a lack of quality-of-life data leaves uncertainty around comprehensive outcomes such as quality-adjusted life-years (QALYs).[12] These clinical uncertainties, in conjunction with a price of $850 000 per patient to treat both eyes, indicate that the value of these treatments to our healthcare system and society warrant evaluation. Nevertheless, the relationship between the clinical benefit and costs of VN have yet to be studied. Our objective was to estimate the clinical and economic impact of VN compared with the standard of care (SoC) in the United States from the health system and societal perspectives.

Methods

Model Structure

We used a disease simulation model that uses a 2-state Markov framework and statistical models of time-varying utilities and transitions probabilities. The Markov aspect of the model consists of an annual transition probability of moving from an "alive" to "dead" state. The time-varying utilities are a function of the natural history of progressive visual impairment and treatment effects. The time-dependent transition probabilities are a function of age- and sex-specific mortality. The model simulated an "expected" person with biallelic *RPE*-mediated IRD, with average values of all characteristics and modifiers of the patient population, to compare VN to SoC. SoC treatment was assumed to be regular physician visits and supportive care. Among those alive in the model, we used equations for patient-level individual modeling of age, VA, visual field (VF), categorical visual impairment or blindness, and quality-of-life. This model structure was selected because of the limited availability of natural history data for biallelic *RPE65*-mediated IRD, which precluded use of a more complex model structure.

We used 2 perspectives: a US healthcare system perspective with direct medical costs only, and a modified societal perspective including direct and indirect medical costs and nonmedical costs. The model used 1-year cycles over a lifetime time horizon and a 3% discount rate for costs and health outcomes. The model was developed in Microsoft Excel. Any data inputs or sources that presented visual acuity in logMAR scale were converted to the decimal scale, using: $VA_{decimal} = 10^{\wedge}(-VA_{logMAR})$.

Target Population

The target population was individuals in the United States with biallelic *RPE65*-mediated IRD. The modeled population reflected the VN clinical trial population, with a mean age of 15 years, mean baseline VA of 0.096 (best eye) decimals, mean baseline VF of 363.8 (average for both eyes) sum total degrees, and 43% male.[12]

Table 1 – Visual acuity (decimal) model and visual field (sum total degrees from Goldmann III4e) inputs.

Clinical category	Value	Source
Average eye VA function		
Functional form	$10^{\wedge}$(function)	Assumed
Intercept	−0.55	Digitized data[21]
Age coefficient	0.0436	Digitized data[21]
Best eye VA function		
Functional form	$10^{\wedge}$(function)	Assumed
Intercept	−0.63	Calculated using the function above and[12]
Age coefficient	0.0436	Assumed same as average eye
Average eye VF function		
Functional form	linear	Assumed
Baseline at age 15	364	[12]
Age coefficient	−24.3	Digitized data[21]
Change in with VN		
VA (decimals)	0.039	[11]
VF (degrees)	282	[12]
Duration of treatment effect	10 years	Assumed
Duration of waning period	10 years	Assumed

VA, visual acuity; VF, visual field; VN, voretigene neparvovec.

Clinical Inputs

We created a function for best eye VA by age based on the natural history of disease for average VA of both eyes, assuming an exponential functional form before converting to the decimal scale, and then used the mean best eye VA from the VN trial, 0.095 decimals at mean age 15, to recalculate the intercept (Table 1).[21] For average VF, we created a linear function using digitized natural history data (Table 1).[21] Individuals were considered visually impaired when they reached VA <0.63 decimals or VF <1200 degrees (as measured by Goldmann III4e), and blind when they reached VA <0.015 decimals or VF <48 degrees (as measured by Goldmann III4e).[2,22] VF for normal vision is 1440 degrees, VA for normal vision is 1.6 decimals, and the minimum for both VF and VA is 0.

The effect of VN compared with SoC was modeled as an increase of 0.039 decimals in best eye VA and an increase of 282 degrees in VF based on results of the voretigene phase III clinical trial (Table 1).[11] Because VN trial data were limited to 2 years,[11] with anecdotal evidence of treatment effect duration up to 7 years (based on personal communication with clinical trial physicians), we assumed that the effect would be maintained for 10 years. After the treatment effect duration ended, individuals entered a waning period of 10 years in which the effect slowly decreased until the rate of decline in vision was the same as with SoC.

To calculate QALYs, we modeled utility values based on VA and VF, using whichever provided a lower utility each year. We created a linear function for utility by best eye VA using published values for utilities over a range of visual acuity from 0.01 (counting fingers/hand motion) to 0.8 (no visual impairment) decimals. A linear function was selected as it provided a better fit to existing data than a piecewise or exponential function. We then applied the same utility values over a range of VF measures from 48 (counting fingers/hand motion) to 1440 (no visual impairment) degrees, and created a linear function. The utility functions were

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utility = 0.5695+0.4865*VA (R^2 0.96) and utility = 0.5410+0.0003*VF (R^2 0.89). We modeled mortality based on sex-specific US life tables.[10] We assumed that both biallelic *RPE65*-mediated IRD and VN did not affect mortality.

Adverse Events

We included the following adverse events in the model that had 5% or greater incidence based on rates observed in the clinical trial: incidence of eye irritation, incidence of ongoing eye pruritus, and incidence of macular hole or degeneration.[12] Eye irritation had a one-time cost of $80 (CPT 99214), eye pruritis had a cost of $80 per year (CPT 99214), and macular hole or degeneration had a one-time cost of $4447 (DRG 124) and a disutility of 0.0533 for 6 months.[23]

Cost Inputs

Direct medical costs included costs for VN treatment and surgery, ophthalmic-related costs (which included physicians or other providers, fundus photography, fluorescein angiography, optical coherence tomography, indocyanine green angiography, laser photocoagulation, intravitreal drug injections, photodynamic therapy), ophthalmic-related depression, and ophthalmic-related trauma (Table 2). Indirect costs included additional education costs owing to visual ability and productivity loss. Direct nonmedical costs included caregiver, transportation, and nursing home costs. Costs were based on top-down sources which provide annual costs, not unit costs, and are presented in Table 2. Direct costs were stratified by VA because we expect these costs to vary with severity of disease. Productivity loss was stratified by age, because we expect these costs to be strongly related to age over severity. Nursing home care and education costs were only applied to relevant age groups based on severity levels. All costs were adjusted to 2017 US dollars.

Model Analysis

We calculated direct medical, direct nonmedical, indirect, and total healthcare costs and QALYs for VN and SoC. We then calculated the incremental cost-effectiveness ratio (ICER), or marginal cost per additional QALY, of VN treatment compared with SoC.

We conducted a range of scenario analyses to assess sensitivity to baseline visual function. For patients with mild (VA = 0.48 decimals, VF = 1080 degrees), moderate (VA = 0.19 decimals, VF = 600 degrees), severe (VA = 0.08 decimals, VF = 216 degrees), or profound visual impairment (VA = 0.03 decimals, VF = 120 degrees); near blindness (VA = 0.01 decimals, VF = 48 degrees); or no light perception (VA = 0 decimals, VF = 0 degrees) at baseline, we calculated the ICER and the necessary discount on VN to reach different cost-effectiveness thresholds from a US healthcare system perspective. To calculate discounts necessary to reach a defined willingness-to-pay-threshold, we incrementally increased the discount on voretigene price, hence decreasing the total cost while keeping health outcomes constant. We also conducted a 2-scenario analysis around duration of treatment effect, a 3-year effect duration with 3-year waning period, and a lifetime effect duration.

We conducted a one-way sensitivity analysis to identify key drivers of the model using standard errors or plausible ranges for each input. We also completed a probabilistic sensitivity analysis by jointly varying all model parameters over 5000 simulations and then calculating 95% credible range estimates for each model outcome based on the results. We used normal distributions for mean age; sex; baseline VA and VF; slope and intercept for VA, VF, and utility functions; change in VA and VF with voretigene; duration of treatment effect and waning period; VA and VF

Table 2 – Cost inputs, annual

Cost category	Value	Source
Direct medical costs		
Voretigene neparvovec	$850 000	Manufacturer
Surgery	$4 876	DRG 117, Intraocular procedures without CC/MCC
Ophthalmic related*		31
VA 0 to <0.05	$4 778	
VA 0.05 to <0.2	$5 204	
VA 0.2 to <0.4	$1 308	
VA 0.4 to <0.8	$1 994	
VA ≥0.8	$0	
Ophthalmic-related depression*		31
VA 0 to <0.05	$235	
VA 0.05 to <0.2	$259	
VA 0.2 to <0.4	$62	
VA 0.4 to <0.8	$257	
VA ≥0.8	$0	
Ophthalmic-related trauma*		31
VA 0 to <0.05	$2 870	
VA 0.05 to <0.2	$315	
VA 0.2 to <0.4	$393†	
VA 0.4 to <0.8	$1 690†	
VA ≥0.8	$0†	
Indirect costs‡		
Education§		32
Visually impaired, age 0-17	$11 984	
Blind, age 0-17	$11 984	
Productivity loss		32
Visually impaired		
Age 18-39	$9 930	
Age 40-64	$21 074	
Age 65+	$7 316	
Blind		
Age 18-39	$18 068	
Age 40-64	$27 221	
Age 65+	$7 315	
Direct nonmedical costs†		
Caregivers*		31
VA 0 to <0.05	$32 652	
VA 0.05 to <0.2	$25 468	
VA 0.2 to <0.4	$11 972	
VA 0.4 to <0.8	$4 860	
VA ≥0.8	$0	
Transportation*		31
VA 0 to <0.05	$10 563	
VA 0.05 to <0.2	$8 287	
VA 0.2 to <0.4	$6 118	
VA 0.4 to <0.8	$2 764†	
VA ≥0.8	$0	
Nursing home care		32
Visually impaired, age 65+	$3 829	
Blind, age 65+	$7 988	

VA, visual acuity; DRG, diagnosis related group; CC/MCC, complication or comorbidity/major complication or comorbidity.
* Subtracted costs of the control cohort from each subcohort cost.
† These values were corrected from those printed in the Brown et al.[31] article based on communication with the author, including a change to $0 for trauma costs for the control cohort.
‡ Used in modified societal perspective only.
§ Additional compared with normal-sighted child.

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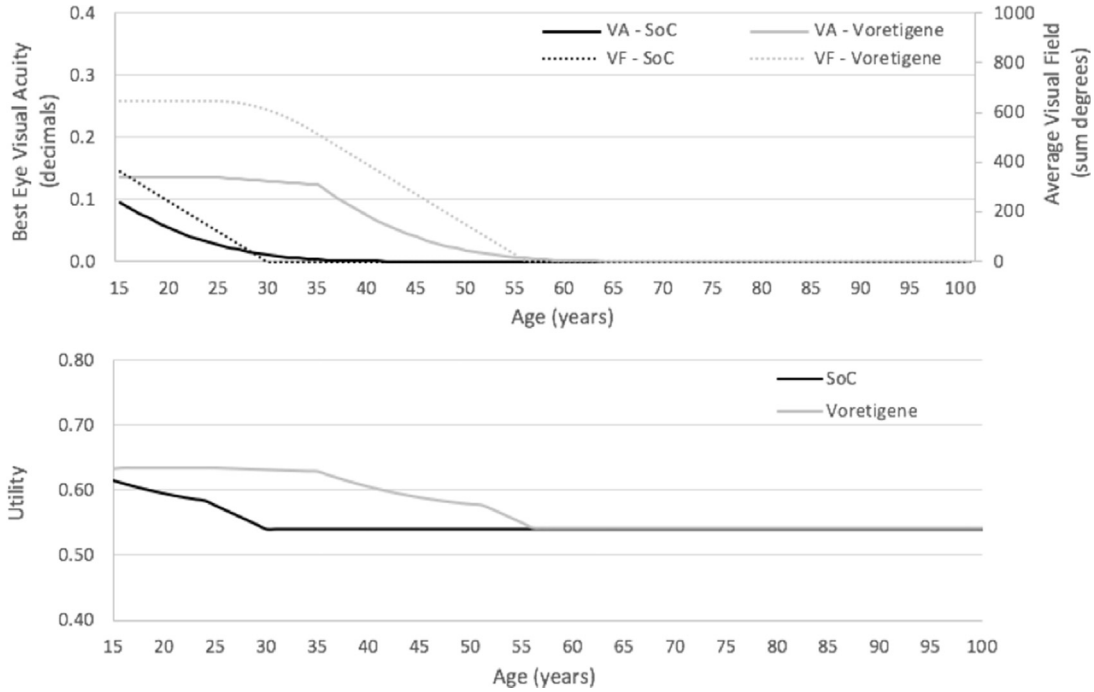

Fig. 1 – Best eye visual acuity, average visual field (*top*), and overall utility (*bottom*) over time for individuals treated with voretigene neparvovec and standard of care.

threshold for visual impairment and blindness; each annual cost category; adverse event costs and adverse event rates; and beta distributions for adverse event disutilities.

Results

We modeled best eye VA, average VF, and the resulting utility function over time for individuals treated with VN and SoC (Fig. 1). The VA function had $R^2 = 0.95$ with F-statistic $P < 0.001$, and the VF function had $R^2 > 0.99$ with F-statistic $P < 0.001$. VN provided an additional 1.3 QALYs over the remaining lifetime of an individual (Table 3). The average total lifetime direct medical costs for individuals treated with VN were $1 039 019 from a US healthcare system perspective, including VN costs of $854 876, $7171 in ophthalmic-related depression costs and $31 957 of ophthalmic-related trauma costs. The average total lifetime direct medical costs for individuals treated with SoC were $213 399, including $6834 in ophthalmic-related depression costs and $67 731 in ophthalmic-related trauma costs. This led to an ICER of $643 813/QALY from the US healthcare system perspective (Table 3). Direct nonmedical costs were $1 070 866 for VN and $1 203 308 for SoC. This included caregiver costs ($791 951 for VN and $892 528 for SoC), transportation costs ($257 132 for VN and $288 997 for SoC), and nursing home costs ($21 783 for both groups). Indirect costs were $405 435 for VN and $482 899 for SoC. This included productivity loss costs ($359 579 for VN and $437 043 for SoC) and additional education costs compared with a nonvisually impaired child ($45 856 for both groups). Combining direct medical costs, direct nonmedical costs, and indirect costs led to an ICER of $480 130/QALY from the modified societal perspective (Table 3).

Results were sensitive to the utility function, baseline VA, and cost of VN (Fig. 2). At a willingness-to-pay threshold of $250 000, VN had a 1.9% probability of being cost-effective from the US healthcare system perspective and a 17.8% probability of being cost-effective from the modified societal perspective (Fig. 3).

The ICER decreased with increasing visual ability at baseline. For people with mild, moderate, sever, or profound visual impairment, near blindness, or no light perception, the ICER was $185 797, $320 594, $386 164, $471 568, $534 263, and $638 800/QALY, respectively, with a 0%, 20%, 33%, 46%, 52%, and 59% discount required to reach the cost-effectiveness threshold of $250 000/QALY from a US healthcare system perspective. From a US healthcare system perspective, the ICER with a 3-year duration of benefit and 3-year waning period was $1 230 656/QALY and for a lifetime duration of benefit was $384 624/QALY.

Summary

We found that the ICER for VN compared with supportive care was $643 800/QALY from a US healthcare system perspective and $480 100/QALY from a modified societal perspective. This is well above the commonly used threshold of $150 000/QALY for cost-effectiveness and above a higher threshold of $250 000/QALY that may be used for ultra-rare conditions.[7] We did find VN to be more cost-effective for those with better visual ability at the time of treatment. Because this is a progressive condition, treating younger patients would correlate with improved visual ability at time of treatment.

Discussion

Despite the potential benefits of VN and future gene therapies, at $850 000, the cost of the treatment is substantial and may raise concerns about value and affordability. The healthcare system is generally willing to pay more to treat rare conditions.[24,25] This will likely hold true for VN, especially given its status as the first approved gene therapy in the United States targeting a disease caused by mutations in a specific gene in an ultra-rare population and in the presence of other contextual factors related to the disease itself (eg, the lack of any standard treatment for a condition affecting younger individuals). Although a treatment for a

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Table 3 – QALYs and costs over the remaining lifetime of an individual treated with VN and SoC.

Treatment	SoC	VN	Incremental
QALYs	16.0	17.3	1.3
Direct medical costs			
Voretigene costs	$0	$854 876	$854 876
AE costs	$0	$222	$222
Direct ophthalmic medical costs	$138 833	$144 793	$5 960
Direct medical costs, depression	$6 834	$7 171	$336
Direct medical costs, trauma	$67 731	$31 957	–$35 774
Total	$213 399	$1 039,019	$825 621
ICER, U.S. Health Care System Perspective	—	—	$643 813/QALY*
Direct nonmedical costs			
Caregiver	$892 528	$791 951	–$100 577
Transport	$288 997	$257 132	–$31 865
Nursing home	$21 783	$21 783	$0
Total	$1 203,308	$1 070,866	–$132 442
Indirect costs			
Productivity	$437 043	$359 579	–$77 464
Education	$45 856	$45 856	$0
Total	$482 899	$405 435	–$77 464
Total costs, modified societal perspective	$1 899,605	$2 515,320	$615 715
ICER, modified societal perspective	—	—	$480 130/QALY*

AE, adverse effects; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life-years; SoC, standard of care; VN, voretigene neparvovec.
* Any inconsistencies in ICER values are due to rounding.

single rare disease may not produce a substantial budget impact, there are many rare diseases. As additional expensive treatments such as gene therapies are approved, the aggregate cost may not be sustainable within existing healthcare budgets.[26] In addition, gene therapies are somewhat unique in that the treatment is a one-time procedure with the entire cost up front, but the benefits last over a longer time horizon. Therefore, even high-value treatments may cause short-term affordability issues. VN has the potential to set a positive precedent for the introduction of gene therapies to improve health and also to create new cost pressures that may require innovative approaches to attain sustainable access. Given the unique aspects of treatments for rare diseases, and especially gene therapies, there is an opportunity for VN to develop new pricing or reimbursement structures to offset costs to the healthcare system, such as value-based pricing or refunds based on efficacy (ie, outcomes guarantees).

The duration of treatment benefit is a significant source of uncertainty for VN. Published data are only available out to 2 years,[11] with anecdotal reports out to 7 years (personal communication with clinical trial team). Without long-term data, it cannot be known how long benefit will be maintained, and there are theoretical reasons to be concerned that it may wane over time.[27-29] The *RPE65* mutation does cause continued retinal degeneration over time, and it is not yet known whether VN reduces or eliminates this degeneration given that the treatment is not administered to the entire retina. There is evidence of retinal degeneration continuing after other gene therapies targeting *RPE65*, but these treatments used a different vector.[26] Decisions regarding costs of therapies and reimbursement strategies will have to be made despite uncertain durations of benefit.

The high ICER estimated here was driven partially by the high price of VN and partially by the relatively small marginal QALYs gained after VN use. Because VN has not been shown to impact mortality, the marginal QALYs were driven by quality-of-life alone. Although improving vision from completely blind to fully sighted would lead to a large increase in quality-of-life, the individuals eligible for VN were not fully blind, nor did they reach full sight after the treatment. The perception of gene therapies may be that they are uniformly "curative," but this is not the case with all gene therapies, including VN. If VN were a "cure,"

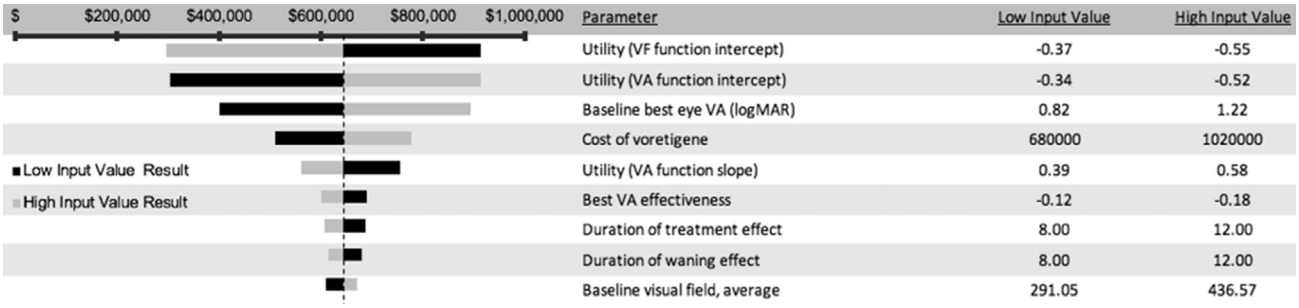

Fig. 2 – Tornado diagram representing one-way sensitivity analysis of resulting incremental cost-effectiveness ratio (ICER) from the US healthcare system perspective.

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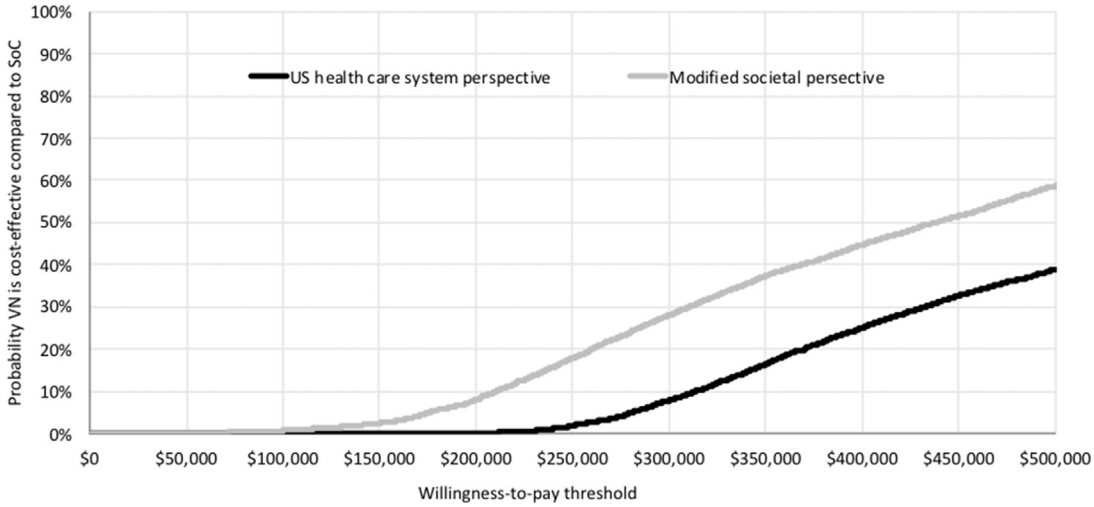

Fig. 3 – Probability of cost-effectiveness based on probabilistic sensitivity analysis of incremental cost-effectiveness ratio (ICER).

immediately restoring all patients to normal vision for their remaining lifetime, the ICER could be as low as $52 000/QALY from a US healthcare system perspective (calculated using an exploratory scenario analysis using a lifetime duration of benefit and increasing the change with voretigene to maximum values of VA and VF). We do show that the value of VN was better for patients with better baseline visual ability, which may suggest that treatment policies should target patients with better visual ability. These policies may also be considered in relation to patient age, given the progressive nature of this condition and the existing data on natural history that suggests an inverse relationship between increasing age and visual ability. Nevertheless, it can be difficult to detect children with *RPE65*-mediated IRD early in the course of the disorder.

Because the drivers of cost-effectiveness were the price of VN and the magnitude of the treatment response, it could be feasible to implement a price reimbursement strategy in which health payers were reimbursed based on individual outcomes. The manufacturer, Spark Therapeutics, has announced that it will provide an option to insurers where they can receive rebates 2.5 years after VN treatment if the treatment effect is not sustained at that time.[26] Spark has also announced several individual measures it is taking to address cost concerns.[30] Specifically, Spark has stated a negotiated plan with Harvard Pilgrim that will pay rebates, likely up to 20%, if VN is not effective at 30 to 90 days or 30 months, based on light sensitivity tests. They may offer this plan to other insurers as well. Nonetheless, if 30% of patients received a rebate (in the clinical trial, 30% of people did not meet the clinically meaningful 1 log unit of change), even with a 100% rebate the ICER from a US healthcare system perspective would be $445 000/QALY. Spark is also partnering with Express Scripts to provide VN directly through a pharmacy benefit manager rather than directly to hospitals, to avoid the significant facility markups typically added in the health system, with Express Scripts potentially paying additional rebates. Finally, Spark is negotiating with the Centers for Medicaid and Medicare Services to potentially allow for multiyear payment plans and larger rebates if the treatment effect is smaller than anticipated.

There were several limitations to this analysis. First, we applied utility values based on visual ability. Data were significantly limited in this area, as quality-of-life data specific to *RPE65*-mediated retinal disease do not exist. Therefore, we used utility values from other retinal disease populations, which were often older and potentially included other disease-related comorbidities. This may have led to biased estimates of quality-of-life and hence overall health outcomes. Nevertheless, this bias was likely conservative because older patient populations and those with more comorbidities may be more likely to report lower utilities—establishing a lower utility floor for the analysis. Second, we assumed a 10-year duration of treatment effect and 10-year waning period. There were anecdotal reports of sustained benefits out to 7 years, but effects in later years could not be ensured. Third, we would ideally have used additional measures, such as the MLMT, to categorize individuals' visual ability. Nonetheless, data for these outcomes from VN trials were not available in metrics that could be linked and validated to relevant categories of visual ability. We believe that incorporation of the MLMT may have increased the modeled benefit of voretigene, and hence decrease the ICER, because the MLMT incorporates a wider array of benefits than just VA and VF. Unfortunately, the MLMT was not correlated with quality-of-life utility values. We would ideally have data available to complete a full individual simulation model tracking each vision-related health outcome over the lifetime of an individual. In the absence of these data, we used a Markov model and tracked more limited vision-related outcome among those in the "alive" health state.

Overall, we found that VN was unlikely to be cost-effective compared with SoC at the current price and at commonly used cost-effectiveness thresholds. Nevertheless, given the multiple contextual factors and small patient population, it is likely to be covered by payers. The willingness of Spark to engage in outcomes guarantees may further support favorable coverage policies. Further, data on the optimal target population for the intervention and duration of treatment effect will be important to establish more precise estimates of the value of VN in the United States. We found that VN was more cost-effective for people with better visual ability before treatment. VN has important implications for both development and pricing of future gene therapies; therefore clinical and economic analyses must be carefully considered.

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