



Voretigene Neparvovec for Biallelic *RPE65*-Mediated Retinal Disease: Effectiveness and Value

Response to Public Comment on Draft Evidence Report

January 12, 2018

Prepared for



##	Commenter	Comments on Voretigene Draft Report	ICER Response
1	Center for Value Based Medicine	<p>At a minimum, we believe current standardization should include: 1) the same utility instrument (we prefer time tradeoff), 2) patient utility respondents, 3) the national average, Medicare Fee Schedule, 4) Net Present Value analysis with a 3% annual discount rate for value and cost parameters, 5) third party insurer and societal cost perspectives, and 6) comparisons against the null assuming no treatment is given (average cost-utility analysis), as well as of one treatment versus another (incremental cost-utility analysis).² We are pleased that ICER researchers addressed variables 3-6.</p>	<p>The models used in our cost-effectiveness analyses follow ICER's Reference Case guidelines to the extent possible. For utility estimates in this model, we now use values from a study by Lloyd et al. (2008), that were collected using standard gamble ratings (considered the gold standard for utility measurement) from the general public (considered appropriate for a health care system/payer perspective).</p>
2	Center for Value Based Medicine	<p>The ICER Report assumes, "Vision loss-related disability is linearly proportional to visual acuity or visual field." This tends to be linear in part, but when the vision or fields reach the point of severe loss, the time tradeoff utility drops much further than expected with a straight-line function. The ICER authors¹ state that RPE65-mediated ocular disease can go to no light perception. A time tradeoff utility of 0.26 is associated with no light perception bilaterally. This equates to a loss of three-fourths of life's value---similar to the quality-of-life associated with the most severe stroke. A time tradeoff utility of 0.35 has been associated with hand motions vision in the better-seeing eye. These utilities associated with poor or no vision have been validated in multiple peer-reviewed studies and shown to have good to excellent one-month (intra-class correlation coefficient = 0.76) and one-year (intra-class correlation coefficient = 0.52) reliability. Importantly, they are not typically influenced by age, gender, level of education, or income, the underlying cause of vision loss, or systemic</p>	<p>We have changed the utility values used in the base case to the community-based utilities from Lloyd et al. 2008. The utility data points that we see in this study show a linear decline up until counting fingers. It is possible that there is a steep decline from counting fingers to NLP, but we do not have sufficient data to inform that specific estimate using community-based values. We are also including a scenario analysis that includes data from Table 4 in the Brown et al, 2003 publication, incorporating a non-linear relationship, specifically using a piecewise function.</p>

		comorbidities. Failure of ICER to take very low vision utilities into account diminishes the utility loss associated with untreated RPE-65-mediated disease. Thus, the patient value (QALY) gain from voretigene therapy is also diminished.	
3	Center for Value Based Medicine	Not all the studies the ICER authors referenced utilized utilities from patients with vision loss, thus obfuscating actual patient utilities. For example, it has been shown that ophthalmologists who take care of patients with age-related macular degeneration (AMD) underestimated the quality-of-life (utility) loss associated with AMD by 95% to 750% compared to actual AMD patients with the same level of vision loss. NICE (National Institute for Health and Care Excellence) in the UK recommends using a generic utility instrument (e.g. EuroQOL 5-D) based upon time tradeoff or standard gamble utilities and preferences gathered from the general public. There are arguments pro and con for using specific utility respondent cohorts. But mixing general public and patient utility cohorts , as in the ICER RPE-65 analysis, seems to negate standardization of utility acquisition. It also likely minimizes the patient value (QALY) gain from voretigene therapy since the public underestimates utility loss associated with medical conditions in 90% of instances referent to patients with the actual condition.	See response to comment 2 above.

4	Center for Value Based Medicine	<p>The natural history of RPE 65-mediated retinochoroidal disease is well elucidated in the peer-reviewed literature. While it is difficult to be certain from the methodological explanation in the ICER manuscript, unless Figure 5.2 takes this into account, we are uncertain that a control vision cohort was utilized. <i>If so, using the utilities associated with the more advanced levels of vision loss associated with untreated RPE65-mediated disease in a control cohort would increase the patient value (QALY) gain associated with voretigene therapy. If not, a control cohort is needed.</i></p>	<p>Figure 5.2 shows visual acuity and average visual field over time for two sets of modeled patients: one receiving voretigene treatment and one receiving standard of care (SoC) without voretigene. The latter set represents the natural history of disease in the absence of voretigene treatment. Utilities decreased over time to reflect increasing visual impairment, as shown in Figure 5.3, for both sets of patients.</p>
5	Center for Value Based Medicine	<p>The authors subtracted the disutility of -0.38 calculated from their model from the expected utility of 1.00 for a healthy individual under age 35. This presents a problem as a person ages and their expected overall utility decreases. Does the visual disutility remain proportional to the overall utility? Since close to 50% of people will die from cardiovascular disease, how would the disutility for cardiac angina be treated when cardiac disease also accounts for a considerable degree of the overall decrease in systemic utility at age 75?</p>	<p>We have switched the base utility to 1. Please note this had no impact on the incremental results.</p>
6	Center for Value Based Medicine	<p>Data from ophthalmic patients with multiple discrete health conditions suggest that disutilities are not additive to the disutility from vision loss, and that overall quality-of-life correlates closely with the single disease that causes the greatest quality-of-life diminution, which is likely RPE65-mediated disease herein. <i>Using disutility and subtracting it from systemic utility can, depending upon the exact methodology, compress the ocular value gain component and decrease overall ocular therapeutic gain</i></p>	<p>We agree that disutilities may not be additive, and so have removed the age-based disutility and are applying vision-related disutilities alone.</p>

7	Center for Value Based Medicine	Data from the Salisbury Eye Evaluation Study suggest that decreased vision is associated with increased mortality. The increased mortality does not seem to be related to a specific visual disease, thus should apply to RPE65-mediated disease. Taking increased mortality into account increases the patient value gain associated with voretigene therapy, since better vision is associated with decreased mortality	The 2017 meta-analysis by Zhang of 29 prospective studies confirms the association between visual impairment and mortality. However, most of the studies include populations older than 65 years and the authors specifically point out that the association may be based on visual impairment being a marker for frailty or comorbid disease. Considering the much younger population with RPE65-mediated disease and the absence of any study showing that improving visual acuity diminishes mortality, we have not included differences in mortality in our model.
8	Center for Value Based Medicine	The authors selected a disutility of -0.13 for the development of macular hole. The average vision associated with untreated macular hole is 20/200. Since Figure 5.2 indicates that the authors are assuming that the mean vision in a 15-year-old person with RPE65-mediated disease is 20/200, <i>it seems that the vision associated with a macular hole would cause negligible, if any, deterioration in quality-of-life.</i> The reference (#72 in the ICER Report ¹) given for the disutility of -0.13 is from our Center for Value-Based Medicine®. Yet, upon review of our article, ²⁴ we do not see that disutility listed.	We have revised the source for this disutility and are now using data from a study (Ternent et al. 2012) evaluating surgical repair of macular hole. The disutility is now -0.053 over 6 months.
9	Center for Value Based Medicine	The incidence of depression is higher in an age-related macular degeneration population than in an age-matched general population. While the disutilities associated with most comorbidities do not appear to be additive to that associated with a serious ophthalmic condition, depression may be an exception. This has been demonstrated for depression associated with diabetes mellitus. The McSad depression specific classification system, a multi-attribute classification, has suggested very low utilities (0.04 for severe monopolar depression) associated with depression. In view of the severe vision	We appreciate that depression may be associated with both RPE65-mediated disease and lower quality of life. However, data are limited to non-existent for incidence of depression and quality-of-life in this population.

		<p>loss associated with RPE65-mediated ocular disease, it seems that select patients could well be affected by a higher incidence of depression. This area deserves further investigation, but <i>we anticipate that there may be a component of additive disutility to untreated RPE65-mediated disease for the comorbidity of depression</i>. This would likely increase the potential patient value gain associated with voretigene treatment of RPE65-mediated disease.</p>	
10	Center for Value Based Medicine	<p>The timeline associated with therapeutic benefit from voretigene neparvovec is uncertain at this time. Since recipients of this therapy are typically young, a prolonged time of therapeutic benefit will substantially increase the patient value (QALY) gain and result in a more favorable cost-utility ratio. This is in contrast to the method the ICER authors have applied in which there is 10 years of benefit followed by 10 years of diminishing benefit to no benefit. Recommendations from the World Health Organization in the <i>WHO Guide to Cost-Effectiveness Analysis</i> state that "costs and health effects related to the intervention should be followed for the duration of lifetime of the beneficiaries." <i>In view of this recommendation, we suggest that the base case should be one that uses the lifetime of the average patient undergoing voretigene therapy</i>. Other model length scenarios can be addressed in the sensitivity analysis.</p>	<p>Our model uses a lifetime horizon for the base case analysis, following patients "for the duration of lifetime of the beneficiaries." In the absence of long-term data on effectiveness of this one-time treatment, our base case assumed a 10-year period of full effect, followed by diminishing effect over the next 10 years. We also performed a scenario analysis where the treatment benefit is assumed to be lifetime, again using a lifetime horizon.</p>

11	Center for Value Based Medicine	<p>While we believe the authors have assumed reasonable direct ophthalmic medical costs, it is our opinion that <i>other relevant societal costs are likely greater than assumed. Among these are: 1) direct non-ophthalmic medical costs, such as for depression, trauma, facility admissions, etc. 2) direct non-medical costs, such as for caregivers, activities of daily living, residence and transportation, and 3) indirect medical (productivity) costs from decreased wages.</i> We agree with the educational costs used by the authors. Utilizing published Medicare and internal commercial insurance population costs obtained from 400 patients with vision loss, we <i>calculated the societal costs accruing against the direct ophthalmic medical costs (voretigene implantation and the voretigene neparvovec injectable agent) to be higher than those calculated by the authors.</i> They exceed \$1.1 million in 2017 U.S. real dollars when therapy occurs at age 15 and a lifetime model is utilized. When therapy is administered at age 3, the societal costs accrued against the direct ophthalmic medical costs are conservatively \$1.3 million. Assuming a \$1 million cost of voretigene, the societal costs accrued against the direct ophthalmic medical costs of therapy exceed the therapeutic costs. The overall cost of therapy in this scenario is negative, resulting in voretigene therapy dominating observation by delivering greater patient value for lesser cost.</p>	<p>We have changed our approach for some of the indirect costs. The educational, productivity, and residential costs are estimated from the same original source (Wittenborn 2013), as these were considered to be more relevant to a population of the age modeled here. The direct medical and remaining direct non-medical costs are now from the Brown et al. 2016 study, which presented data by visual impairment categories but in a considerably older population. The cost-saving calculation provided in the comment does not consider the incremental nature of the analysis, nor the fact that data do not support an assumption that voretigene returns every patient to perfect vision for their remaining lifetime.</p>
12	Spark Therapeutics	<p>Spark believes that there are fundamental problems with the base model that prevent ICER from sufficiently capturing the full clinical and economic value of VN. Our <i>greatest concern relates to the health utilities used in the analysis, which currently suggest a small treatment effect resulting from VN treatment and a high disease burden even among those who have not progressed past moderate visual impairment.</i> The fact that these utilities</p>	<p>We agree that there is an unfortunate lack of data around quality-of-life for this ultra-rare condition. We have done our best to address this limitation using data available. See above responses related to the utilities used in the model.</p>

		do not comport with patient testimonies and clinical experience in this ultra-rare disease is particularly worrisome as the accuracy of these measures is vital to valuing this treatment appropriately.	
13	Spark Therapeutics	The health utilities used in ICER's analysis are sourced from studies of age-related macular degeneration, diabetic retinopathy, and other retina disorders. The pathology of these diseases is significantly different from RPE65 mutation-associated inherited retinal disease (IRD), and the average age of patients in these studies is over age 60, differing significantly from the average age of 15 in the VN trials, suggesting the data may be of limited relevance to patients with RPE65 mutations. Although health utility data for the RPE65 IRD population are not currently available, we believe ICER has not sufficiently disclosed or acknowledged the shortcomings of an analysis based on diseases with pathologies and populations that are markedly different from the disease that VN would treat. Further, ICER has not attempted to mitigate the bias these differences would have on their health utility estimates	We agree that the lack of utility data available to inform this model is a limitation. Please see above responses related to the utilities used in the model. Note that using utilities from older patients with other diseases that include visual impairment likely increases the size of the disutility applied to blindness in the model, to the advantage of the new intervention.

14	Spark Therapeutics	<p>According to Figure 5.3 of ICER's report, the "calculated overall expected utility over time" for an RPE65 mutation-associated IRD patient eligible for treatment at age 15 does not exceed 0.70. This figure may be reasonable for an elderly patient with diabetic retinopathy, but seems to be far too low for a 15-year-old with moderate visual impairment (a decimal value of visual acuity (VA) greater to or equal to one). In the United States, average health utility of a 60-year-old is significantly lower than that of a 15-year-old (0.830 vs. 0.924), reflecting the importance of adjusting health utility values to reflect the younger population that would typically be treated with VN.</p>	<p>According to the voretigene trial data, mean VA for the untreated best eye was 0.1, corresponding to severe visual impairment. The mean average VF was 363, which also corresponds with severe impairment. Treatment with voretigene improves both of the measures to 0.13 and 645, respectively. These values are in the middle to lower range of moderate vision loss. The utility values for these levels of visual impairment are in line with our estimates. Essentially, the mean visual impairment observed in the trial population is reflected in the utilities in the model. Please note that the utility values after treatment in the 3-year old model population analysis are higher.</p>
15	Spark Therapeutics	<p>Figure 5.3 also illustrates that the lowest health utility a patient can have in ICER's model is slightly above 0.40, which is over 0.10 higher than estimates of complete blindness (i.e., no light perception (NLP)). The fact that the highest health utility a 15-year-old patient eligible for VN can have is lower than it should be and the lowest health utility this same patient can have is higher than it should be has the net effect of compressing the potential QoL gains in ICER's model. As a result, ICER is underestimating the impact of blindness on a person's QoL.</p>	<p>Please see above responses related to the utilities used in the model.</p>
16	Spark Therapeutics	<p>The upper bound health utility of 0.70 in ICER's model is problematic for another reason; it suggests that the average QoL for a patient treated with VN will be approximately that of a multiple myeloma patient unresponsive to multiple treatments. This characterization of QoL for VN-treated patients is inconsistent with, and drastically different from, the testimony given by VN-treated patients and IRD clinical</p>	<p>Please see above responses related to the utilities used in the model. The average utility for patients after voretigene treatment is influenced by their level of visual impairment prior to starting treatment and the incremental impact of treatment.</p>

		<p>experts at the FDA Advisory Committee meeting on October 12, 2017, which is the most real-world evidence available for VN as it is undergoing FDA review.</p>	
17	Spark Therapeutics	<p>The level of health utility values of individuals treated with VN is not the only aspect of the health utilities that does not comport with available evidence. The benefit of VN vs. the standard of care (SoC) treatment in terms of QoL (on an annual scale of 0 to 1, where 0=death and 1=perfect health) appears to be no larger than 0.07 in Figure 5.3. Again, this seems at odds with patient testimony at the FDA Advisory Committee Meeting, which spoke to substantial QoL improvements following treatment. For example, Shaw et al. (2005), the recommended reference for estimation of EQ-5D-based health utility in the United States, reflects that the difference between “no problems” on all of the five dimensions of health-related QoL (i.e., mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and “some problems” with the “usual activities” dimension is 2 times (i.e., 0.14) the average benefit of VN vs. SoC treatment that ICER estimates (i.e., 0.07). Patient testimony at the FDA advisory meeting poignantly described the dramatic improvements in independence and ability to perform normal activities after VN, as epitomized by a patient who stated that only days after being treated at age 20, “I could use adaptive technology, the iPhone accessibility apps, zoom features, and more. I was independent and mobile, which I had not been for some time. I may not have gained normal vision, but I gained all of my independence.” Improvement from “unable” to “no problems” on the “usual activities” dimension of the EQ-5D is associated with improvement of 0.37 (per Shaw et al.), greater than 5 times the average</p>	<p>Our model requires the use of quantifiable scales for vision-related disutility. Due to paucity of data on voretigene's impact on all the potential dimensions of blindness and their link to health-related quality of life, we are basing the utility gains on VA and VF. We do not see dramatic changes in the overall patient population because we are using the average impact across all treated patients, not just the best responders, and we are also limited to using the changes in VA and VF, which may be more modest. We could have used HrQoL data if it had been quantitatively collected in the trial.</p>

		<p>QoL benefit that ICER estimates for VN vs. SoC treatment. Given that VN treatment is likely to improve QoL not only in terms of the “usual activities” dimension, but also in terms of “mobility”, “self-care”, and “anxiety/depression”, it therefore seems that the average QoL benefit that ICER estimates drastically understates available evidence on patients’ experiences after being treated with VN.</p>	
18	Spark Therapeutics	<p>The AMA guidelines provide a useful way to assign various levels of visual impairment to VA and visual field (VF) values. Particularly, it relates the radius of VF to levels of visual impairment. Dividing the sum total degrees for the Goldmann VF by 24 will result in a radius measure (assuming a concentric VF). We believe using this source to define the relationship between visual impairment and health utilities, rather than assuming a linear functional relationship, is a preferable approach.</p>	<p>Please see above responses related to the utilities used in the model. Please note that the currently available AMA guidelines do not provide explicit relationships with utilities, either linear or otherwise; therefore, we are unable to use the guidelines in this way.</p>
19	Spark Therapeutics	<p>Although not ideal, given the study was conducted on an older population, ICER should consider Brown et al. (2003) as a source for mapping. Table 4 provides utilities associated with not only legal blindness, but extent of visual impairment ranging from none (i.e., 20/20) to no light perception (NLP). Given the fact that the natural history data provided by Spark show patients progressing towards NLP, it is important that the model capture the larger disutility associated with this health state. These results are also consistent with other literature that has examined utilities associated with extent VA impairment of count fingers, hand motion, light perception, and NLP.</p>	<p>Please see above responses related to the utilities used in the model.</p>

20	Spark Therapeutics	<p>Furthermore, while the use of the EQ-5D is generally encouraged by most international health-technology-assessment bodies for purposes of reimbursement decision-making, the most appropriate measure for capturing QoL may vary depending on the disease under consideration. Longworth et al. (2014) note that, “EQ-5D was valid and responsive for skin conditions and most cancers; in vision, its performance varied according to aetiology; and performance was poor for hearing impairments.” This is another reason why Brown et al. (2003) and Sharma et al. (2003) are preferable to averaging across all studies as ICER suggests, as both studies utilize the time-trade-off (TTO) method.</p>	<p>Please see above responses related to the utilities used in the model. The base case is now using utility values derived from a community sample and the standard gamble. A scenario analysis will use the Brown et al. 2003 values.</p>
21	Spark Therapeutics	<p>Furthermore, ICER assigned the adverse event of macular hole/degeneration as having a disutility of 0.13, which is equivalent to almost double the extent of the benefits of the VN treatment in the first year (a 0.07 utility). This seems at odds with the information available for the two patients who experienced macular holes in the Phase III clinical trial. The macular hole for both patients resolved by the 90-day follow-up visit after the surgical procedure. Moreover, the burden of macular holes is often less for patients with poor central vision and associated decreased visual acuity. The average visual acuity of treated patients in the trial was 1.18 LogMAR which correlates to legal blindness. Thus, the burden of a macular hole is much lower for the patients in the VN clinical trial than an average population. These facts suggest that the disutility associated with the macular holes is far too large and should be weighted appropriately or removed altogether. We suggest using a disutility associated with a population with poorer visual acuity and weighting it by ¼, as the disutility was only experienced by these patients for 90 days. Finally, since both cases resolved, all costs</p>	<p>See response above regarding the change in the macular hole disutility. The macular hole adverse event was considered serious, and it is not clear that all macular holes will resolve without surgery. Please note that this input has little to no impact on the results given the low incidence of this AE.</p>

		<p>associated with macular holes should be removed as there was no surgical intervention required in any of the cases that occurred during the clinical trial. It should be noted that spontaneous resolution is not unexpected, since treatment for macular holes normally involves vitrectomy to remove causative vitreous traction and this procedure had already been performed during the administration of VN.</p>	
22	Spark Therapeutics	<p>Benefits of VN treatment in terms of reduction of indirect/societal costs also are significantly underestimated. In Table 5.6 of the Draft Evidence Report, the difference between the total cost under a US health care system versus the modified societal perspective suggests that the incremental effect on indirect costs of VN treatment is not substantial. This stands in direct contrast to patient testimony, where lost wages were indicated to be upwards of \$1 million for one caregiver, as well as other available literature on the subject. Brown et al. (2016) found that annual societal ophthalmic costs were \$6,116 for a control group of patients with normal visual acuity, whereas the costs were \$30,230 for individuals with moderate visual impairment and \$82,984 for individuals with visual acuity of 20/800 to NLP. They also found that the percent of these costs associated with direct medical costs was 74% for the control group, 18% for those with moderate visual impairment and 10% for those with visual impairment from 20/800 to NLP. These indirect costs, which do not take into account costs of education, are higher than ICER's indirect costs for a blind individual.</p>	Please see above response related to indirect costs.

23	Spark Therapeutics	<p>Furthermore, as evidenced by Table 5.5, in many instances the source relied upon by ICER does not show differences in indirect costs between individuals who are visually impaired relative to those who are blind. This again is likely to underestimate the indirect and societal costs associated with blindness, and is inconsistent with available literature on the topic. As indicated by Brown et al. (2016), the societal costs of ophthalmological related diseases vary greatly by the level of visual impairment. In another study, caregiver burden was shown to increase with the severity of the disease and has been estimated to be high even for the care of adult populations (see Schmier J et al. Impact of visual impairment on use of caregiving by individuals with age-related macular degeneration Retina, 2006,25:1056-1062). Even if the caregiver burden for adults is lower than for children, this is partially due to institutionalization. The entry into assisted living occurs earlier for individuals with severe visual impairment relative to the rest of the population and is a cost often borne by the family or government.</p>	<p>Please see above response related to indirect costs. We now include some direct and indirect costs that vary by severity.</p>
24	Spark Therapeutics	<p>There is no study that provides indirect costs related to <i>RPE65</i> mutation-associated inherited retinal disease. Although ICER has focused on a study that provides estimates for a younger population, this study does not reflect the unique progression and experience of patients with this disease. At the very least, ICER should incorporate the difference in indirect costs across levels of visual impairment as suggested by Brown et al. (2016) and Shmier et al. (2006) as well as how the disease effects educational attainment and thus productivity loss.</p>	<p>Please see above response related to indirect costs.</p>

25	Spark Therapeutics	But more generally, this suggests that the timing of ICER's assessment of VN is inappropriate and given the lack of data for this population it becomes even more important that the testimonies from patients and advocacy groups are taken into consideration when estimating these costs.	We agree that there are limited data. However, voretigene will be entering the healthcare market and a variety of stakeholders will need to make decisions based on the best data that are available.
26	Spark Therapeutics	ICER's results indicate that QoL improvements associated with VN vs. SoC are 60% lower for a 15-year-old vs. a 3-year-old (1.30 vs. 3.25 QALY gains in their base case, and 2.14 vs. 5.31 QALY gains in their lifetime treatment-effect scenarios), which seems inconsistent with the testimony provided by clinical experts. Due to sample size limitations, the Phase III study was not powered to determine if the treatment effect was different across age. However, the clinical trial was stratified for subjects less than 10 years of age and 10 years of age and older, and post hoc analyses comparing bilateral MLMT score change, MLMT score change for the first eye, and FST white light averaged over both eyes, showed no statistical difference in the treatment effect between the two age groups. It is therefore incumbent upon ICER to explain the departure of modeling results, suggesting substantial lower benefit of treatment in 15-year-old vs. 3-year-old patients, from the existing clinical evidence.	We did not model a different treatment effect by age group. The same treatment effect on the logmar and sum total degrees scales were applied to each group. The younger age group has a better baseline VA and VF than the older patient group, which leads to a larger treatment effect on the decimal scale because of the non-linear transformation from logmar to decimals. Also, because changes on the decimal scale are not linear over time, the better baseline VA has a faster decline and hence bigger treatment effect differential. These two factors, both due to baseline VA, drove the difference between age groups, not a differential treatment effect. We have emphasized this point in the text.

27	Spark Therapeutics	<p>ICER’s base case analysis only allows for a 10-year treatment effect, then assumes waning of the treatment effect over the subsequent 10 years. As we have stated previously, given that there is no evidence indicating that the effect diminishes over time, it seems more reasonable to assume a lifetime treatment effect for VN in the base case model. We believe more generally that due to data limitations associated with ultra-orphan drug therapies, assuming lower values of durability will lead value-based pricing to be biased against investment in treatment of the underlying causes of disease, and towards short-term alleviation of symptoms.</p>	<p>There are certainly limited data on the durability of treatment effect given that there are only data up to 3 years from the trial. We have received anecdotal evidence that two patients have not experienced meaningful declines in the treatment effect up to 8 years post-treatment. Given the lack of long-term data and the fact that the injection does not cover the entirety of the eye, we feel that the 10-year assumption is reasonable. We have also included scenario analyses with the lifetime treatment effect.</p>
28	Sofia Sees Hope	<p>1. The Phase 3 trial (Study 301) was only given a “fair” quality rating by ICER. The ICER report cited an imbalance in the randomized cohort’s ability to pass the MLMT, the inability to fully blind investigators or participants, and changes in endpoints from the original study design led to the fair rating”. These factors are not considered to necessarily impact the quality of a study, if handled properly from a procedural standpoint and in the analysis. Nevertheless, in the absence of knowledge of whether or not there was impact of these issues, the report assumed the quality of inference was “fair.” This is despite:</p> <ul style="list-style-type: none"> • A unanimous vote for approval at the recent FDA Advisory Committee meeting; • An impending decision by FDA with respect to approval, which arguably would shed significant light on the extent to which these issues were properly accounted for during the conduct of the study. 	<p>We believe that Study 301 is best described by the USPSTF "fair" rating: Fair: Any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are addressed. Intention to treat analysis is done for RCTs.</p>

29	Sofia Sees Hope	<p>2. Figure 4.4 of the report is not supportive of the contention that there is an imbalance in MLMT at baseline (one of the criticisms of the quality of study 301), as indicated by nearly identical means at the start of the trial. If there are differences, those differences are dwarfed by the magnitude of benefit seen after initiation of treatment.</p> <p>With respect to duration of effect, from the report: "Whether VN has the potential to reduce or eliminate retinal degeneration is currently unknown; however, at least one researcher has published evidence that, in humans, RPE65 gene therapy does not affect the progressive nature of retinal degeneration. These studies used gene therapies other than VN, however. Multiple differences existed between these therapies and VN including the vector, manufacturing process, surgical procedure, and patients enrolled in the trials."</p> <p>Nevertheless, the base case in the report assumes a reduction in benefit, in part perhaps based on the study with these "multiple differences," despite ICER admission: "This makes comparing outcomes across trials difficult." The outcomes across trials are outcomes of differing therapies, different patient populations, different vector, surgical procedure, etc. Accordingly, this would hardly seem able to contribute any information with respect to duration of effect for this particular potential therapy.</p>	<p>Russell et al. state: "Baseline MLMT passing level was not completely balanced between the two groups (table 1). With four strata and a small trial, these results are not unexpected." We acknowledge in our report that small numbers may have driven this imbalance. In regard to the base case comment, the decision to assume a reduction in benefit was driven by the lack of long-term data on VN, not by data from other products.</p>
30	Sofia Sees Hope	<p>3. Out of necessity (lack of available data), the cost-effectiveness model did not consider the primary endpoint for the study (MLMT) but rather visual acuity. It also assumed disutility was linearly related to visual acuity. It is unlikely this is the case and does not appear to be consistent with patient testimonials, which suggest disutility associated with a fixed amount of decrease in</p>	<p>We have switched to a non-linear function for utility.</p>

		visual acuity is very much a function of the current degree of visual impairment.	
31	Sofia Sees Hope	<p>4.Additional factors to consider:</p> <ul style="list-style-type: none"> • Quality of patient life • Reduced medical costs associated with gradual vision loss over patient's lifetime • Ability to gain employment • Reduction in need for assisted living/caregivers • Civil decisions that place the value of vision at \$1M+ 	Thank you, we have included all of these factors in our analysis.