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Modelling the Long-Term Benefits of Photodynamic Therapy (PDT) with Verteporfin for Age-Related Macular Degeneration (AMD)

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Discussion Paper 187

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Abstract

Age related macular degeneration (AMD) is the leading cause of blindness in the United Kingdom and the rest of the western world. It occurs in 15% to 30% of individuals over 75 years of age. About 15% of these patients develop a more aggressive wet form of the disease that causes severe loss of vision. This report contains estimates of the benefits of photodynamic therapy (PDT) with verteporfin therapy using a modeling approach based on clinical trial data.

While this report covers only the effects of the treatment, the model built was customizable so that it could be populated with local cost data. This made it possible to use the model to help inform local formulary decisions.

Introduction

Age related macular degeneration (AMD) is the leading cause of blindness in the United Kingdom and western world. It occurs in about 30% of individuals over 75 years of age. About 15% of these patients develop a more aggressive wet form of the disease, which causes severe loss of vision. This has significant public health implications as affected patients experience severe visual loss, suffer chronic morbidity and also require the provision of long-term social medical support services. A treatment that prevents the loss of vision associated with wet AMD could potentially make significant quality of life improvements for patient suffering from AMD and also save resources from both the medical and social services sector.

Photodynamic therapy (PDT) involves the intravenous administration of verteporfin, a photosensitizing agent, and application of a light source (laser) to area of the eye affected by AMD. The non-thermal laser used activates the verteporfin and causes occlusion of the neovascular vessels associated with wet AMD.

Objective

The objective of this research is to quantify the potential long-term benefits of PDT with verteporfin (Visudyne®, Novartis AG, Switzerland) in the treatment of AMD. This is accomplished by employing modeling, using data from a 2-year randomized clinical trial.

We also present an appendix that uses follow-up data for an additional year (on the treated group only) made available after the 2-year trial ended.

Data Source

This analysis used data from the Treatment of AMD with PDT (TAP) clinical trial.(Bressler, 2001) The TAP clinical trial included patients presenting with subfoveal choroidal neovascularization (CNV) lesions due to AMD, having a greatest linear dimension of $\leq$5,400 um, evidence of classic CNV, and best corrected visual acuity between 20/40 and 20/200. There were 609 patients in total; 402 were randomized to treatment with verteporfin (6mg/m^2) and 207 randomized to placebo (D_5W), both infusions followed by 50 J/cm^2 of light at 689 nm after 15 minutes of starting the infusion. At each follow-up visit of 3 months, patients were retreated with the baseline regimen if fluorescein leakage from CNV was identified on angiography. One eye from each patient was enrolled in the study.

The primary study outcome was moderate vision loss defined as loss of <3 lines of visual acuity (15 letters). Of those on verteporfin, 53% lost <3 lines of vision compared to 38% of placebo treated eyes ($p<0.001$). The outcome of avoidance of severe vision loss (defined as a loss of <6 lines, or <30 letters) was experienced by 82% of those on verteporfin and 70% of those on placebo ($p<0.001$). The study results indicate that more individuals in the placebo group had a visual acuity at 24 months that was < 20/200 compared to those in the verteporfin group (55.2% versus 41.0%; $p<0.001$).

Prospectively planned subgroup analysis was done based on the presence of classic CNV in the lesion being treated. Those with minimally classic lesions (>0% and <50% out of the entire area of the lesion being classic) were found to have no clinically meaningful difference with respect to the primary visual acuity outcome; 47.5% of the verteporfin versus 44.2% of the placebo patients with minimally classic

lesions lost fewer than 15 letters (p0.58). Those patients with predominately classic lesions (at least 50% of the entire lesion being classic) fared much better with verteporfin treatment on the primary visual acuity outcome; 59% of those on verteporfin versus 31% of those on placebo lost <15 letters.

Since the approved labeling for PDT with verteporfin indicates that only those with predominately classic CNV should be treated, this analysis focuses on the subset of 243 patients with that particular form of disease.

Modelling the Benefits of PDT with Verteporfin

We used the clinical trial data to estimate the benefits for two time periods; two years (within-trial estimate), and over five years. In order to make estimates of the effect that treatment would have on disease progression we used a Markov process. The health states used in the Markov model came directly from clinical trial measurements. Visual acuity (measured during the clinical trial as a Snellen Score) was used as the indicator of a patient's disease severity. The health states used are shown below. Death is included as a health state due to the advanced age of the cohort. Costs of care and health state valuations for both groups (treatment and placebo) can be attached to each of these health states in order to calculate incremental costs and benefits of treatment with verteporfin.

Table 1: Health States

Health State
Vision = 20/40
Vision = 20/50
Vision = 20/64
Vision = 20/80
Vision = 20/100
Vision = 20/126
Vision = 20/160
Vision = 20/200
Vision = 20/250
Vision = 20/320
Vision = 20/400
Vision = 20/500
Vision = 20/640
Vision = 20/800
Vision = worse than 20/800
Death

We used survival analysis to estimate transition probabilities from the clinical trial data to populate the Markov model. These transition probabilities were estimates of the daily probability of moving to a lower state of visual acuity. We used survival analysis regression to estimate time (days) to a drop in one level of visual acuity, controlling for baseline visual acuity, gender and age. Specifically, there are 15 levels of visual acuity possible in the trial (from 20/40 to > 20/800). Therefore a person starting at the best level of acuity would need to experience 14 Snellen 'drops' to get to the worst level of acuity in the trial. Likewise, a person with a starting acuity of 20/100 would get to 20/200 in three Snellen drops. Using the regression results, the predicted time to transition to a state n Snellen levels lower was calculated, controlling for baseline visual acuity level. The predicted transition rates

(hazards) were then used to calculate the probability of progression for verteporfin and placebo.

We used an accelerated life model with a Weibull parametric hazard to estimate the impact of treatment controlling, for baseline severity and other potential confounders. The regressions performed were accelerated failure time models with an assumed Weibull distribution for the hazard, the hazard being the conditional probability of a given level of transition. The survival function from this hazard can be written as:

$$\exp(-(\lambda t)^{\alpha})$$

where λ is the Weibull scale parameter, modelled as a loglinear function of the regressors (i.e. $\lambda=\exp(-\mathbf{bx})$), and α is the Weibull shape parameter, which determines whether the hazard slopes up or down. The time component (t) was varied to produce estimates of the hazard for points in time outside the trial.

One practical difficulty with the above approach is that measurement of disease severity is not done continuously, but rather at discrete intervals; every 3 months in the case of the clinical trial used here. Since we were interested in predicting time to progression based on the number of lines of visual acuity lost (Snellen drops), we would have liked to have known precisely when the event (loss of a line of visual acuity) occurred. To overcome this issue, we used linear interpolation to predict the date of progression when a person lost more than one line of vision between visits. For example, suppose a person experiences a loss of vision equivalent to 2 Snellen drops between their 3-month follow-up visits (eg. from 20/64 to 20/100). This person has entered one other health state (specifically, 20/80) during those 3 months, but we don't know precisely when. Our estimate was based on a linear assumption that the person spent an equal amount of time in each health state moved through in between visits.

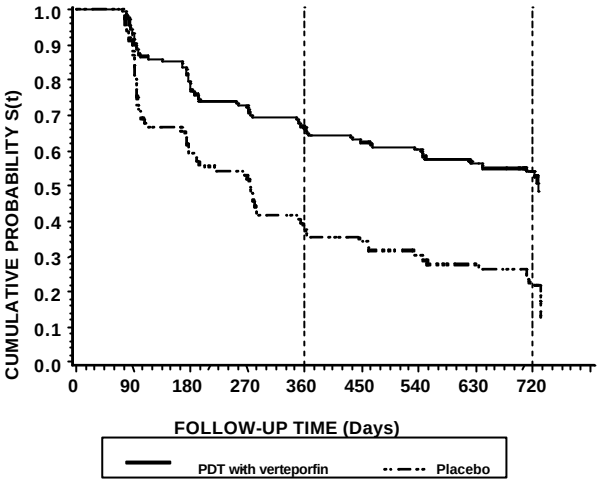
Outcome Measures

There are two principal outcome measures used in the analysis; vision years gained, and quality adjusted life years gained.

Vision years gained

Vision years gained was calculated as the amount of time spent above a visual acuity level of 20/200. This level of vision was chosen as the cut-off as it had been used in many previous studies, and because it is commonly considered 'legal blindness' in many countries.

The Kaplan-Meier plot from the clinical trial for time to visual acuity of 20/200 (34 letters or less) is shown below. This plot shows the data for patients with predominately classic CNV. Patients treated with PDT with verteporfin have a statistically significantly longer time to progression to vision of 20/200 ($p<0.001$). For the economic analysis, the measure of interest from the Kaplan-Meier plot is the area between the PDT with verteporfin curve and the placebo curve. This area reveals the incremental number of months (over the 2-year trial period) spent above 20/200 by those treated with PDT with verteporfin. This incremental number of months, converted to the proportion of a year, is the vision years gained by PDT with verteporfin. In the plot shown, this is about 141 days, or 0.39 vision years. We used a model to estimate this area so that extrapolations could be made outside the duration of the clinical trial. A comparison of the actual data (below) to our modelled estimates is discussed later.



Quality of life

Quality of life estimates were from a study undertaken by Brown, et al. (2000). These estimates were obtained using valuations from 80 patients with AMD, using time trade-off methods to obtain utility estimates for best-corrected visual acuity. The Brown study provided utility estimation for various levels of visual acuity, so we were able to map utilities from their study to the clinical trial data through visual acuity. Estimates of quality adjusted life years were obtained from the model through weighting the time spent in each visual health state by the utility as calculated by Brown. The study by Brown et al did not use exactly the same visual acuity designations as were used in the TAP study, so some slight adaptation was necessary. The categories from the Brown study were: group 1) 20/20 to 20/25; group 2) 20/30 to 20/50; group 3) 20/60 to 20/100; group 4) 20/200 to 20/400; and group 5) the ability to count fingers to light perception. The utilities they found were, group 1) 0.89 (95% CI, 0.82-0.96); group 2, 0.81 (95% CI, 0.73-0.89); group 3, 0.57 (95% CI, 0.47-0.67); group 4, 0.52 (95% CI, 0.38-0.66); and group 5, 0.40 (95% CI, 0.29-0.50). The TAP trial did not include anyone with vision better than 20/40, so group 1 of the Brown study was not used.

For the extrapolated analysis (using the Markov model) results within the model were discounted at a rate of 6% for costs and 2% for benefits following recommendations from the HM Treasury (1991).

Model Calibration

In order to test the reliability of the Markov model predictions, we compared the underlying clinical trial data with the predicted outcomes. The model predicts gains in vision years based on a given baseline visual acuity level. In order to compare the model predictions to the actual data, we used an average of the model predictions, weighted by the proportion of people represented in the trial at each visual acuity level. To facilitate the comparison with the clinical trial data, transition to the death state was not allowed, and the results are undiscounted. As previously mentioned, the clinical trial showed a vision year gain of about 0.39 years. The model predicted a gain of 0.34 years over the 2-year period, or 87% of the actual gain. The model thus appears to supply conservative estimates over the trial period. While it is not

possible to say for certain, the model may also thus give conservative estimates when extrapolating outside the clinical trial.

Assumptions in the Model

Retreatments

Patient follow-up is suggested at 3-month intervals for those receiving PDT with verteporfin treatment. In the clinical trial, all patients in the verteporfin-treated group received a baseline treatment, followed by further treatment if there was evidence of leakage from CNV on fluorescein angiography. The trial collected data on the proportion of patients who received treatment over 2 years. In order to estimate the proportion of patients continuing to receive treatment after the 2-year trial follow-up, we used a simple linear trend based on the previous (2 year) data as shown below. This extrapolation predicted that no patients would be treated after 3 years.

Table 2: Retreatments

Visit	Proportion of patients with (re)treatment	Average cumulative treatments
Baseline	1.00	1.00
Month 3	0.95	1.95
Month 6	0.81	2.76
Month 9	0.69	3.45
Month 12	0.57	4.02
Month 15	0.56	4.58
Month 18	0.51	5.09
Month 21	0.39	5.48
Month 24	0.29*	5.77*
Month 27	0.20*	5.97*
Month 30	0.12*	6.09*
Month 33	0.03*	6.12*

* Proportion estimated using least squares best fit line

Treated Eye

Another assumption in the model is that the better seeing eye is treated eye. Since AMD is a progressive, bilateral disease, this assumption implies that the results are applicable, say, in a situation where treatment is initiated when the patient has bilateral AMD involvement. The better seeing eye will often be the second eye involved.

Treatment Alternative

The 12-month results from the TAP Investigation demonstrated that approximately 92% of the patients eligible for PDT with verteporfin therapy would not have been eligible for treatment with laser photocoagulation.(Miller et al. 1999) The majority of the lesions that are eligible for laser photocoagulation are extrafoveal, whereas the patients included in the TAP Investigation had subfoveal CNV. The proposed guidelines for clinical use of PDT with verteporfin are expected to result in the treatment of a similar patient population, the great majority of whom would also be ineligible for laser photocoagulation according to the MPS treatment guidelines.(Macular-Photocoagulation-Study-Group, 1991) Therefore, the best

assessment of the costs and benefits is obtained by comparing verteporfin therapy with no treatment, rather than by comparing it with laser photocoagulation.

Improvements in Vision

A conservative assumption was applied, in that although the clinical trial showed some improvement in visual acuity associated with verteporfin treatment, the Markov process used here did not allow for improvement in vision. Rather, once a person had crossed into a given level of acuity, they stayed at that level until worsening of their visual acuity. Mortality data for the model was based on the UK population death rates.

Survival Analysis Results

The results of the survival analysis – upon which the Markov transition probabilities were based – are shown below. The regression shown here is for a drop of one Snellen visual acuity state. In the Markov model, transitioning from one state of visual health to the next worse state of visual health (i.e. one Snellen drop) is dependent on one's baseline visual acuity and values of the other covariates in the model from the regression shown.

Parameter	DF	Estimate	Standard Error	95% Confidence Limits	Chi Square	Pr ChiSq
Intercept	1	3.7905	0.3759	3.0536 4.5273	101.66	<.0001
Gender	1	-0.1769	0.1838	-0.5372 0.1834	0.93	0.336
Baseline Snellen	1	0.1184	0.0435	0.0331 0.2037	7.4	0.0065
Prior treatment (Y/N)	1	-0.13	0.1962	-0.5146 0.2547	0.44	0.5078
Treatment Group	1	0.5109	0.1926	0.1334 0.8885	7.04	0.008
Scale	1	1.3366	0.0678	1.2101 1.4762		
Weibull Shape	1	0.7482	0.0379	0.6774 0.8264		

Markov Model Results

The following tables show the benefits as obtained by the Markov model. The effect of PDT with verteporfin is shown for two outcomes, vision years gained and quality adjusted life years gained. There are also two levels of starting visual acuity for treatment shown; one on a cohort with good vision (20/40), and one on a cohort with poorer vision of 20/100. Table 3 shows the estimated benefits from the model. The 0.89 vision year difference (approximate 95% CL; 0.22-1.4) suggests that those in the treatment group would expect to spend an extra 325 days (10.8 months) above a visual acuity level of 20/200 versus those in the placebo group over a 5-year period, when treatment begins at a level of 20/40. Likewise, the 0.17 QALY difference (approximate 95% CL; 0.05 – 0.30) suggests that an extra 62 quality-adjusted days (2 months) are gained by verteporfin therapy for the base case.

Table 3: Vision Years and Quality Adjusted Life Years (QALYs) for the Base Case: 5-year time frame, cohort with baseline best corrected visual acuity=20/40

	Placebo	Verteporfin	Difference	(approximate 95% CL*)
Vision Years	2.16	3.05	0.89	(0.22 - 1.40)
QALYs	2.21	2.38	0.17	(0.05 - 0.30)

*CL=Confidence Limits

The following tables illustrate a series of one-way sensitivity analyses. These analyses demonstrate variations from the base-case regarding baseline visual acuity, number of years of follow-up, discount rate and assumed extent of treatment effect. In Table 4, it can be seen that the expected outcomes diminish as the cohort's baseline visual acuity decreases. The incremental change (difference) is more dramatic with vision years than QALYs, indicating that the expected relative decrease in vision years is greater (as compared to QALYs) as the baseline visual acuity worsens. Treating a cohort with a baseline visual acuity of 20/160 (instead of 20/40) yields 53% of the expected difference in QALYs (0.09/0.17 QALYS) over the base-case, whereas the same cohort would expect only 27% of the expected difference in vision years (0.24/0.89 vision years).

Table 4: Sensitivity Analysis on Baseline Visual Acuity

QALYs over a 5 year timeframe			
Baseline VA	Placebo	Verteporfin	Difference
20/40	2.21	2.38	0.17
20/64	2.06	2.16	0.10
20/100	2.00	2.10	0.10
20/160	1.92	2.01	0.09

Vision Years over a 5 year timeframe			
Baseline VA	Placebo	Verteporfin	Difference
20/40	2.16	3.05	0.89
20/64	1.8	2.62	0.82
20/100	1.22	1.86	0.64
20/160	0.42	0.66	0.24

In Table 5, the number of years of follow-up is clearly related to the anticipated incremental difference for both measures, with increasing returns for greater follow-up. This table also indicates that over half of the gains predicted by the model accrue after the trial period in the case of QALYs, and more than 80% accrue after the trial period in the case of vision years. In effect, this increase in treatment benefit with longer time horizons is mainly due to the continuation of efficacy gains established during the trial period.

Table 5: Sensitivity Analysis on Number of years of Follow-up:

QALYs for a cohort with baseline best corrected visual acuity=20/40			
Yrs of Follow-up	Placebo	Verteporfin	Difference
2	1.14	1.21	0.07
3	1.56	1.65	0.09
4	1.91	2.04	0.13
5	2.21	2.38	0.17

Vision Years for a cohort with baseline best corrected visual acuity=20/40			
Yrs of Follow-up	Placebo	Verteporfin	Difference
2	1.62	1.77	0.15
3	1.96	2.39	0.43
4	2.11	2.8	0.69
5	2.16	3.05	0.89

The discount rate is varied in Table 6. Varying the discount from 3% to 10% yields 74% of the expected difference for both outcomes (0.14/0.19 for QALYs, and 0.89/0.70 for vision years).

Table 6: Sensitivity Analysis on Baseline Discount Rate

5-year timeframe, QALYs for a cohort with baseline best corrected visual acuity=20/40			
Discount Rate	Placebo	Verteporfin	Difference
3%	2.21	2.40	0.19
5%	2.07	2.24	0.17
10%	1.88	2.02	0.14

5-year timeframe, Vision Years for a cohort with baseline best corrected visual acuity=20/40			
Discount Rate	Placebo	Verteporfin	Difference
3%	2.16	3.05	0.89
5%	2.07	2.88	0.81
10%	1.94	2.64	0.70

In Table 7 the extent of the treatment effect is varied. This reflects the number of years that the model uses the hazard rate from the treatment group. When the assumed treatment effect is two years, the modelled treatment effect for those on verteporfin follows the hazard predicted by the regression model for those on verteporfin for two years, then follows that for the placebo group for three years. If the extent of effect is set to five years (as in the base case), the assumed effect of treatment for those on verteporfin follows that predicted by the regression model for those on verteporfin for the full five years. In the case of QALYs, the treatment effect duration of two years is 82% of that expected in the base-case (0.14/0.17), and in the case of vision years the treatment effect duration of two years is 71% of the base case (0.63/0.89). What this demonstrates is that modelled changes in the treatment effect after the trial period has a relatively modest impact on the 5-year gain estimates. Of far more significance is the choice of time horizon over which the trial results are extrapolated (see Table 5 above).

Table 7: Sensitivity Analysis on Extent of Treatment Effect*

5 Year results on QALYs for a cohort with baseline best corrected visual acuity=20/40			
Extent of Effect	Placebo	Verteporfin	Difference
2.0 Years	2.21	2.35	0.14
2.6 Years	2.21	2.36	0.15
3.2 Years	2.21	2.36	0.15
3.8 Years	2.21	2.37	0.16
4.4 Years	2.21	2.38	0.17
5.0 Years	2.21	2.38	0.17

5 year results on Vision Years for a cohort with baseline best corrected visual acuity=20/40			
Extent of Effect	Placebo	Verteporfin	Difference
2.0 Years	2.16	2.78	0.63
2.6 Years	2.16	2.84	0.68
3.2 Years	2.16	2.89	0.73
3.8 Years	2.16	2.95	0.79
4.4 Years	2.16	3	0.84
5.0 Years	2.16	3.05	0.89

**After the specified time, the hazard rate for the treatment group (ie the treatment effect) is set to be identical to the hazard rate for the placebo group. For example, extent of effect=2 years assumes no difference in treatment and placebo rates of vision loss after the trial period; extent of effect=5 years is the base case.*

Discussion

The model described within this paper suggests that treating predominately classic, subfoveal AMD lesions using PDT with verteporfin has a greater effect when initiated at better levels of visual acuity. Further, the anticipated gains are expected to increase as follow-up increases. At five years, a cohort with baseline visual acuity of 20/40 is projected to gain 0.89 vision years and 0.17 QALYs.

There is anecdotal evidence that clinicians are treating patients with fewer courses of therapy than were administered in the trial (i.e. 2-3 versus 5-6). To the extent that this is the case, any cost-effectiveness ratios resulting from calculations made using the model presented here will be approximately halved – provided, of course, that similar outcomes are observed. However, without the benefit of further study it is not possible to determine if outcomes would indeed be similar with fewer treatments.

There are several caveats to keep in mind with this work. We have not considered any side-effects that may occur from PDT with verteporfin treatment. These side-effects include visual disturbance (22.1% verteporfin and 15.5% placebo), injection site adverse events (15.9% verteporfin and 5.8% placebo), infusion-related back pain (2.5% verteporfin and 0% placebo), allergic reaction (2% verteporfin and 3.9% placebo) and photosensitivity reactions (3.5% verteporfin and 0% placebo). All side-effects, with the exception of allergic reactions, were more prominent in the verteporfin arm. A total of 7 patients (1.7%) withdrew from treatment due to adverse events.(Bressler, 2001, 198-207) While some of these events would surely impact on quality of life, the relatively small number of withdrawals suggests that the overall impact may have been modest.

Another caveat is that these results are applicable only to the situation where the eye being treated is the better-seeing eye, has subfoveal CNV wherein the lesion diagnosis is at least 50% Classic CNV. Since AMD is a progressive, bilateral disease the better-seeing eye will often be the second eye involved in the disease process. If, in clinical practice, the worse-seeing eye (the first eye involved with AMD) is treated, the results shown here are probably too optimistic. Further, if the treatment is used outside the context of those with predominately classic, subfoveal CNV, the results are less valuable and should be treated with caution.

The gains predicted by the model in the base case come largely as a result of extending the time horizon beyond the trial period. This should be kept in mind when interpreting the results, and the findings should be treated with appropriate caution. This is the best available evidence on which to base the model however. The results favour treatment over a range of assumptions.

Conclusion

Earlier treatment (i.e. treating eyes at less severe stages of disease) leads to more favourable outcome estimates. Consideration should be given to early detection and treatment, particularly in the second eye to become involved.

Appendix A

Since the modeling effort described here was completed, further follow-up data has become available from the clinical trial upon which the model is based. This data suggests that those treated with PDT experience stabilization in their vision during the third year.(TAP Study Group, 2001) This three year follow-up data is not controlled, however, because the trial was designed as a two-year follow-up study. Thus the subsequent years of data do not have a placebo group comparison. Nonetheless, this added information is felt to be of importance because it extends the outcome experience of the treated group by 50% (from 2 years to 3 years).

This appendix describes a sensitivity analysis undertaken to try and understand the possible effects of this new data on our modeling results. Given that there is not similar follow-up information from the control group, using this information requires certain additional assumptions to be made. There are at least two possibilities regarding the implications of these results for the cost-effectiveness of the drug. Under one scenario, the stabilization in vision in the treated group is a result of the drug treatment, which would imply that the model we have used is too conservative with regard to the effectiveness of the treatment. Alternatively, the stabilization of vision may be due to the natural disease process in the specific cohort being treated in the trial, implying that we would have observed a similar effect if we could have followed the placebo group for the additional year, making the effectiveness results difficult to predict. To model these two possibilities, we have undertaken two sensitivity analyses. In the first sensitivity analysis, we make the assumption that the stabilization in vision is due to the effect of the drug. For this analysis (sensitivity analysis I) those in the treatment group have their visual function held constant after two years, while those in the placebo continue to experience a decrease in visual acuity as predicted by the Weibull hazard used in the model. A second sensitivity analysis has also been done where the assumption is that the stabilization in vision is part of the natural history of the disease. In this analysis (sensitivity analysis II), we hold constant the visual loss in both groups (treated and placebo) after two years. With both analyses we have extrapolated to a five year time-frame.

The results of this sensitivity analysis are shown in the table below. There are two sets of results, one for vision year gained, and one for QALY gained; both sets of results are stratified by starting visual acuity (20/40 or 20/100). Three scenarios are shown: the base case, wherein the effects for both groups are extrapolated to five years based on the two-year follow-up from the clinical trial; sensitivity analysis I, where it is assumed that the treatment group experiences no further deterioration in visual functioning after two years, and the placebo continues to lose vision at the rate predicted by the model; and sensitivity analysis II, where it is assumed that the vision in both groups stabilizes after two years.

In the vision year gained analysis, sensitivity analysis I suggests greater effectiveness for all levels of starting visual acuity. As with the main analysis the effect is even greater when the cohort has better starting visual acuity. Sensitivity analysis II shows a more mixed set of results, but they are generally lower than the base case.

Taken together, these scenarios suggest a range of effectiveness from 0.76 to 1.52 vision year gained over five years for those starting treatment at a visual acuity of 20/40, and a range of 0.64 to 1.14 vision years gained over five years for those starting treatment at a visual acuity of 20/100. The quality adjusted life year gained analysis suggests, over a 5 year period, a range of 0.15 to 0.25 QALYs gained for those with a starting visual acuity of 20/40, and 0.06 to 0.15 QALYs gained for those

starting at a visual acuity of 20/100. This analysis shows that the benefit estimates are sensitive to assumptions about the visual functioning after the end of the clinical trial period.

Analysis of the three year data suggests that at least in one case (vision years gained under sensitivity analysis II) that those starting at a worse level of visual acuity may benefit more than those with better visual acuity.

This additional analysis has made use of additional follow-up data of the treatment group from the clinical trial by undertaking a series of sensitivity analyses. These sensitivity analyses here reinforce the notion that treatment at higher visual acuity levels may yield more efficient use of resources, but perhaps not in all cases.

Appendix Table
Sensitivity Analysis Using 3 Year Data:
Vision Years Gained over a 5 year timeframe

	Base Case			Sensitivity Analysis I			Sensitivity Analysis II		
	Placebo	**Treatment**	**Difference**	**Placebo**	**Treatment**	**Difference**	**Placebo**	**Treatment**	**Difference**
Cohort with starting vision of 20/40	2.16	3.05	0.89	2.16	3.68	1.52	2.92	3.68	0.76
Cohort with starting vision of 20/100	1.22	1.86	0.64	1.22	2.36	1.14	1.52	2.36	0.84

Sensitivity Analysis Using 3 Year Data:
QALYs Gained over a 5 year timeframe

	Base Case			Sensitivity Analysis I			Sensitivity Analysis II		
	Placebo	**Treatment**	**Difference**	**Placebo**	**Treatment**	**Difference**	**Placebo**	**Treatment**	**Difference**
Cohort with starting vision of 20/40	2.21	2.4	0.19	2.21	2.46	0.25	2.31	2.46	0.15
Cohort with starting vision of 20/100	2.01	2.14	0.13	2.00	2.15	.15	2.09	2.15	0.06

Sensitivity Analysis I: Extrapolated to 5 years, VA constant after 2 years for **Treated Group**
Sensitivity Analysis II:Extrapolated to 5 years, VA constant after 2 years for **Both Groups**
Base Case is over a 5 year time frame for the indicated starting visual acuity

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