Ranibizumab for the treatment of choroidal neovascularisation associated with pathological myopia

ERRATUM

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This document contains the ERG report errata in response to the manufacturer's factual inaccuracy check.

1 SUMMARY

1.1 Scope of the submission

The manufacturer's submission from Novartis Pharmaceuticals addressed the use of ranibizumab (0.5mg) in adults presenting with visual impairment due to choroidal neovascularisation associated with pathological myopia.

1.2 Summary of clinical effectiveness evidence submitted by the manufacturer

The main clinical effectiveness evidence submitted by the manufacturer consists of a phase-three RCT sponsored by Novartis. The Novartis phase III trial consisted of a 3-month double-blind phase during which the efficacy and safety of ranibizumab was compared to those of vPDT, and a 9-month non-comparative phase which provided data on the efficacy and safety of ranibizumab only. Further evidence for the efficacy and safety of ranibizumab was provided by two RCTs designed to assess ranibizumab versus bevacizumab and 6 non-RCTs (the phase II REPAIR trial, conducted in 12 UK centres, and five case series). Further evidence of the effects of vPDT was derived from the VIP trial.

Efficacy of ranibizumab

The Novartis Phase III trial assessed ranibizumab (disease activity arm or disease stabilisation arm) versus vPDT, the only licensed treatment for this indication. For the primary outcome, mean average change from baseline (for months 1 to 3), the ranibizumab disease activity group had mean (SD) change 10.6 ([redacted]) letters, disease stabilisation, 10.5 ([redacted]) letters and vPDT, 2.2 ([redacted]) letters. These differences of ranibizumab versus vPDT were statistically significant.

The proportion of patients gaining 10 letters or more from baseline to 3 months was [redacted] for ranibizumab disease activity, [redacted] for ranibizumab disease stabilisation and [redacted]% for vPDT, with statistical significance for each of the ranibizumab arms compared to vPDT. Greater reductions in central retinal thickness were seen for the ranibizumab arms compared to vPDT. The mean (SD) number of ranibizumab injections received in the first 3 months was lower for patients treated under disease activity criteria [1.8 (0.8)] compared to disease stabilisation [2.5 (0.6)]. Improvements in BCVA were observed in both ranibizumab arms over 12 months, but no clinically relevant statistical comparisons could be made to vPDT beyond 3 months due to the switching of treatments in this group.

with pathological myopia and the development of geographic atrophy at the macula could affect long-term visual outcomes, as it has been shown to be the case in age-related macular degeneration.

1.4 Summary of cost effectiveness submitted evidence by the manufacturer

The manufacturer developed a cost utility Markov model with a quarterly cycle and a lifetime horizon. It is principally a one eye model, though some additional costs are included for bilateral disease at baseline. The distribution of the visual acuity of the treated eyes is divided into eight health states, the majority of which span a range of 10 ETDRS letters. The baseline distribution and proportions that have their baseline BSE treated are drawn from the Novartis phase III trial.

For the first cycle of the model, the transitions between the health states are drawn from the Novartis phase III trial of ranibizumab versus vPDT. For the next three cycles, the transitions between the health states are drawn from the Novartis phase III trial for ranibizumab and from the VIP trial for vPDT. Thereafter, extrapolation assumes a slow worsening of visual acuity in both arms based upon an estimate drawn from the literature. This results in the average difference in BCVA between the arms at the end of the first year being maintained over the lifetime of the modelling.

Dosing for ranibizumab of 3.5 injections in year 1 is drawn from the Novartis phase III trial and that of 1.0 injection in year 2 is drawn from manufacturer expert opinion. Dosing for vPDT of 3.4 treatments in year 1 and 1.7 treatments in year 2 is drawn from the VIP trial.[3]

Quality of life estimates for the base case are not drawn from the EQ-5D quality of life data collected during the Novartis phase III trial, but rather are drawn from the experimental lenses study of Czoski-Murray et al.[4]

Adverse events that occurred in at least five patients, and those that were suspected to be related to the study drug and/or ocular injection in the Novartis phase III trial for ranibizumab and in the VIP trial for vPDT, are included in the analysis, affecting both costs and QALYs.

Quite large costs offsets are estimated due to the costs of blindness. Costs of blindness of around £17,300 are applied to those whose BSE is modelled as falling into either HS07 or HS08. This results in ranibizumab, with the PAS, being estimated to save £2,751 and result in an additional 0.43 QALYs and so to dominate vPDT. Probabilistic modelling is broadly in line with this, and estimates that there is little to no likelihood of vPDT being cost effective,

regardless of the willingness to pay. Manufacturer sensitivity analyses suggest that results are relatively insensitive to most variables, though the price of ranibizumab and the monitoring cost might affect results at extreme values.

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

There are concerns about the differences between the Novartis phase III trial and the VIP trial from which the ranibizumab and vPDT data respectively are drawn. In particular, the higher rate of non-subfoveal involvement in the Novartis phase III trial may be to the benefit of ranibizumab.

The model structure appears to be broadly reasonable with the exception of the handling of cross-over from the better seeing eye (BSE) being treated to the worse seeing eye (WSE) as patients change health states. The impact of this may be to underestimate the patient gains and cost offsets of the more effective treatment.

EQ-5D data were collected during the Novartis phase III trial, but is not used within the submission. The EQ-5D data supplied during the clarification process did not indicate that changes in the BCVA of the WSE had any particular impact upon patients' HRQoL. In the absence of EQ-5D data from the trial to populate the economic model, instead of focussing exclusively on the Czoski-Murray et al 2009 HRQoL, it seems more reasonable to use the HRQoL derived from both Brown et al 1999 and Czoski-Murray et al 2009, as done in previous STAs.[4,5]

A number of variables within the modelling may require revision. In particular:

- The year 2 dosing for ranibizumab might be better informed by the three year open label study than by expert opinion. This appears to suggest a similar dosing frequency for ranibizumab and vPDT in year 2, much as in year 1 as drawn from the RCT trials' data.
- The calculation of the quarterly proportion worsening drawn from natural history data requires correction. This was acknowledged by the manufacturer at clarification. There is also the possibility of using data from a wider range of studies than just

- While it may be a misinterpretation on the part of the ERG, there is no obvious link between the patient level data supplied by the manufacturer at clarification and the transition probability matrices (TPMs) of the model. This applies with particular force to the ranibizumab arm. As a consequence, there is a lack of clarity about what trial data have been used to populate the model.
- The manufacturer has not used any of the EQ-5D data collected during the Novartis phase III trial. EQ-5D data supplied at clarification appears to provide little or no evidence that changes in the BCVA of the WSE have any discernible impact upon patients' quality of life. Thus, the 0.1 quality of life impact of the WSE moving from HS01 to HS08 may be an overstatement.
- The model includes cross-over from BSE to WSE and vice versa as patients change health states. While cross-over will occur to some extent, the method used seems to underestimate the net QALY gains and costs of blindness offsets that will arise from the more effective treatment.
- It seems optimistic that the average BCVA gains modelled at the end of year 1 will, roughly speaking, continue indefinitely. This has to some extent been addressed through ERG sensitivity analyses limiting the duration of this, which again reduces the estimated net savings and net QALY gains from ranibizumab when compared to vPDT but does not reverse them.
- The method used to calculate the cyclical worsening from natural history studies is unclear for most of the studies. Including all these studies again reduces the estimated net savings and net QALY gains from ranibizumab when compared to vPDT but typically does not reverse them.
- The implementation of the probabilistic modelling is peculiar in its use of multipliers. This applies with particular force to the probabilistic modelling of the TPMs. For this reason, the ERG does not have complete confidence in the probabilistic results of the model.
- The main body of the submission does not include a comparison with bevacizumab despite this was included in the NICE scope. However, a preliminary network analysis, including bevacizumab, is presented in Appendix 16 of the submission.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

Effectiveness

The ERG presented the results of the bevacizumab arms of the Gharbiya 2010 and Iacono 2012 trials[1,2]. The ERG also searched for other studies involving bevacizumab and presents a summary of the main characteristics of the identified studies in Tables 21 and 22. No further analyses of these data were undertaken by the ERG.

Cost-effectiveness

A number of ERG revisions to the manufacturer base case tend to reduce the estimated cost savings and the net patient benefits from ranibizumab over vPDT. Cost savings fall from £2,751 to £2,474 for what could be described as the revised base case. Using Brown et al 1999 as the utility source results in an estimate of a 0.344 QALY gain and a net health benefit of £9,360.[5] Using Czoski-Murray et al as the utility source results in an estimate of a 0.266 QALY gain and a net health benefit of £7,804.[4]

However, the revised base case retains a number of questionable assumptions. Most notable is that the benefits at the end of year 1 continue undiminished indefinitely. This seems likely to be optimistic. Revising this to 5 years duration of gain with equalisation of BCVAs between the arms thereafter causes the net savings, QALYs and net health benefits to fall to £1,866, 0.143 QALYs and £4,725, respectively, using Brown et al 1999.[5] The corresponding figures using Czoski-Murray et al are £1,866, 0.065 and £3,169, respectively.[4]

The revised base case also does not include the impact of all the natural history studies. Doing so reduces the cost savings to £2,029, and the net gain to 0.189 QALYs and net health benefits to £5,810 using Brown et al 1999[5] and to 0.119 QALYs and £4,415 using Czoski-Murray et al.[4]

Applying both a 5-year duration of benefits and all the natural history studies reduces the net savings to only £1,963. Using Brown et al 1999 as the utility source results in an estimate of a 0.065 QALY gain, and a net health benefit of £3,257[5]. Using Czoski-Murray et al as the utility source results in an estimate of a 0.005 QALY loss and a net health benefit of £1,862.[4] Given the QALY loss for this scenario the ICER for vPDT compared to ranibizumab is £391k per QALY, which remains well outside usual cost effectiveness thresholds.

Despite all the above, it appears that ranibizumab is cost effective and, in all probability, cost saving compared with vPDT. The apparently perverse results from some of the ERG

Ranibizumab (Lucentis, Novartis UK), like bevacizumab, inhibits the action of VEGF, thereby leading to the regression of the CNV. Both bevacizumab and ranibizumab are administered as injections into the vitreous cavity (the space in the centre of the eye), so called "intravitreal injections".

Ranibizumab was granted a UK marketing authorisation for the treatment of myopic CNV on 4th July 2013. It had already a UK marketing authorisation for the treatment of wet age-related macular degeneration, visual impairment due to diabetic macular oedema and visual impairment due to macular oedema secondary to retinal vein occlusion.[26] Ranibizumab has been studied in clinical trials of people with visual impairment due to CNV associated with PM, as a monotherapy compared with bevacizumab and with vPDT.

A recent systematic review showed superiority of anti-VEGF treatments over PDT with higher improvements in best corrected visual acuity (BCVA) at 12 and 24 months in patients treated with anti-VEGF therapies [23]. In addition, similar performance of ranibizumab and bevacizumab in improving BCVA at up to 18 months follow up has been reported .[27] As a result, anti-VEGF has been recommended as first line treatment for CNV secondary to PM.[23,28]

2.1 Critique of manufacturer's description of underlying health problem

On the whole, the manufacturer's description of CNV associated with PM in terms of prevalence, symptoms and complications was found to be accurate.

2.2 Critique of manufacturer's overview of current service provision

The manufacturer points out that there are currently no guidelines or treatment algorithms for CNV associated with PM. Treatment practice varies between clinical centres in the UK and there is no preferred treatment. Verteporfin photodynamic therapy (vPDT) is the only licensed treatment for this indication. However, its use in clinical practice is marginal due to the fact that the VIP trial has not demonstrated differences between vPDT and placebo with regard to the proportion of people losing > 8 ETDRS letters at 24 months. Rather than vPDT, some clinical centres in the NHS opt for the use of bevacizumab off-license for the treatment of myopic CNV. This is implicitly acknowledged by the manufacturer who states in the current submission that: "*the use of unlicensed bevacizumab is not considered as established practice across the NHS*". In contrast to the final NICE scope, the current submission did not include bevacizumab as a comparator to ranibizumab.

3 DEFINITION OF THE DECISION PROBLEM

3.1 Population

The manufacturer's submission states that ranibizumab (Lucentis) is indicated for adults with visual impairment due to choroidal neovascularization (CNV) associated with pathological myopia (PM). This population is in line with the scope for this STA and the licensed indication for ranibizumab. There is no current indication for ranibizumab in children and adolescents below 18 years of age.

3.2 Intervention

Ranibizumab is a humanised monoclonal antibody fragment produced in Escherichia coli cells by recombinant DNA technology. Ranibizumab is targeted against human vascular endothelial growth factor A (VEGF-A). Binding of VEGF-A to its receptors leads to endothelial cell proliferation and neovascularisation, as well as vascular leakage, all of which are thought to contribute to the pathophysiology of CNV secondary to PM. This is supported by the observation that eyes with active CNV secondary to PM have higher levels of VEGF in the aqueous humour than control eyes.[29] Ranibizumab binds with high affinity to the VEGF-A isoforms thereby preventing binding of VEGF-A to its receptors.

Ranibizumab is formulated as a solution for intravitreal treatment and is administrated with a single 0.5mg injection. Once the disease is controlled following treatment, patients are monitored and if activity of the disease is still observed on follow up (e.g. reduced visual acuity and/or signs of active CNV such as blood or fluid), further treatment is recommended. Monitoring for disease activity may include clinical examination, optical coherence tomography (OCT) and/or fundus fluorescein angiography (FFA).

While many patients may only need one or two injections during the first year, some patients may require more frequent treatment. The summary of product characteristics states that monitoring is recommended monthly for the first two months and at least every three months thereafter during the first year. After the first year, the frequency of monitoring should be determined by the treating physician. The interval between two doses should not be shorter than one month. Treatment duration depends on patient's response to treatment.

Ranibizumab was granted a UK marketing authorisation for visual impairment due to CNV secondary to PM on 4 July 2013.

Ranibizumab has regulatory approval in Europe and the USA for the treatment of neovascular (wet) age-related macular degeneration and visual impairment due to diabetic macular oedema and macular oedema secondary to retinal vein occlusion.[26]

3.3 Comparators

The NICE scope for this STA states that bevacizumab and vPDT should both be considered as relevant comparators for ranibizumab. The manufacturer's submission differs from the scope in that only vPDT was considered as a comparator.

In their submission, the manufacturer provided an argument against bevacizumab being used as a comparator in this appraisal. They argued that, as bevacizumab has not yet been granted market authorization for use in CNV associated with PM, its unlicensed use cannot be considered as established practice across the NHS and it should not be administered when a licensed alternative is available.

It is worth noting that even if vPDT is currently the only licensed treatment for myopic CNV, it is rarely used in clinical practice in the UK because its long term benefits have not been demonstrated (the VIP trial showed that, at 24 months, 36% patients in the verteporfin-treated group compared with 51% patients in the placebo-treated group (P= 0.11) lost at least 8 letters of visual acuity; approximate Snellen equivalent loss, at least 1.5 lines).[30]

The ERG are of the opinion that bevacizumab should have been included as a relevant comparator for this assessment as it is used for the treatment of CNV secondary to pathological myopia in the NHS.

3.4 Outcomes

The outcomes considered by the manufacturer were best corrected visual acuity (BCVA) in the study eye, adverse effects of treatment and health related quality of life (HRQoL). The manufacturer did not consider i) BCVA of both eyes and ii) contrast sensitivity, which were both included in the NICE final scope for this assessment. In the submission, the manufacturer explained that the effects on BCVA were only considered for the affected eye because there was insufficient information regarding the effects of vPDT on both eyes. They did not assess contrast sensitivity as they maintained that the impact of visual impairment on HRQoL was likely to be related to the treatment effects on BCVA. Moreover, they pointed

[redacted]

Gain of letters

A secondary outcome was the proportion of patients gaining two lines or more (≥10 letters) or three lines or more (≥15 letters) from baseline to 3, 6 or 12 months (Table 8). As for the primary outcome, the manufacturer initially did not present data for the vPDT group after three months, but did so following the ERG request during the clarification process. [redacted]

Table 8 Proportion of patients gaining ≥ 10 or ≥ 15 letters from baseline at 3, 6 and 12 months during treatment with ranibizumab or vPDT

	Ranibizumab disease activity, n = 116	**Ranibizumab disease stabilisation, n = 105**	**vPDT, n = 55**
Patients gaining ≥ 10 letters, n (%)			
At 3 months	[redacted]	[redacted]	[redacted]
OR (95% CI), versus vPDT	[redacted]	[redacted]	[redacted]
RR (95% CI), versus vPDT	[redacted]	[redacted]	[redacted]
At 6 months	[redacted]	[redacted]	[redacted]
At 12 months	[redacted] (69.0)	[redacted] (69.5)	[redacted]
Patients gaining ≥ 15 letters, n (%)			
At 3 months	[redacted]	[redacted]	[redacted]
OR (95% CI), versus vPDT	[redacted]	[redacted]	[redacted]
RR (95% CI), versus vPDT	[redacted]	[redacted]	[redacted]
At 6 months	[redacted]	[redacted]	-
At 12 months	[redacted] (51.7)	[redacted] (53.3)	-

CI, confidence interval; NA, not applicable; OR, odds ratio; RR, risk ratio; vPDT, verteporfin photodynamic therapy; [a] provided to the ERG after clarification. *p < 0.05; ***p < 0.001 vs vPDT

Change from baseline in central retinal thickness (CRT)

[redacted]

Table 9 Change from baseline in central retinal thickness during treatment with ranibizumab or vPDT

	Ranibizumab disease activity, n = 116	**Ranibizumab disease stabilisation, n = 105**	**vPDT, n = 55**
Change from baseline in CRT (µm) mean (SD)			
0-3 months	[redacted]	[redacted]	[redacted]
0-6 months	[redacted]	[redacted]	[redacted]
0-12 months	[redacted]	[redacted]	[redacted]
[a] obtained after clarification; *** p<0.0001 versus vPDT			

[redacted]

5.2 Summary and critique of manufacturer's submitted economic evaluation by the ERG

Table 23 NICE reference case checklist

Attribute	Reference case and TA Methods guidance	Does the *de novo* economic evaluation match the reference case?
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice	The scope specifies vPDT and bevacizumab as comparators. The submission focuses upon the comparison with vPDT. Bevacizumab is not considered within the main body of the submission[1].
Patient group	As per NICE scope. Adult patients with visual impairment due to CNV secondary to pathological myopia.	Yes.
Perspective costs	NHS & Personal Social Services	Yes.
Perspective benefits	All health effects on individuals	Yes.
Form of economic evaluation	Cost-effectiveness analysis	Yes.
Time horizon	Sufficient to capture differences in costs and outcomes	Yes.
Synthesis of evidence on outcomes	Systematic review	The base case modelling comparing ranibizumab with vPDT uses data from the phase III trial and the VIP trial[2].
Outcome measure	Quality adjusted life years	Yes.

[1] The manufacturer presents some cost effectiveness results comparing ranibizumab with bevacizumab in Appendix 16 of the submission. The assumptions and inputs underlying these estimates are not presented. But in response to the ERG clarification question B22 the manufacturer highlights that "*bevacizumab has not been considered as a comparator to ranibizumab in this single technology appraisal*" and states various methodological weaknesses related to the Gharbiya 2010 and Lacono 2012 papers, which underlie the manufacturer estimates reported in Appendix 16. Appendix 2 of this report summarises the results presented in Appendix 16 of the manufacturer submission.

[2] Appendix 16 of the submission has undertaken a review of the literature and an indirect treatment comparison (ITC). The comparisons of ranibizumab with bevacizumab and of ranibizumab with observation of Appendix 16 appear to rely upon the results of the manufacturer ITC.

Attribute	Reference case and TA Methods guidance	Does the *de novo* economic evaluation match the reference case
Probabilistic modelling	Probabilistic modelling	Probabilistic modelling is presented within the submission. There may be some problems with the distributions that are placed upon some parameters, and in particular with the probabilistic approach adopted for the transition probability matrices (TPMs).
Sensitivity analysis		A range of sensitivity analyses are presented.

Model structure

The manufacturer developed a cost utility Markov model. The model adopts a quarterly cycle and a lifetime horizon. It is principally a one eye model, though some additional costs are included for the rate of bilateral disease at baseline with these costs being spread over the 24 months treatment period.

The distribution of the visual acuity of the treated eyes is divided into eight health states, the majority of which span a range of 10 ETDRS letters. The baseline distribution and the proportions of patients who have their baseline BSE treated are drawn from the trial (Table 24).

Table 24 BCVA health states for treated eye, baseline distribution and baseline proportions as BSE

Health state	BCVA	Distribution	% BSE
HS01	86-100	[redacted]	[redacted]
HS02	76-85	[redacted]	[redacted]
HS03	66-75	[redacted]	[redacted]
HS04	56-65	[redacted]	[redacted]
HS05	46-55	[redacted]	[redacted]
HS06	36-45	[redacted]	[redacted]
HS07	26-35	[redacted]	[redacted]
HS08	<25	[redacted]	[redacted]

For the first cycle of the model, the transitions between the health states for both ranibizumab and vPDT are drawn from the Novartis phase III trial. For the next three cycles, the transitions between

the health states are drawn from the Novartis phase III trial for ranibizumab and from the VIP trial for vPDT[3].

Thereafter, extrapolation assumes a slow worsening of visual acuity in both arms based upon an estimate drawn from the literature. This results in the average difference in BCVA between the arms at the end of the first year being maintained over the lifetime of the modelling.

Dosing for ranibizumab of 3.5 injections in year 1 is drawn from the Novartis phase III trial, and 1.0 injection in year 2 is drawn from manufacturer expert opinion. Dosing for vPDT of 3.4 treatments in year 1 and 1.7 treatments in year 2 is drawn from the VIP trial.

Quality of life estimates for the base case are not drawn from the quality of life data collected during the Novartis phase III trial, but instead are drawn from the study by Czoski-Murray et al on experimental lenses.[4]

There is a bilateral involvement of 15% at baseline and an annual recurrence of treatment of 6% after year 2. These affect costs but not QALYs.

Adverse events that occurred in at least five patients, and those that were suspected to be related to the study drug and/or ocular injection in the Novartis phase III trial for ranibizumab and in the VIP trial for vPDT, are included in the analysis and they affect both costs and QALYs.

Quite large costs offsets are estimated due to the costs of blindness. Costs of blindness of around £17,300 are applied to those whose BSE is modelled as falling into either HS07 or HS08.

Population

The population are adults with visual impairment due to CNV secondary to pathological myopia as reflected in the Novartis phase III trial and the VIP trial.

Most patient characteristics appear to be broadly in line between the two trials. But note that the proportion of patients with non-subfoveal involvement in the ranibizumab arm of the Novartis phase III trial may be higher than in the vPDT arm of the VIP trial.

Interventions and comparators

The main body of the submission compares ranibizumab disease activity dosing with vPDT.

myopia. As a consequence, the 5.5% incidence estimate for the annual incidence of bilateral disease may not really be applicable to the current modelling. Nevertheless, it does illustrate that there will be some ongoing incidence of bilateral disease.

Recurrence

Recurrence only affects costs within the modelling. Based upon manufacturer expert opinion, it is assumed to occur among 6% of patients each year subsequent to the first two years of the modelling.

Adverse events

Adverse events affect both costs and quality of life within the modelling. Their rates are drawn from the Novartis phase III trial for ranibizumab and the VIP trial for vPDT. It is not clear from the submission whether only the 1st year rates or the entire VIP trial rates are used for vPDT. Only adverse events that occurred in at least 5 patients (i.e. 4% to 6% of the trial patients) and were suspected of being related to the study drug were included within the modelling. Therefore, adverse events such as retinal tears were not included. The manufacturer notes that:

[redacted]" The possibility of ranibizumab accelerating atrophy is also not considered in the submission due to the fact that atrophy was not evaluated during the Novartis phase III trial.

The impacts of adverse events are modelled as one offs, and, as a consequence, treatment for recurrence and bilateral disease are assumed to not have any adverse event.

Table 25 Adverse event rates

	Ranibizumab	vPDT
Conjunct. haemorrhage	8.50%	[redacted]
IOP increased	4.20%	[redacted]
Visual Disturbance	0.00%	[redacted]
Injection site AEs	0.00%	[redacted]

Cross-over from BSE to WSE and from WSE to BSE

Within the model, as the BCVA of the treated eye changes, the likelihood of the treated eye being the BSE also changes. For instance, among patients whose treated eye at baseline was in HS05 with a

BCVA of between 46 letters and 55 letters, [redacted] are modelled as having their BSE treated and [redacted] are modelled as having their WSE treated.

However, suppose that a proportion of these patients are modelled as declining to, say, HS06 with a BCVA of 36 letters to 45 letters. Only [redacted] of these patients are modelled as having their BSE treated. In effect, the deterioration in the BCVA, causes the treated eye to cross-over to become the WSE for a

year 2 based upon manufacturer expert opinion, while the estimate of 1.7 vPDT treatments for year 2 is drawn from the VIP trial.

The direct drug costs are [redacted] for ranibizumab, including the PAS, and £850.00 for vPDT.

Table 30 Injection and monitoring visits

	Year 1		Year 2		Year 3	
Visit type	**Treatment**	**Monitoring**	**Treatment**	**Monitoring**	**Treatment**	**Monitoring**
Ranibizumab	3.5	8.5	1.0	4.0	0.0	0.0
vPDT	3.4	4.0	1.7	4.0	0.0	0.0

Treatment visits for ranibizumab are costed at £117.26, based upon the NHS reference cost for the OP procedure BZ23Z vitreous retinal procedures category 1, while treatment visits for vPDT are costed at £123.62 based upon the NHS reference cost for a consultant led outpatient appointment. Monitoring visits add a cost of OCT of £51.27 based upon the NHS reference cost RA23Z outpatient diagnostic procedure cost for an ultrasound scan of less than 20 minutes to the cost of a consultant led outpatient appointment to arrive at a total cost of £174.89.

Adverse event costs

The unit costs for the adverse events are drawn from the literature for conjunctival haemorrhage, a weighted average of drug costs for raised IOP, zero by assumption for visual disturbance and £100 by assumption for injection site AEs. This results in the following.

Table 31 Adverse event costs

		Ranibizumab		vPDT	
	Cost	**%**	**Average**	**%**	**Average**
Conjunct. haemorrhage	£1,234.31	8.50%	£104.92	[redacted]	
IOP increased	£31.67	4.20%	£1.33	[redacted]	
Visual Disturbance	£0.00	0.00%		[redacted]	[redacted]
Injection site AEs	£100.00	0.00%		[redacted]	[redacted]
Total Cost			£106.25		[redacted]

For most of the variables, the ranges that are applied are probably wider than those one would apply in reality. However, despite these wide ranges the net health benefit from ranibizumab relative to vPDT remains positive. This applies even when the cost of vPDT is set to zero. The exceptions to this are the upper values for the cost of a monitoring visit and the cost of ranibizumab, though setting these at £1,500 and £3,000 is of questionable relevance. The submission further notes that ranibizumab remains cost effective up to a monitoring cost of £1,425. Ranibizumab is also estimated to be cost effective up to a cost of around £1,850.

It is difficult to know how to interpret the multipliers for the transition probabilities. The multiplier appears to be applied to all the probabilities within the TPM with the exception of those on the principal diagonal (i.e. to all probabilities except the probabilities of remaining in the same state). As this causes the probabilities of each column of the TPM to no longer sum to 100%, all the probabilities within each column are divided by the sum of that column to make them sum to 100%.

Some elements of the model are also not explored, such as the assumed lifetime duration of benefit, though baseline age woul, to some extent, proxy for this.

Scenario analyses pooling patient level data

In the light of some transitions being populated with small patient numbers, the manufacturer also presents two scenario analyses use alternative calculations for the transitions.

- Scenario 2: Calculating the transitions for the top two health states based upon the patient level data, but pooling the patient level data for the other health states with the additional assumption that patients could only gain or lose between two and four lines between cycles. This scenario is undertaken to try to avoid the possible ceiling effects that the top two health states might impose upon the analysis of scenario 3 outlined below.
- Scenario 3: Pooling the patient level data with the additional assumption that patients could only gain or lose between two and four lines between cycles.

The more usual approach for a pooled analysis would be for the likelihoods of gains and losses in the ranibizumab arm to have been conditioned by the relative risks of these for vPDT. These relative risks could have been drawn from the Novartis phase III trial for the first 3 months, and from the indirect comparison with the VIP trial thereafter.

The scenario analyses results in an estimated 0.43 QALY gain and a £4,078 cost saving for scenario 2, and in an estimated 0.42 QALY gain and £4,032 cost saving for scenario 3: roughly the same QALY gain but somewhat larger cost savings compared to the base case. The intuition underlying this is not clear.

Model validation and face validity check

The modelled BCVA of the treated eye over the first 12 months of the model can be compared with the results of the trial for both ranibizumab and vPDT at month 3, and for ranibizumab at month 6 and month 12.

Table 35 Model validation against trial data

	Ranibizumab			vPDT		
	Model		Trial	Model		Trial
	BCVA	change	change	BCVA	change	change
Baseline	55.6			55.6		
Month 3	67.6	12.0	12.5	55.0	-0.7	1.4
Month 6	67.6	12.0	12.7	55.3	-0.4	
Month 12	69.8	14.2	14.4	56.8	1.1	

There appears to be good correspondence between the model and the trial results for the ranibizumab arm as reported in Table 2 of the manufacturer's response to the ERG clarification question A2, but there is a slight discrepancy by month 3 for the vPDT arm. The 1.1 letter gain at month 12 for the vPDT arm is in line with Figure 21 on page 195 of the submission.

Adjusted for covariates, the direct effects modelling gave hazard ratios of 1.28 for severe visual impairment and 1.13 for some visual impairment. Inclusion of the indirect effects gave hazard ratios of 1.54 for severe visual impairment and 1.23 for some visual impairment. The manufacturer applies the 1.54 and 1.23 from the model that incorporates indirect effects.

The number of non-ocular health comorbidities was included as a covariate within the modelling, defined as none, one or more than one. Whether this is sufficient to take into account the range of comorbidities is questionable. For instance, diabetics will tend to have a worse BCVA than the national average and will also tend to have a higher mortality. However, it is likely that for these patients it is the diabetes that is causing the raised mortality rather than any direct vision related mortality effect.

The discussion section of Christ et al[114] also notes that running the model for the subset of respondents with data on smoking status reduced the hazard ratio of 1.54 for severe visual impairment to 1.48 and reduced the hazard ratio of 1.23 for some visual impairment to 1.16. It is unclear why Christ et al do not prefer these estimates to the estimates that do not control for smoking.

Given the definitions for severe visual impairment and some visual impairment of Christ et al[114] and assuming that the SEM model is the most appropriate, it could be argued that an alternative set of mortality multipliers could be applied, as shown in Table 39.

Table 39 Christ et al mortality hazard ratios by BCVA: model and alternative interpretation

	Model		1st alternative		2nd alternative		3rd alternative	
	BSE	**BSE**	**BSE**	**WSE**	**BSE**	**WSE**	**BSE**	**WSE**
HS01	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
HS02	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
HS03	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
HS04	1.00	1.00	1.00	1.00	1.00	1.23	1.00	1.00
HS05	1.23	1.00	1.00	1.00	1.00	1.23	1.00	1.00
HS06	1.23	1.00	1.00	1.00	1.00	1.23	1.00	1.00
HS07	1.54	1.54	1.54	1.23	1.54	1.23	1.54	1.00
HS08	1.54	1.54	1.54	1.23	1.54	1.23	1.54	1.00

Applying the 1st alternative interpretation of the results of Christ et al[114] as above decreases the gain from ranibizumab from the 0.432 QALYs of the base case to 0.400 QALYs. However, it causes the net cost savings to rise slightly from £2,751 to £2,765, presumably for the reasons already alluded to

Given the worse prognosis for patients with subfoveal CNV, the analysis may be biased in favour of ranibizumab. It is impossible for the ERG to quantify the degree of such a bias. A possible approach, given the manufacturer's access to patient level data from both trials, would be the use of data from the subfoveal subgroup only. This would, however, further reduce the relatively low patient numbers for vPDT derived from the Novartis phase III trial for months 0 to 3 (from 56 patients to 38 patients). An alternative approach might be to replicate non-subfoveal patients in the vPDT data in order to arrive at the same balance between subfoveal and non-subfoveal CNV as in the ranibizumab data.

Ranibizumab dosing

The base case draws ranibizumab dosing data for year 1 from the Novartis phase III trial, suggesting 3.5 doses. Expert opinion is then used to derive estimates of only one additional dose in year 2, and none thereafter.

Franqueira et al[92] report the results of a three-year retrospective, non-randomised study of 40 eyes of 39 patients with pathological myopic CNV. Fifteen eyes had previous photodynamic therapy, while the remainders were naïve to treatment. The mean number of injections was 4.1 in year 1, 2.4 in year 2 and 1.1 in year 3. In year 3, 53% of eyes had no requirement for further treatment. 25% of patients gained at least 3 lines at 12 months, 30% at 42 months and 35% at 36 months. The 25% of patients gaining at least 3 lines at 12 months is somewhat less than the [redacted] of the Novartis phase III trial, which might have implications for the dosing frequencies reported by Franqueira et al.[92] Nevertheless, the 4.1 injections and 3.5 injections for year 1 are broadly in line, and suggest that the assumption of only 1 injection being required in year 2 and none in year 3 may be optimistic. A crude adjustment of the Franqueira et al data by 3.5/4.1 could be seen as suggesting 1.7 injections in year 2 and 0.8 injections in year 3.[92] This would bring the number of ranibizumab treatments in year 2 into line with the number of vPDT treatments.

both arms. Of more concern are the 3 empty columns within the vPDT arm for months 3 to 6, these relating to HS01, HS07 and HS08.

While a slightly arbitrary classification, the number of cells populated by a single patient gives some indication of how uncertain the overall probabilities are within the TPM. For these cells, it would only have taken one patient to be reclassified for the relevant transition probability to fall to zero or to double. Subsequent to month 3, the number of cells populated by a single patient is quite a large proportion of the total number of cells that are populated, in some case half of all the populated cells. This may question the reliability of the approach for the base case modelling and whether the patient numbers within the trials provide sufficient patient level data to be able to sensibly populate a model with 8 health states and the resulting 64 cell TPMs.

The probabilistic modelling

The approach adopted for making the TPMs probabilistic within the probabilistic modelling is questionable. This draws a separate multiplier for each TPM from a lognormal distribution of mean ln(1) and standard deviation 0.1. This multiplier is then applied to all the probabilities within the TPM with the exception of those on the principal diagonal (i.e. to all probabilities except the probabilities of remaining in the same state). As this causes the probabilities of each column of the TPM to no longer sum to 100%, all the probabilities within each column are divided by the sum of that column to make them sum to 100%. The ERG is not familiar with this method and no reference is given for it. The standard approach would be to employ dirichlet sampling, or possibly a nested beta.

The number of "holes" within the TPMs could also argue for applying an uninformed prior to the TPMs within the probabilistic modelling as a scenario analysis as a minimum, if not for the base case.

Note that other parameters within the probabilistic model also simply have a random multiplier to them. For instance, the multiplier for the utilities of the BSE is randomly drawn from a normal distribution with a mean 1.0 of and standard deviation of 0.05. The number of treatment visits each have a multiplier drawn from a gamma distribution with a mean 1.0 of and standard deviation of 0.05.

5.4 Exploratory and sensitivity analyses undertaken by the ERG

In the light of the above the ERG has amended the manufacturer model as follows:

- Applied 1.7 doses for ranibizumab in year 2[3].

[3] Implemented within the *Cost_Inputs* worksheet by setting cell F30=1.7

- Applied a 1.48 blindness mortality multiplier for when the BSE is in HS07 or HS08[4].
- Applied £7,510 for the cost of blindness in the incident year and £7,429 thereafter[5].
- Correction to the calculation of natural history quarterly worsening as per the manufacturer response to ERG clarification question B17[6].
- Correcting the calculation of the adverse events impacts upon quality of life[7].

The impact of these changes is assessed for the ERG utility values[8], with both Brown 1999 and Csozki-Murray 2009 being explored.[4,5]

Sensitivity analyses are undertaken around the assumed duration of benefit, the proportion of eyes that are BSEs[9], including all the natural history studies rather than just Yoshida et al, and applying a one stop model for monitoring and dosing.

Table 51 Revised base case: Brown 1999 utility values

	Ranibizumab	vPDT	Incremental
Total costs	£10,055	£12,529	-£2,474
Total QALYs	14.514	14.170	0.344
Life years (undiscounted)	27.344	27.287	0.058
Life years (discounted)	16.861	16.835	0.025
Incremental cost per QALY			Dominant
Incremental cost per life year			Dominant
Net benefit at WTP £20k/QALY			£9,360

Table 52 Revised base case: Czoski-Murray 2009 utility values

	Ranibizumab	vPDT	Incremental
Total costs	£10,055	£12,529	-£2,474
Total QALYs	13.105	12.838	0.266
Life years (undiscounted)	27.344	27.287	0.058
Life years (discounted)	16.861	16.835	0.025
Incremental cost per QALY			Dominant
Incremental cost per life year			Dominant
Net benefit at WTP £20k/QALY			£7,804

[4] Implemented within the *Mortality* worksheet cells H11:I18
[5] Implemented within the *Resource_Use* worksheet cells D19:D20
[6] Implemented within the *Natural_history* worksheet cells H25:H31
[7] Implemented within the *Tx_QALYs* worksheet and the *Comp_QALYs* worksheet by not dividing cell O11 by the cohort size
[8] Implemented within the *QoL* worksheet cells D86:K86 and D89:K89
[9] Implemented within the *Inputs_(2)* worksheet by setting cells D24:D31 to all be 0% or to all be 100%.

The ERG revisions reduce the net savings, the net patient benefits and the net health benefits at a willingness to pay of £20,000 per QALY. Nevertheless, ranibizumab is still estimated to result in cost savings and patient benefits and so to dominate vPDT.

Table 53 Sensitivity analyses: Brown 1999 utility values

	Δ cost	Δ QALY	NHB
Base case	-£2,474	0.344	£9,360
Duration of benefit			
1 year	-£1,795	0.078	£3,362
5 years (a)	-£1,866	0.143	£4,725
10 years	-£2,045	0.209	£6,218
20 years	-£2,363	0.296	£8,278
Proportion BSE			
0%	-£1,769	0.282	£7,401
100%	-£20,272	1.260	£45,473
All natural history studies (b)	-£2,029	0.189	£5,810
(a) and (b) together	-£1,963	0.065	£3,257
1 stop treatment	-£2,493	0.344	£9,380

Table 54 Sensitivity analyses: Czoski-Murray 2009 utility values

	Δ cost	Δ QALY	NHB
Base case	-£2,474	0.266	£7,804
Duration of benefit			
1 year	-£1,795	0.001	£1,806
5 years (a)	-£1,866	0.065	£3,169
10 years	-£2,045	0.131	£4,661
20 years	-£2,363	0.218	£6,722
Proportion BSE			
0%	-£1,769	0.282	£7,400
100%	-£20,272	1.478	£49,840
All natural history studies (b)	-£2,029	0.119	£4,415
(a) and (b) together	-£1,963	-0.005	£1,862
1 stop treatment	-£2,493	0.266	£7,823

The assumed duration of benefit is clearly one of the key parameters of the modelling. The assumption that the average benefit of treatment at 1 year will continue indefinitely may be optimistic. For both the Brown utility values[5] and the Czoski-Murray utility values,[4] the sensitivity analyses around the proportion whose BSE is treated result in net health benefits that are only slightly worse

than for the base case if all are assumed to be WSEs and that are very much higher if all are assumed to be BSEs. The net health benefits of the latter may be too high, in that it assumes that there is no cross over once the treated eye falls into blindness. However, in the opinion of the ERG, this illustrates the problem with the implementation of cross over within the model and its impact upon the QALY calculation. This is underlined by the Brown 1999 utilities resulting in a higher net health benefit than the Czoski-Murray utilities, the reverse of the usual. This is with the exception of the sensitivity analysis that sets the BSE proportion to 100% which is as would be expected.

Including all the natural history studies identified by the manufacturer has quite a sizeable impact upon both the net costs and the net benefits, reducing the net health benefits to between 55% and 65% of those of the revised base case. This underlines the importance of understanding how the manufacturer has derived the estimates from the natural history studies.

The scenario of 5 years duration of benefits coupled with the inclusion of all the natural history studies considerable reduces the anticipated QALY gains, to the extent that a small loss is anticipated when using Czoski-Murray et al as the utilities source.[4] However, the latter may highlight possible problems around the calculation of utilities and cross over as summarised in section 5.3 above.

5.5 Conclusions of the cost effectiveness section

The model structure appears broadly reasonable with the possible exception of the treatment of cross over. The latter may have underestimated both the patient benefits and possible cost savings of ranibizumab compared with vPDT.

The patient level data supplied at clarification does not appear to tally with the transition probability matrices of the model. While this may be a misinterpretation on the part of the ERG, it is of concern and raises questions about what data has been used to populate the model.

For the comparison with vPDT two potential sources of bias are:

- The differing proportions of non-subfoveal involvement in the ranibizumab arm of the Novartis phase III trial and the vPDT arm of the VIP trial.
- The assumption of a lifetime of benefit with the average net gain in BCVA at the end of year 1 being maintained for the patient lifetime.

EQ-5D data from the Novartis phase III trial were not used in the cost-effectiveness section of the submission but were supplied to the ERG during the clarification process. These data suggest that

6 IMPACT ON THE ICER OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

As outlined in greater details in section 5.4 above, a number of ERG revisions to the manufacturer base case tend to reduce the estimated cost savings and the net patient benefits from ranibizumab over vPDT. Cost savings fall from £2,751 to £2,747 for what could be described as the revised base case. Using Brown et al[5] as the utility source results in an estimate of a 0.344 QALY gain, and a net health benefit of £9,360. Using Czoski-Murray et al[4] as the utility source results in an estimate of a 0.266 QALY gain and a net health benefit of £7,804.

However, the revised base case retains a number of questionable assumptions. Most notable is that the benefits at the end of year 1 continue undiminished indefinitely. This seems likely to be optimistic. Revising this to 5 years duration of gain with equalisation of BCVAs between the arms thereafter causes the net savings, QALYs and net health benefits to fall to £1,866, 0.143 QALYs and £4,725 respectively using Brown et al 1999.[5] The corresponding figures using Czoski-Murray et al are £1,866, 0.065 and £3,169[4].

The revised base case also does not include the impact of including all the natural history studies. Doing so reduces the cost savings to £2,029, and the net gains to 0.189 QALYs and the net health benefits to £5,810 using Brown et al[5] and to 0.119 QALYs and £4,415 using Czoski-Murray et al.[4]

Applying both a 5-year duration of benefits and all the natural history studies reduces the net savings to only £1,963. Using Brown et al[5] as the utility source results in an estimate of a 0.065 QALY gain, and a net health benefit of £3,257. Using Czoski-Murray et al[4] as the utility source results in an estimate of a 0.005 QALY *loss* and a net health benefit of £1,862. Given the QALY loss for this scenario the ICER for vPDT compared to ranibizumab is £391k per QALY, which remains well outside usual cost effectiveness thresholds.

It is likely that the method used for the calculation of the net QALY gain underestimates the patient benefits of the more effective treatment. It also seems likely that this is the source of the 0.005 QALY loss for the 5 year duration of benefits, inclusion of all the natural history studies and use of Czoski-Murray et al[4] utilities outlined above. The method used for the calculation of the costs of blindness may also tend to underestimate the cost savings which might accrue.

There are concerns about the differences between the Novartis phase III trial, from which the data for ranibizumab are derived, and the VIP trial, from which the majority of the data for vPDT are derived.

- The implementation of the probabilistic modelling is peculiar in its use of multipliers. This applies with particular force to the probabilistic modelling of the TPMs. For this reason, the ERG does not have complete confidence in the probabilistic results of the model.
- The main body of the submission does not include a comparison with bevacizumab despite the indication of the NICE scope. Nevertheless, a network meta-analysis, including bevacizumab, is presented in Appendix 16 of the submission.

Despite all the above comments, it appears that ranibizumab is cost effective and in all probability cost saving compared with vPDT. The apparently perverse results from some of the ERG sensitivity analyses are likely to be a consequence of the model structure, and in particular of its treatment of cross-over of the best and worse seeing eyes.

7.1 Implications for research

Future well-designed randomised trials assessing patients with myopic CNV should:

i) Evaluate visual acuity in both eyes and its relation with scores achieved on generic health status as well as vision specific patient reported measures;

ii) Assess main outcomes at longer term (1 and 2 years);

iii) Assess presence of geographic atrophy among possible adverse events of the anti-VEGF therapy.

It would be useful to assess 0.5mg ranibizumab versus 1.25mg bevacizumab in large head to head well-designed randomised trials, with particular attention to cost-effectiveness and adverse events.

Appendix 2 Appendix 16 of the manufacturer's submission: comparison with bevacizumab

Deterministic results

The deterministic results of Appendix 16 of the submission include pairwise comparisons with vPDT, observation, and bevacizumab. The manufacturer maintains that '*these results were attached as a mean of demonstrating any early discussions around modelling assumptions only'*." There is no detail provided of the inputs and assumptions underlying the results presented in Appendix 16.

Table 55 Deterministic results: ranibizumab vs vPDT

	Section 7.7.6			**Appendix 16**		
	Ranibizumab	**vPDT**	**net**	**Ranibizumab**	**vPDT**	**net**
Costs						
Treatment	£1,939	£4,177	-£2,238	[redacted]	[redacted]	[redacted]
Admin	£734	£860	-£126	[redacted]	[redacted]	[redacted]
Monitor	£2,108	£1,340	£768	[redacted]	[redacted]	[redacted]
Bilateral	£717	£957	-£240	[redacted]	[redacted]	[redacted]
Recurrence	£3,258	£3,724	-£466	[redacted]	[redacted]	[redacted]
AEs	£106	£10	£96	[redacted]	[redacted]	[redacted]
Blindness	£830	£1,377	-£547	[redacted]	[redacted]	[redacted]
Total	£9,694	£12,445	-£2,751	[redacted]	[redacted]	[redacted]
Life years (undisc.)	27.34	27.07	0.27	[redacted]	[redacted]	[redacted]
QALYs	13.18	12.75	0.43	[redacted]	[redacted]	[redacted]
ICER	Dominant	Dominated	..	[redacted]	[redacted]	[redacted]

The similarity of the initial treatment and administration costs suggests that the same dosing and monitoring schedules are assumed in both sets of analyses. But the undiscounted life years suggests that alternative all-cause mortality estimates may have been used in the analysis of appendix 16 compared to that of section 7.7.6[11] given that the blindness mortality multipliers are apparently the same for both analyses, or a different patient distribution at baseline. The costs of blindness are also noticeably different between the two analyses, with a very much larger cost offset being estimated in the analysis of appendix 16, which might also suggest a different patient distribution at baseline.

[10] Note that this has been adjusted to be the with PAS treatment on the basis of [redacted] suggesting a discounted number of administrations of [redacted] which broadly ties in with the ex PAS price of [redacted] resulting in the treatment cost of [redacted], and so a treatment cost of [redacted] when [redacted] is applied to the with PAS price of [redacted].

[11] This could also be accounted for by a shorter time horizon, but this may be less likely given that the submitted electronic model provides a drop down menu of the lifetime horizon or the longest curtailed horizon of 15 years.

Table 57 Deterministic results: ranibizumab vs bevacizumab

	Section 7.7.6			Appendix 16		
	Ranibizumab	**Bevacizumab**	**net**	**Ranibizumab**	**Bevacizumab**	**net**
Costs						
Treatment	..	..	..	[redacted]	[redacted]	[redacted]
Admin	..	..	..	[redacted]	[redacted]	[redacted]
Monitor	..	..	..	[redacted]	[redacted]	[redacted]
Bilateral	..	..	..	[redacted]	[redacted]	[redacted]
Recurrence	..	..	..	[redacted]	[redacted]	[redacted]
AEs	..	..	..	[redacted]	[redacted]	[redacted]
Blindness	..	..	..	[redacted]	[redacted]	[redacted]
Total	..	..	..	[redacted]	[redacted]	[redacted]
Life years (undisc.)	..	..	..	[redacted]	[redacted]	[redacted]
QALYs	..	..	..	[redacted]	[redacted]	[redacted]
ICER			..			[redacted]

On the assumption that the administration costs are as previously outlined, this suggests a total of around [redacted] ranibizumab injections compared to [redacted] bevacizumab injections. This also broadly ties in with an injection cost of [redacted] for ranibizumab and of £95 for bevacizumab. Despite this change in the number of ranibizumab injections, the undiscounted life years and the costs of blindness within the ranibizumab arm are virtually the same as for the comparison with observation, which had a total of around [redacted] ranibizumab injections.

If the number of ranibizumab injections is increased to 4.5 this would increase the treatment and administrations costs to the [redacted] and [redacted] of the comparison with observation analysis. This would appear to worsen the cost effectiveness of ranibizumab compared to bevacizumab to perhaps as much as [redacted] per QALY.

In response to the ERG clarification question B22 the manufacturer also notes a number of weaknesses with the Gharbiya 2010[1] and Iacono 2012[2] papers that underlie the estimates relative to bevacizumab.

"*…there is a lack of reliable and robust efficacy and safety data for bevacizumab in the treatment of CNV secondary to PM as there are only two small head to head trials comparing ranibizumab and bevacizumab,21,22 which have considerable methodological weaknesses. Gharbiya 2010 is unclear with respect to how randomisation and allocation concealment were performed. It is also unclear whether patients were similar at baseline in terms of prognostic factors and whether the treating investigator(s) and outcomes assessors were*