- Please note that the ERG report was prepared before publication of the RADIANCE and REPAIR trials, therefore, some of the redacted information in this report is no longer confidential.

Ranibizumab for the treatment of choroidal neovascularisation associated with pathological myopia

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Rider on responsibility for report

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Ewen Cummins reviewed the cost-effectiveness evidence, carried out further sensitivity analyses, and drafted Section 5. Moira Cruickshank and Miriam Brazzelli reviewed the methods of the clinical effectiveness evidence synthesis and drafted Sections 2 and 3. Shona Fielding critiqued the statistical methods used and checked all the numerical results, tables, and figures and drafted Section 4. Cynthia Fraser critiqued the methods used for identifying relevant studies in the literature. Noemi Lois provided clinical advice and contributed to the background and the critique of the manufacturer's decision problem. Miriam Brazzelli supervised the work throughout the project. All authors assisted in preparing the final manuscript and commenting on early drafts.

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LIST OF ABBREVIATIONS

AE	Adverse event
AIC	Academic in confidence
AMD	Age-related macular degeneration
BCVA	Best corrected visual acuity
BSE	Best seeing eye
CFT	Central foveal thickness
CI	Confidence interval
CIC	Commercial in confidence
CNV	Choroidal neovascularisation
CMT	Central macular thickness
CRD	(York) Centre for reviews and dissemination
CRT	Central retinal thickness
EQ-5D	Euroqol 5 dimensions
ERG	Evidence review group
ETDRS	Early treatment diabetic retinopathy study
FA	Fluorescein angiography
FCT	Foveal centre thickness
HCHS	Hospital and Community Health Services
HRQoL	Health-related quality of life
HUI3	Health utilities index mark 3
ICER	Incremental cost effectiveness ratio
IOP	Intraocular pressure
ITC	Indirect treatment comparison
IVB	Intravitreal bevacizumab
IVR	Intravitreal ranibizumab
LOCF	Last observation carried forward
logMAR	Logarithm of the minimum angle of resolution
mLOCF	Modified last observation carried forward
MS	Manufacturer's submission
MTA	Multiple technology appraisal
NEI VFQ-25	National eye institute visual functioning questionnaire - 25
NHB	Net health benefit
NHS	National Health Service
NHIS	National health interview survey
NICE	National Institute for health and Care Excellence

OCT	Ocular coherence tomography
OP	Outpatient
OR	Odds ratio
PDT	Photodynamic therapy
PM	Pathological myopia
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PRN	Pro re nata
PSS	Personal social services
PSSRU	Personal social service research unit
QALY	Quality adjusted life year
QoL	Quality of life
RPE	Retinal pigment epithelial/epithelium
RCT	Randomised controlled trial
RR	Risk ratio
SD	Standard deviation
SE	Standard error
SEM	Structured event equation model
SG	Standard gamble
STA	Single technology appraisal
TPM	Transition probability matrix
TTO	Time trade off
VA	Visual acuity
VIP	Verteporfin in photodynamic therapy (trial)
vPDT	Verteporfin photodynamic therapy
VEGF	Vascular endothelial growth factor
WPAI-GH	Work Productivity and Activity Impairment Questionnaire: General Health
WSE	Worse seeing eye
WTP	Willingness to pay

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 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.

Superseded – see erratum

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 15 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 statistical comparisons could be made to vPDT beyond 3 months due to the switching of treatments in this group.

In addition to the Novartis Phase III trial, the manufacturer presented the results for the ranibizumab arms of two small RCTs comparing ranibizumab with bevacizumab. These two studies showed improvements in outcomes from baseline with ranibizumab at 6 months[1] and 18 months.[2]

Safety of ranibizumab

Within the Novartis Phase III trial, any ocular AE occurred in [redacted] of ranibizumab disease activity patients, [redacted] of ranibizumab stabilisation patients and [redacted] of vPDT patients from baseline to three months. None of these were classified as severe AEs. [redacted] Ocular AEs related to study medication or ocular injection occurred in [redacted] Development of geographic atrophy or extension of pre-existing geographic atrophy (as it has been recognised now as a potential side effect in patients with age-related macular degeneration undergoing anti-VEGF treatment) was not assessed in the Novartis phase III trial.

Limited safety data were available for the two other RCTs (comparing ranibizumab to bevacizumab) and from four of the non-RCTS. Iacono 2012 reported that 'no significant adverse ocular or systemic effects were registered over the entire course of the follow up in either group'.[2] Gharbiya 2010 reported that none of the patients experience systemic complications related to intravitreal ranibizumab and bevacizumab.[1]

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The ERG was concerned at the exclusion of bevacizumab as a comparator given it is used off-label for the treatment of myopic CNV in the UK. In comparison, vPDT is rarely used in clinical practice because, according to the VIP 2-year report published in 2003, its efficacy is not maintained at long term.

The ERG was concerned at the choice of the 3-month primary outcome assessment. The ERG's opinion is that 3 months is insufficient for assessing visual acuity as it does not provide data on longer term gain or possible deleterious effects. The ERG is also concerned that the potential development of geographic atrophy following ranibizumab was not investigated in the Novartis phase III trial. Atrophy is already a common feature in patients

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.

Superseded – see erratum

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 affected more than around 5% of the patients of the Novartis phase III trial for ranibizumab and 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.

Superseded – see erratum

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]

The model appears to assume that ranibizumab monitoring visits can double as treatment visits but that vPDT monitoring visits cannot double as treatment visits. In the absence of other evidence, it seems more reasonable to assume that both ranibizumab and vPDT can have "1 stop" monitoring and treatment, or that neither can, and that a "2 stop" model is required.

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

Yoshida et al.[6] The manufacturer's method of calculation from these other studies remains unclear, with there being no obvious read across to the papers themselves. But the data from Yoshida et al[6] was most obviously aligned with the model structure.

- The manufacturer's estimate of the annual cost of blindness, £17,245, appears to be too high. An estimate of £7,429 it is likely to be more reasonable.
- The mortality multiplier for blindness is derived from a paper that is only unambiguous for blindness in the BSE. However, it is less clear whether to include mortality multipliers for visual impairment other than blindness and, if so, how. Therefore, in order to maintain consistency with previous STAs, it would be more reasonable to restrict the blindness mortality multiplier to blindness in the BSE.

1.6 ERG commentary on the robustness of evidence submitted by the manufacturer

Strengths

The submission focuses on the Novartis phase III trial of ranibizumab versus vPDT. No other trials, with vPDT as the comparator, were identified.

The submission presents a clear and well-documented economic model structure, which shows good validation with the trial data at 1 year for ranibizumab.

Weaknesses and areas of uncertainty

- The manufacturer did not include bevacizumab as a comparator, despite the fact that it is used off-label for myopic CNV, but opted to include only vPDT which is not widely used in clinical practice due to its lack of long term effects.
- The main outcome in theNovartis phase III trial was assessed at short term (3 months). Given the progressive nature of pathological myopia we do not know how long the effects of ranibizumab may last.
- The manufacturer did not assess geographic atrophy within the possible adverse events of ranibizumab.
- The Novartis phase III trial from which the effectiveness data for ranibizumab are drawn and the VIP trial from which the majority of the effectiveness data for vPDT are drawn are not balanced in terms of the proportion of patients with non-subfoveal involvement. This may result in an inflated effect of the benefit of ranibizumab.
- The ERG has revised a number of model inputs, which tend to reduce the estimated net savings and net QALY gains from ranibizumab compared with vPDT, without, however, reversing them.

- 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.
- Adverse events were only included if they affected more than around 5% of the patients in the relevant arm of the Novartis trial. Consequentely, retinal tears were not included. Retinal tears, if untreated, may lead to retinal detachment with the subsequent risk of visual loss. This is likely to be the case especially in eyes affected by pathological myopia in which retinal detachment rates are already higher than those in the general population.
- 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.

Superseded – see erratum

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 £1,786 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 £8,673.[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 £7,116.[4]

Superseded – see erratum

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 £1,178, 0.143 QALYs and £4,037, respectively, using Brown et al 1999.[5] The corresponding figures using Czoski-Murray et al are £1,178, 0.065 and £2,481, 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 £1,342, and the net gain to 0.189 QALYs and net health benefits to £5,123 using Brown et al 1999[5] and to 0.119 QALYs and £3,728 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 £1,276. 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 £2,570[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 £1,175.[4] Given the QALY loss for this scenario the ICER for vPDT compared to ranibizumab is £254k 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

sensitivity analyses are likely to be a consequence of the model structure, and in particular its treatment of cross-over of the best and worse seeing eyes.

2 BACKGROUND

Myopia is a visual problem resulting from excessive growth of the eye-ball which increases its axial length [7-9] or a steeply curved cornea. Myopia causes light rays to focus in front of the retina; close objects are seen clearly whilst distant ones appear blurred. Approximately 29% of people in the UK suffer from myopia.[10,11]

Myopia can be classified as mild, moderate or high, depending on the length of the eye and curvature of the cornea. The focusing power of a lens is measured in dioptres. A negative dioptre (-) indicates an eye with myopia, with the higher the negative value the more severe the myopia. Myopia up to - 3 dioptres is termed mild, -3 to -6 dioptres is moderate, and > -6 is considered high. High myopia, also known as pathological or degenerative myopia, is a chronic condition associated with degenerative changes at the back of the eye. As the myopic eye is longer, the layers at the back of the eye including the sclera (the most external layer that covers the eye), the choroid (the vascular layer of the eye) and the retina (the innermost layer of the eye) are stretched and thinned. Changes in the gel that fill the eye (vitreous) also occur in myopia, namely earlier liquefaction (the "gel-like" structure becomes more liquefied). Furthermore, pathological adhesions between vitreous and retina develop.

The prevalence of pathological myopia (PM) is difficult to determine due to inconsistent definition of the condition in the literature and a dearth of appropriate population-based cohort studies.[8] Thus, there are only limited data on the prevalence of PM in the general population. In general, the prevalence in Asian countries is reported to be up to 5 times greater than that in America or Europe.[12,13] A population-based study conducted in Australia in a Caucasian population reported a prevalence of 1.2% in people aged 49 years or older.[14] In the UK, there are approximately 200,000 people with PM, but data are scarce.

People with myopia may develop choroidal neovascularisation (CNV) which occurs when abnormal blood vessels originating from the choroid develop (neovascularisation). These blood vessels can grow through the thin retina into the subretinal space, where the visual cells (photoreceptors) lie. As these new vessels have abnormal walls, they leak fluid and blood which then accumulate around the visual cells, causing visual loss.[15] As the disease progresses, the CNV scars down causing further retinal damage. Moreover, many studies indicate that, over time, atrophy may develop in eyes with CNV and this can contribute to poor visual acuity. Yoshida et al,[16] for example, reported that in 96% of eyes with myopic CNV, chorioretinal atrophy developed around the regressed CNV within 5 years of CNV

onset. CNV is a common cause of vision loss in people with PM, in particular those under 50 years of age.[17]

There is a paucity of data with respect to the incidence and prevalence of CNV associated with PM. A Japanese study conducted in Tokyo over an 11-year period reported that about 10% of patients with PM developed CNV and 35% developed bilateral CNV. Approximately, 30% of people who develop CNV in one eye will develop it in the other eye within 8 years.[18,19] A retrospective French study reported a prevalence of bilateral CNV of 14% in myopic people younger than 50 years of age.[17] Prevalence rates of bilateral CNV in people with PM may range from 12%[20] to 35%.[21] Moreover, the association between degree of high myopia and risk of developing myopic CNV has yet to be established.[8]

The aim of current management of CNV is to restrict the growth of these neovessels as much as possible, as well as to induce their regression, subsequently halting the decline in visual acuity and even improving vision.

Verteporfin photodynamic therapy (vPDT) is the only treatment with a marketing authorisation for use in subfoveal CNV associated with PM. Verteporfin PDT involves the intravenous injection of verteporfin, a photosensitizing drug, which is activated focally by illumination with light from a laser source at a wavelength corresponding to an absorption peak of the drug. This causes a photochemical reaction which results in direct cellular injury to vascular endothelial cells and subsequent vessel thrombosis, thereby inducing occlusion of the CNV. [22] Verteporfin PDT works by occluding the CNV with moderate damage to surrounding retinal pigment epithelium and photoreceptors.

Vascular endothelial growth factor (VEGF) has been shown to play an important role in the development and progression of neovascularization in the eye, including in eyes with CNV secondary to PM.[8,23,24] Nguyen et al first reported positive outcomes in patients with subfoveal CNV associated with PM after the use of systemic bevacizumab.[25] Since then there has been a growing number of publications reporting the use of intravitreal VEGF inhibitors (i.e. anti-VEGF) for the treatment of myopic CNV.

Bevacizumab (Avastin, Genetech, USA) is an inexpensive, full-length monoclonal antibody that binds and inhibits all isoforms of anti-VEGF A. It is currently unlicensed for all eye conditions but used off-label in the NHS for the treatment of CNV associated with PM.

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 does not currently have a UK marketing authorisation for the treatment of myopic CNV. However, it does have 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]

Superseded – see erratum

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, clinical centres tend to use bevacizumab off-license for myopic CNV. 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.

Superseded
see erratum

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 at present does not have a UK marketing authorisation for visual impairment due to CNV secondary to PM. A European Union regulatory submission was made on [redacted] to the Committee for Medicinal Products for Human Use (CHMP; European

Medicines Agency). A CHMP positive opinion was received in May 2013 and marketing authorisation is expected between July and September 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.

Superseded
see erratum

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

out that the effects of treatment on contrast sensitivity were not assessed in studies of ranibizumab and vPDT for CNV associated with PM. While we are not particularly concerned about the omission of contrast sensitivity, as other more relevant outcomes have been included in the current submission, we are of the opinion that, ideally, BCVA should have been assessed in both eyes.

The Novartis phase III trial was the only trial included in the submission that was designed to evaluate two different dosing regimens of ranibizumab in comparison with vPDT. The main outcome reported in the Novartis phase III trial was the mean average change in BCVA from baseline to month 3. The ERG believes that a 3-month assessment is too short to demonstrate efficacy and even potential side effects of any particular new treatment (or of a treatment for a new indication). The ERG's position is that outcomes, which assess the effects and safety of ranibizumab versus any relevant comparator, should be measured at 1 or 2 years (as for other trials published in this clinical area).

Table 1 summarises the differences between the manufacturer's decision problem and the NICE final scope.

Table 1 Differences between the final scope issued by NICE and the decision problem addressed in the manufacturer's submission

	Final scope issued by NICE	Decision problem addressed in the submission
Population	• People with visual impairment due to choroidal neovascularisation associated with pathological myopia	• People with visual impairment due to choroidal neovascularisation associated with pathological myopia
Intervention	• Ranibizumab	• **Ranibizumab**
Comparator(s)	• Verteporfin photodynamic therapy • Bevacizumab	• **Verteporfin photodynamic therapy**
Outcomes	• Best corrected visual acuity (affected eye) • Best corrected visual acuity • (both eyes) • Contrast sensitivity • Adverse effects of treatment • Health-related quality of life.	• **Best corrected visual acuity (study eye)** • Adverse effects of treatment • Health-related quality of life
Economic analysis	• Incremental cost per quality-adjusted life year • Time horizon should be sufficiently long to reflect differences in costs or outcomes between technologies being compared • Costs will be considered from an NHS and Personal Social Services perspective	• Incremental cost per quality-adjusted life year • **Lifetime horizon** • Costs were considered from an NHS and Personal Social Services perspective

4 CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review(s)

Description of manufacturer's search strategies and critique

The manufacturer searched an appropriate range of databases that included MEDLINE, EMBASE, Science Citation Index, the Cochrane Library and the major international trials registries. The websites of some Health Technology Assessment and Regulatory Agencies and recent conference proceedings of the major professional ophthalmology organisations were also searched. Searches were initially undertaken in March 2012 and updated in November 2012. The search strategies used for each database are detailed in Appendix 10.2 and were reproducible. The approach adopted by the manufacturer was to search for any publication concerning CNV associated with myopia. No terms relating to the intervention, comparators or study design were included in the strategy. The facets of the search (CNV and myopia) were correctly constructed using both appropriate text and controlled vocabulary terms and were combined using the correct Boolean operators. By adopting this approach, it is likely that the literature search was highly sensitive.

Because these searches were disease-specific without further restriction by intervention or study design, no additional searches were undertaken for the indirect comparisons or adverse events. This seems entirely appropriate.

Inclusion criteria

The inclusion criteria used in the systematic review of clinical effectiveness are presented in Table 2.

Table 2 Inclusion criteria for systematic review of clinical effectiveness

Population	Patients of any age undergoing treatment for CNV secondary to PM, including patients with concomitant ocular disease
Intervention	Any types of treatment for CNV, including (but not restricted to) thermal laser photocoagulation therapy, surgery, vPDT and anti-VEGF therapy (e.g. bevacizumab and ranibizumab)
Comparator	'Standard care' defined as vPDT or laser

	treatment and other treatments identified in RCTs were eligible for inclusion
Outcomes	Visual acuity (ETDRS letters or logMAR); other measures of visual acuity such as blindness and lack of response; structural changes (e.g. foveal thickness and central retinal thickness), HRQoL, ocular and systemic AEs
Study design	RCTs of any duration; cross-over RCTs if data were presented at the time of cross-over; prospective randomised studies; open-label extension studies of RCTs; case series of ≥ 25 patients for ≥ 6 months
Language restriction	None

The inclusion criteria detailed in Table 2 specified "any types of treatment for CNV" were eligible for inclusion in the review. However, Figure 7 (PRISMA flow diagram) on page 51 of the manufacturer's submission stated that 13 studies "that do not include ranibizumab" were excluded at the final stage of screening. This criterion was not evident in the exclusion criteria and the reason for excluding these studies is not clear.

Identified studies

The manufacturer's search identified three RCTs and six non-randomised studies that involved ranibizumab and a relevant comparator. The RCTs were the Novartis phase III trial that forms the main body of the manufacturer's submission and two trials that compare ranibizumab with bevacizumab.[1,2] Details of the ranibizumab arms only of the Gharbiya 2010 and Iacono 2012 trials are described within the submission; no details of the bevacizumab arms are presented. These trials both involved one author with a connection to Novartis (Fantozzi received a fellowship from Novartis & Bandello was an advisory board member of Novartis, respectively).

Characteristics of the included RCTs

The Novartis phase III trial randomised participants 2:2:1 to ranibizumab 0.5mg disease activity group, ranibizumab 0.5mg stabilisation group or vPDT. Both ranibizumab groups received ranibizumab 0.5mg on day 1. For the disease activity group, from month 1 onwards, dosing was stopped if no disease activity was seen (i.e. vision impairment, attributable to intra

or subretinal fluid or active leakage secondary to PM as assessed by OCT and/or FA). Treatment was resumed when the disease activity criterion was fulfilled and continued until no disease activity was seen. Participants in the stabilisation group also received ranibizumab 0.5mg at month 1. For the following months, treatment was stopped if the stabilisation criterion for BCVA was fulfilled (i.e. no change in BCVA as compared with the two preceding monthly visits). Treatment was resumed with monthly injections when there was a loss of BCVA due to disease activity and was continued until stable BCVA was re-established for three consecutive monthly assessments. The vPDT group received vPDT [redacted] on day 1. For months 3 to 11, patients with disease activity could receive ranibizumab 0.5mg, vPDT, or ranibizumab 0.5mg plus vPDT. Treatment was stopped if no disease activity was seen. Treatment was resumed when the disease activity criterion was fulfilled (defined as for the ranibizumab group) and continued until no disease activity was seen. One eye was selected and treated as the study eye. If both eyes were eligible, the eye with the worse visual acuity (VA), as assessed at Visit 1, was selected for study treatment. The eye with better VA could be selected, based on medical reasons and according to local ethical requirements.

The Gharbiya 2010 trial[1] was a prospective, comparative, randomised, interventional study in which 32 eyes from 32 consecutive patients with subfoveal or juxtafoveal CNV secondary to PM were randomised 1:1 to either ranibizumab 0.5mg or bevacizumab 1.25mg. If both eyes were eligible for inclusion in the study, the eye with the worse VA was the study eye unless the other eye was considered more suitable for medical reasons. All participants received treatment according to randomisation on day 1. Participants were then followed up every 4 weeks and retreated as necessary for a duration of 6 months. Each 4 week visit involved a complete ocular examination and assessment of BCVA, OCT, FA, IOP and blood pressure.

The Iacono 2012 trial[2]involved similar methods: 55 participants with subfoveal CNV secondary to PM were randomised 1:1 to ranibizumab 0.5mg or bevacizumab 1.25mg. Treatment on day 1 was followed by monthly examinations and retreatment was administered as required, up to 18 months. Baseline and monthly visits involved complete ophthalmologic examination with BCVA, FA and OCT.

Baseline demographic and CNV characteristics of the three identified RCTs are presented in Table 3. Table 4 presents the study characteristics of the three identified RCTs.

Table 3 Baseline demographic and CNV characteristics of identified RCTs

	Novartis phase III trial			**Iacono 2012 [2]**		**Gharbiya 2010 [1]**	
	Ranibizumab 0.5mg DA (n=116)	**Ranibizumab 0.5mg STAB (n=106)**	**vPDT (n=55)**	**Ranibizumab 0.5mg (n=27)**	**Bevacizumab 1.25mg (n=28)**	**Ranibizumab 0.5mg (n=16)**	**Bevacizumab 1.25mg (n=16)**
Age, years, mean (SD) range	56.1 (14.4) [redacted]	54.0 (14.0) [redacted]	57.4 (12.8) [redacted]	65 (12) NR	61 (11) NR	60.6 (10.5) NR	59.1 (11.4) NR
Sex, females, n (%)	87 (75.0%)	82 (77.4%)	40 (72.7%)	20 (74%)	22 (79%)	12 (75%)	10 (63%)
Ethnic information, n (%) Caucasian Asian Other	 70 (60.3%) 46 (39.7%) 0 (0%)	 60 (56.6%) 45 (42.5%) 1 (0.9%)	 32 (58.2%) 23 (41.8%) 0 (0%)	NR	NR	NR	NR
CNV location, n (%) Subfoveal Juxtafoveal Extrafoveal Unable to grade Not applicable Missing Subfoveal or juxtafoveal	 81 (69.8%) 24 (20.7%) 3 (2.6%) [redacted] [redacted] [redacted] -	 71 (67.0%) 26 (24.5%) 7 (6.6%) [redacted] [redacted] [redacted] -	 38 (69.1%) 16 (29.1%) 1 (1.8%) [redacted] [redacted] [redacted] -	 27 (100%) - - - - - -	 28 (100%) - - - - - -	 - - - - - - 16 (100%)	 - - - - - - 16 (100%)
Visual acuity ETDRS letters, mean (SD) LogMAR, mean (SD)	 55.8 (12.6) NR	 55.4 (13.4) NR	 54.7 (13.8) NR	 NR 0.60 (0.29)	 NR 0.60 (0.26)	 26.4 (NR) NR	 29.5 (NR) NR
Axial length, mm, mean (SD)	[redacted]	[redacted]	[redacted]	NR	NR	29.4 (2.9)	30.1 (2.5)

	Novartis phase III trial			Iacono 2012 [2]		Gharbiya 2010 [1]	
	Ranibizumab 0.5mg DA (n=116)	**Ranibizumab 0.5mg STAB (n=106)**	**vPDT (n=55)**	**Ranibizumab 0.5mg (n=27)**	**Bevacizumab 1.25mg (n=28)**	**Ranibizumab 0.5mg (n=16)**	**Bevacizumab 1.25mg (n=16)**
Other measures							
CRT, µm, mean (SD)	373.1 (127.44)	350.2 (95.12)	355.1 (102.35)	NR	NR	NR	NR
CMT, µm, mean (SD)	NR	NR	NR	255 (88)	221 (61)	NR	NR
FCT, µm, mean (SD)	NR	NR	NR	NR	NR	251 (64.8)	237 (40.8)
Lens status (phakic:pseudophakic)	NR	NR	NR	21:6	20:8	NR	NR
Refractive error, mean (SD)	NR	NR	NR	-10.1 (2.7)	-9.3 (2.1)	NR	NR

vPDT: Verteporfin photodynamic therapy, DA: disease activity criteria, STAB: stabilisation criteria, CNV: choroidal neovascularisation, LogMAR: logarithm of minimal angle of resolution, CRT: central retinal thickness, CMT: central macular thickness, FCT: foveal centre thickness, NR: Not reported, SD: Standard deviation

Table 4 Characteristics of included RCTs

	Novartis phase III trial	Iacono 2012[2]	Gharbiya 2010[1]
Study duration	12 months	18 months	6 months
Number of participants randomised	Ranibizumab 0.5mg (disease activity criteria), n=116 Ranibizumab 0.5mg (stabilisation criteria), n=106 vPDT, n=55 Total, n=277	Ranibizumab 0.5mg, n=27 Bevacizumab 1.25mg, n=28 Total, n=55	Ranibizumab 0.5mg, n=16 Bevacizumab 1.25mg, n=16 Total, n=32
Country	[redacted]	Italy	Italy
Intervention & comparator	Ranibizumab intravitreal injection, 0.5 mg, retreatment based on either • disease activity criteria (treatment stopped if no disease activity detected & resumed when disease activity criterion fulfilled) or • stabilisation criteria (treatment stopped if stabilisation criterion for BCVA fulfilled & resumed if loss of BCVA due to disease activity) vPDT, [redacted]	Ranibizumab intravitreal injection 0.5 mg Bevacizumab intravitreal injection 1.25 mg/0.05 mL	Ranibizumab intravitreal injection 0.5 mg Bevacizumab intravitreal injection 1.25 mg/0.05 mL

	Novartis phase III trial	Iacono 2012[2]	Gharbiya 2010[1]
	[redacted]		
Inclusion criteria	[redacted]	Spherical equivalent refractive error of −6.0 D or more (if < −6.0 D, eyes could be eligible if there were retinal abnormalities consistent with PM, such as lacquer cracks, chorioretinal atrophy or posterior staphyloma, and if the axial length of the eye was ≥ 26.5 mm) Naïve subfoveal myopic CNV (subfoveal defined as the presence of CNV under the geometric centre of the foveal vascular zone, confirmed on FA) Baseline BCVA between 20/32 and 20/400 (Snellen equivalent) Women at least 12 months post-menopause or using standard forms of contraception	PM, defined as axial length > 26.5 mm Subfoveal or juxtafoveal CNV (CNV was classified as juxtafoveal if the lesion was closer than 200 µm but not under the geometric centre of the foveal avascular zone) Evidence of leakage from CNV on FA

	Novartis phase III trial	Iacono 2012[2]	Gharbiya 2010[1]
	[redacted]		

	Novartis phase III trial	Iacono 2012[2]	Gharbiya 2010[1]
Exclusion criteria	[redacted]	Intraocular surgery of any kind within 6 months of the day of injection Any other ocular disease that could compromise vision in the study eye Ocular hypertension or glaucoma Uncontrolled systemic hypertension, peripheral vascular disease, and history of thromboembolism, ischaemic heart disease or stroke	Prior treatment for CNV Other ocular diseases that could affect the visual acuity, including angioid streaks, trauma, choroiditis, hereditary diseases in the study or the fellow eye, aphakia, previous vitreoretinal surgery Prior history of bleeding diathesis Prior cerebrovascular accident, pulmonary embolus or deep venous thrombosis Myocardial infarction or uncompensated coronary artery disease within the past 6 months Major surgery within prior 6 weeks Ongoing uncontrolled hypertension

	Novartis phase III trial	Iacono 2012[2]	Gharbiya 2010[1]
	[redacted]		
Primary outcome	Difference between the average level of BCVA (letters) over all monthly post-baseline assessments from month 1 to month 3 (endpoint) and baseline level of BCVA	Change from baseline in mean BCVA at 18-month examination Change from baseline in proportion of eyes improving in BCVA by > 5 and > 15 letters at 18-month examination	Change from baseline in BCVA and FCT at 6 months
Other outcomes	Average change in BCVA from month 1 to month 6 over baseline Mean change from baseline in BCVA at 3, 6 and 12 months Proportion of patients with ≥ 10 and ≥ 15 letters gain or reaching 84 letters, and ≥ 10 and ≥ 15 letters loss from baseline at months 3, 6 and 12	Change in mean CMT and mean CNV area over time Mean number of injections received over 18 months	Proportions of eyes that gained ≥ 10 letters or ≥ 15 letters from baseline at 6 months Proportion of eyes losing or gaining ≥ 10% in FCT at 6 months Mean number of injections over 6 months

	Novartis phase III trial	Iacono 2012[2]	Gharbiya 2010[1]
	[redacted] Proportion of patients with presence of active leakage Number of ranibizumab re-treatments from baseline to months 2, 5 and 11 Impact on HRQoL as assessed by NEI VFQ-25, [redacted] Safety and tolerability		

[redacted]

Summary of identified non-randomised studies

Details of non-randomised studies identified in the manufacturer's search are presented in Table 5.

Table 5 Summary of identified non-randomised studies

Study	Population	Intervention
REPAIR NCT01037348	Patients ≥18 years with subfoveal or juxtafoveal CNV secondary to PM	0.5mg IVR, one dose then retreatment as needed
Calvo-Gonzalez 2011 [31]	Patients with subfoveal or non-subfoveal CNV secondary to PM	IVR, 3 monthly doses then retreatment as needed
Lalloum 2010 [32]	Patients with CNV secondary to PM	0.5mg IVR, 1 dose then retreatment as needed
Ouhadj 2010[33]	Patients with subfoveal or juxtafoveal CNV secondary to PM	0.5mg IVR
Silva 2010 [34]	Patients ≥ 21 years with subfoveal or juxtafoveal CNV secondary to PM	0.5mg IVR, 1 dose then retreatment as needed
Vadala 2011[35]	Patients with subfoveal or juxtafoveal CNV secondary to PM	0.5mg IVR, 1 dose then retreatment as needed

Quality assessment

The manufacturer assessed the quality of the three included RCTs. The methods used for quality assessment were considered adequate by the ERG.

Overall, the methodological quality of the Novartis phase III trial was acceptable. Both the methods of randomisation and the treatment allocation concealment were adequate. Randomisation appears to have been successful and demographic and CNV characteristics were balanced across the randomised groups. Study personnel and participants were masked throughout the trial. The only study personnel who were unmasked were those who administered the randomised study treatment when needed, according to the protocol. All outcomes were assessed by masked personnel. The ERG considers the masking strategies

used to be appropriate. Analysis was on an intention-to-treat basis. The full analysis set involved a modified LOCF approach. The ERG considers this approach to be acceptable in this case (see section 4.3).

The quality of the Gharbiya 2010 trial was unclear due to inadequate reporting.[1] Method of randomisation, concealment of treatment allocation and details of any masking were not reported, although it appears that no masking was involved in the trial. Methods of analysis were also not reported, thus it is unclear whether an intention-to-treat approach was used.

The quality of the Iacono 2012 trial was variable.[2] Appropriate randomisation and concealment of treatment allocation procedures were involved. Baseline disease-related characteristics were comparable across treatment groups. The trial was described as "double-blind" but only masking of the study personnel administering the injection was declared. Thus, it is unclear whether masking of participants was achieved. An intention-to-treat approach was used but methods of accounting for missing data were not described.

The ERG performed a quality assessment of the manufacturer's systematic review using the York Centre for Reviews and Dissemination (CRD) criteria (Table 6). The quality of the systematic review was good and the ERG has no major concerns in any of the quality areas.

Table 6 Quality assessment of the manufacturer's review

CRD quality item	Score
1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question?	**Yes**
2. Is there evidence of a substantial effort to search for all of the relevant research?	**Yes**
3. Is the validity of included studies adequately assessed?	**Yes**
4. Are sufficient details of the individual studies presented?	**Yes**
5. Are the primary studies summarised appropriately?	**Yes**

4.2 Summary of submitted evidence

The manufacturer presented the results of three RCTs and six non-RCTs to show the clinical effectiveness of ranibizumab in the treatment of visual impairment due to choroidal neovascularisation (CNV) secondary to pathological myopia (PM). One RCT, the manufacturer led Novartis phase III trial, compared ranibizumab (0.5mg) with dosing regimens to the identified comparator verteporfin photodynamic therapy (vPDT) in a total of 277 patients. The two other RCTs[1,2] compared ranibizumab (0.5mg) to bevacizumab (1.25mg)

with 32 and 48 patients, respectively. The manufacturer only presented data for the ranibizumab arm of these two trials and did not provide the bevacizumab results.

Within the Novartis phase III trial, 116 patients were recruited to the ranibizumab 0.5mg disease activity group and 106 patients were recruited to the ranibizumab disease stabilisation group. The comparative group of 55 patients received vPDT on day 1. For months 3 to 11, patients in the vPDT group who showed signs of disease activity could receive ranibizumab 0.5 mg, vPDT, or ranibizumab 0.5mg plus vPDT. Treatment was stopped and restarted using the same criteria as the other two groups. To ensure blinding on day 1 and month 1 and 2, patients randomised to either of the ranibizumab regimens received ranibizumab or a sham ranibizumab procedure as required and on day 1 all patients randomised to vPDT received either vPDT or sham vPDT. The study ran for 12 months, with a primary outcome at 3 months of 'difference in average level of BCVA letters over all monthly post-baseline assessments from months 1 to 3 and the baseline level of BCVA'.

The Iacono 2012 study[2] was a prospective single centre RCT conducted in Italy comparing ranibizumab 0.5mg in 27 patients with bevacizumab 1.25mg in 28 patients. The primary outcome was change from baseline in mean BCVA at 18 months. The Gharbiya 2010 prospective randomised study[1] compared the same two treatments as Iacono 2012 with 16 patients in each group. Gharbiya 2010 was also conducted in Italy but used six months as their primary endpoint. Both of these studies treated on day 1 and retreated as needed if predefined criteria for disease progression at monthly monitoring visits were met.

The mean age of the Novartis trial participants was lower than the participants in the two other trials but not substantially so. The three trials were predominantly female with similar proportions. The Novartis trial participants were Caucasian in the majority (around 60%) with the remainder Asian. Iacono 2012 and Gharbiya 2010 did not report ethnic origin, but as they recruited only in Italy, the ERG would assume the participants were predominantly Caucasian (Italian). Novartis phase III trial included participants with subfoveal CNV, juxtafoveal CNV and a few extrafoveal CNV, while Iacono 2012 involved solely subfoveal CNV and Gharbiya was a mixture of subfoveal or juxtfoveal CNV. Baseline visual acuity measured by ETDRS letters was around double for the Novartis patients than for patients in Gharbiya 2010 (Table 3).

Six relevant non-RCTs were identified by the manufacturer; the REPAIR study, Calvo-Gonzalez 2011, Lalloum 2011 Ouhadj 2010, Silva 2010 and Vadala 2011.[31-35] REPAIR was a 12 months, multicentre single arm phase II study performed in 12 UK centres. The other five

were prospective case series involving at least 25 patients for at least 6 months follow up. A summary is provided in Table 5.

Ranibizumab versus vPDT

The only RCT for ranibizumab 0.5mg versus vPDT was that sponsored by the manufacturer (Novartis phase III trial). Their primary analysis was the assessment at 3 months of the mean average change in BCVA from baseline (post baseline assessments for months 1 to 3). Table 7 summarises these results.

Table 7 Summary of efficacy results from the Novartis phase III trial

Outcome	Timeframe	Ranibizumab disease activity (N=116)	Ranibizumab disease stabilisation (N = 105)	vPDT (N=55)
Mean average change in BCVA (letters) from baseline, mean (SD)	0-3 months	10.6 ([redacted])[redacted]***	10.5 ([redacted])[redacted]***	2.2 ([redacted])
	0-6 months	11.7 ([redacted])[redacted]***	11.9 ([redacted])[redacted]***	[redacted]
	0-12 months	[redacted]***	[redacted]***	[redacted]
Change in BCVA (letters) from baseline, mean (SD)	0-3 months	12.5 ([redacted])[redacted]***	12.1 ([redacted])[redacted]***	1.4 ([redacted])
	0-6 months	12.7 ([redacted])[redacted]**	13.7 ([redacted])[redacted]***	[redacted]
	0-12 months	14.4 [redacted]**	13.8 [redacted]*	[redacted]

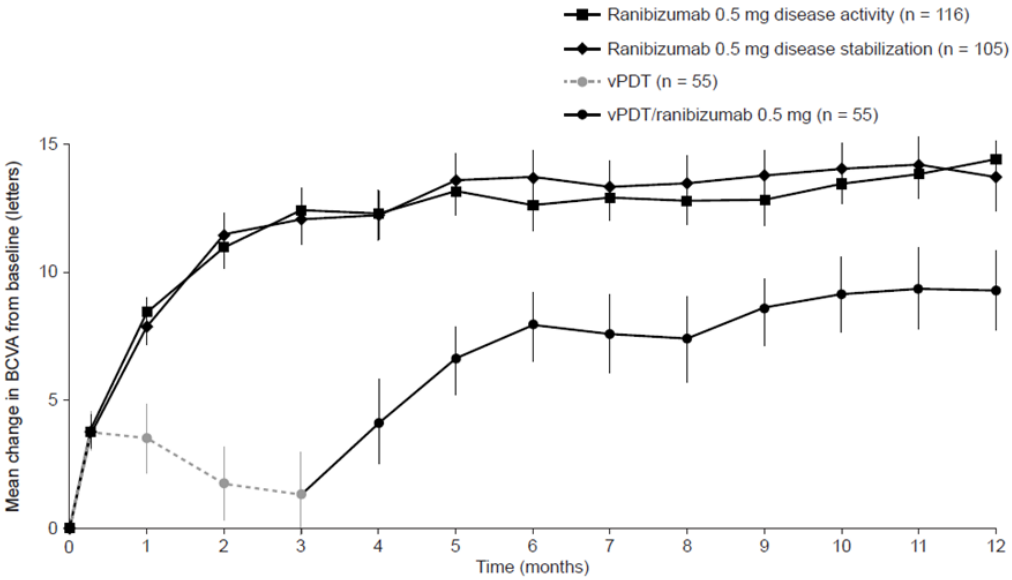
BCVA Best corrected visual acuity score; [a] provided to the ERG in response to clarification A2; *** p< 0.0001; ** p< 0.005; *p<0.05

Comparisons were made for each of the ranibizumab dosing groups to vPDT. For the primary outcome, both groups showed a significant improvement in mean average change in BCVA from baseline to 3 months compared to vPDT. No data were originally provided by the manufacturer for the vPDT group beyond 3 months with the explanation that the patients could receive ranibizumab after that time. The ERG requested these data during clarification, which are included in Table 7. The manufacturer states in their submission that 'during months 3 to11, 38 of the 53 patients who received vPDT at baseline received treatment with ranibizumab'. Looking at the additional data it can be seen that over both the first 6 months and the 12 months the mean average change in BCVA from baseline is significantly greater for each of the ranibizumab groups compared to vPDT, but the magnitude of the difference does reduce over time.

At 3 months, the change in BCVA from baseline was significantly greater in the two ranibizumab groups compared to vPDT. Following clarification, the ERG was provided with

the data for vPDT beyond three months. There was a significant difference in gain of letters for the two ranibizumab arms at both 6 and 12 months compared to the vPDT group, but again the magnitude of the difference was reduced over time.

Figure 1 Mean (± SE) change in BCVA over time during treatment with ranibizumab or vPDT/ranibizumab



BCVA, best-corrected visual acuity; SE, standard error; vPDT, verteporfin photodynamic therapy. From month 3 to 11, the investigators had the option to treat the disease activity of patients randomised to vPDT with 0.5 mg ranibizumab, vPDT, or a combination of 0.5 mg ranibizumab and vPDT.

Figure 1 (presented as Figure 11 in the manufacturer's submission), shows the mean change in BCVA from baseline for each of the groups at each month over the 12 months. This figure shows that the initial gains during the first three months in both ranibizumab groups are maintained over time. In the vPDT group, there are little gains early on but gains are seen once some patients begin to receive ranibizumab.

[redacted]

[redacted]

Superseded –

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 X1). 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]

see erratum

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 OR (95% CI), versus vPDT 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 OR (95% CI), versus vPDT 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]

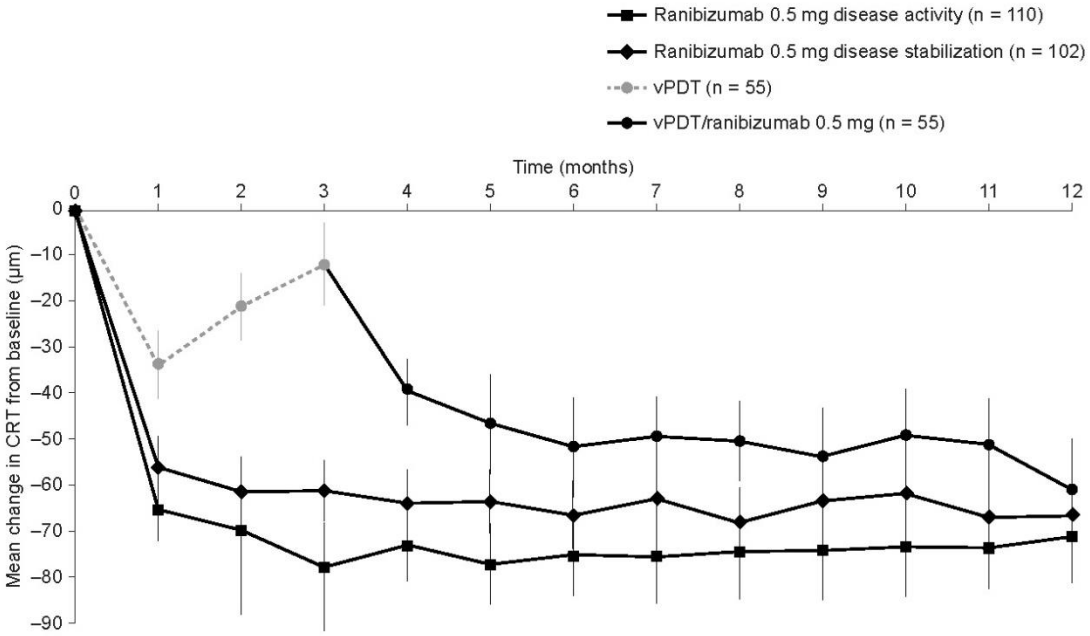
Superseded – see erratum

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]

Figure 2 Mean (± SE) change from baseline in central retinal thickness over time during treatment with ranibizumab or vPDT/ranibizumab



Source, Figure 12 manufacturer submission

Number of injections

The mean (SD) number of ranibizumab injections received in the first 3 months (see Table 10) was lower for patients treated under disease activity [1.8 (0.8)] compared to disease stabilisation [2.5 (0.6)].

Table 10 Mean (SD) number of injections

Timeframe	Ranibizumab disease activity (N=116)	Ranibizumab disease stabilisation (N = 105)
0-3 months	1.8 (0.8)	2.5 (0.6)
0-6 months	2.5 (1.6)	3.5 (1.5)
0-12 months	3.5 (2.9)	4.6 (2.6)

[redacted]

Quality of life

The visual functioning aspect of quality of life was measured by the manufacturer using the National Eye Institute Visual Functioning Questionnaire (NEI VFQ-25), a validated tool with 25 items assessing general health, quality of vision and vision related quality of life. A total score and 11 vision related constructs are measured, with higher scores representing better functioning on a 0 to 100 scale. In the Novartis phase III trial, this instrument was administered at baseline, 3, 6 and 12 months. Table 11 shows the results for 0-3 months (source Table 23 of the manufacturer's submission).

During clarification the manufacturer provided the baseline mean values of the NEI VFQ-25 and its sub scores. No obvious differences were observed by the ERG between the three groups, except for the driving score which was lower in the ranibizumab disease activity group ([redacted]) compared to ranibizumab disease stabilisation ([redacted]) and vPDT ([redacted]).

Over the first 3 months, the change in NEI VFQ-25 composite score was significantly higher for each of the ranibizumab groups compared to vPDT (Table 11). A 4-6 point change is regarded as clinically meaningful. There was also a significantly higher change for general vision, mental health and dependency in both ranibizumab groups and in near activities for the stabilisation group. The manufacturer reported the same information for 0-6 and 0-12 months (Table 24 and 25 of the manufacturer submission) but did not indicate whether there were statistical differences between groups.

Table 11 Mean (± SD) change from baseline in vision-related quality of life as assessed using the NEI VFQ-25 during treatment with ranibizumab or vPDT, month 0−3

NEI VFQ-25 score	Ranibizumab disease activity (n = 116)	Ranibizumab disease stabilisation (n = 105)	vPDT (n = 55)
Composite	**4.3** [redacted]*	**5.3** [redacted]*	**0.3** [redacted]
General health	[redacted]	[redacted]	[redacted]
General vision	[redacted]	[redacted]	[redacted]
Ocular pain	[redacted]	[redacted]	[redacted]
Near activities	5.3 [redacted]	11.5 [redacted]*	0.9 [redacted]
Mental health	4.9 [redacted]*	7.4 [redacted]*	–1.8 [redacted]
Dependency	3.1 [redacted]*	3.7 [redacted]*	–4.7 [redacted]
Distance activities	[redacted]	[redacted]	[redacted]
Driving	[redacted]	[redacted]	[redacted]
Social functioning	[redacted]	[redacted]	[redacted]
Roles difficulties	[redacted]	[redacted]	[redacted]
Colour vision	[redacted]	[redacted]	[redacted]
Peripheral vision	[redacted]	[redacted]	[redacted]

All data are mean (SD); *p < 0.05 vs vPDT

The manufacturer also reported within the text on the EQ5D health score, ranging from 0 to100 - a score of 100 representing the best possible health. [redacted] as the EQ5D is recognised as being insensitive to changes in vision and visual functioning. The ERG agrees with this opinion.

Table 12 Mean[a] change in EQ5D from baseline

Timeframe	Ranibizumab disease activity (N=116)	Ranibizumab disease stabilisation (N = 105)	vPDT (N=55)
0-3 months	[redacted]	[redacted]	[redacted]
3-6 months	[redacted]	[redacted]	[redacted]
0-12 months	[redacted]	[redacted]	[redacted]

[a] Standard deviation not reported

[redacted] This provides a score as a percentage of overall work impairment and higher scores represent greater impairment and less productivity. [redacted] A 20% reduction in work productivity impairment can be in interpreted as equivalent to the productivity lost by many patients with health problems, thereby suggesting productivity may have been regained in the two ranibizumab groups.

Summary of the results of the Novartis phase III trial

Overall the manufacturer indicated that ranibizumab according to disease activity or disease stabilisation significantly improves BCVA and provides greater reductions in CRT compared to vPDT over three months of follow up. The benefits of ranibizumab compared to vPDT at three months were evident regardless of age, sex, race, baseline visual acuity of CNV location. Similar improvements in BCVA were seen with the two ranibizumab groups, but were achieved with fewer injections in the disease activity group.

Ranibizumab versus Bevacizumab

Two studies were identified by the manufacturer for the comparison of ranibizumab versus bevacizumab.[1,2] Iacono 2012 followed up 27 patients for 18 months, while Gharbiya 2012 followed up 16 patients for six months. For comparison, the results for the Novartis disease activity arm and the ranibizumab arm of these two additional trials are shown in Table 13. As the manufacturer did not consider bevacizumab to be a comparator, they only presented data for ranibizumab. The ERG addresses this issue in section 4.3 of this report.

The mean change from baseline in BCVA was larger in Gharbiya 2012 than it was in the Novartis phase III trial at six months, but this may have been due to a lower BCVA at baseline in Gharbiya 2010. In the Novartis phase III trial, [redacted] of patients had gained 10 letters or more compared to 75% in the Gharbiya 2010 study. A higher proportion gaining 15 letters or more was seen with Gharbiya 2010 (56.2%) compared to Novartis trial at six months ([redacted].

The mean change from baseline in BCVA for the Iacono 2012 longer (18 months) study patients was less than that of the Novartis phase III trial (Table 13). The proportion of patients gaining 15 or more letters over 18 months follow up was also smaller (30.4%).

Evidence for ranibizumab from non RCTs

Six relevant non RCT studies evaluating the effectiveness of ranibizumab were identified by the manufacturer (Table 5). The REPAIR study was a phase II open label study based in the UK. The other five were prospective case series with average follow up between 8 and 17 months. Four studies used a treatment regimen of injection at baseline and then as needed, while Calvo-Gonzalez 2011 treated at baseline, at one and two months, and subsequently as needed.[31] Table 14 describes the patient characteristics of these studies.

The primary outcome within REPAIR was mean change in BCVA from baseline to month 12. Within Valdala 2011, the primary outcome was proportion of patients gaining ≥ 5 letters and proportion of patients with stable BCVA.[35] The other studies did not define a primary endpoint, but included outcomes such as mean change in BCVA, proportion of patients gaining ≥ 15 letters and number of injections.

In the REPAIR study, the mean change in BCVA at 12 months was 13.76 which was comparable to the Calvo-Gonzalez case series (mean =12.4, SD = 13.0),[31] Valdala 2011 (mean = 14.5)[35] and Ouhadj 2010 (mean = 15),[33] although there were no fixed time frames for these changes (Table 15). The mean number of injections varied between 2.2 and 4.2 across a range of follow ups. Lalloum 2010 gave the highest proportion of patients that gained ≥ 15 letters (47%) but also included a longer follow up period (up to 29 months, mean = 17 months).[32] Silva 2010 reported outcomes at 12 months but only 24% of patients had gained ≥ 15 letters compared to 37% of those in REPAIR for the same period (Table 15).[34]

Four studies looked at change in BCVA according to baseline characteristics. The manufacturer reported that the benefits of ranibizumab were independent of age, sex, lesion size and refractive error. Calvo-Gonzalez 2011 and Vadala 2011 reported improvements in BCVA were similar in patients who had not been previously treated compared to those who had received vPDT.[31,35] However, Lalloum 2010 and Silva 2010 reported better responses in those without previous treatment.[32,34] While Calvo-Gonzalez 2011 reported greater improvements in BCVA in patients with lower BCVA at baseline, two others studies reported no effect of baseline BCVA on improvement in BCVA following ranibizumab treatment.[32,35]

Table 13 Results for ranibizumab arms of additional RCTs

	Novartis Phase III (n = 116)			Gharbiya 2010[1] (n = 16)	Iacono 2012[2] (n=23)
	3 months	**6 months**	**12 months**	**6 months**	**18 months**
Mean (SD) change from baseline in BCVA letters	12.5 ([redacted])	12.7 ([redacted])	14.4 ([redacted])	17.31 (11.1)	9 (NR)
Patients gaining 10 or more letters n (%)	[redacted]	[redacted]	[redacted]	12 (75)	NR
Patients gaining 15 or more letters n (%)	[redacted]	[redacted]	[redacted]	9 (56.2)	7 (30.4)
Mean (SD) change from baseline in CRT	[redacted]	[redacted]	[redacted]	-45 (NR)	NR
Mean (SD) number of ranibizumab injections	1.8 (0.8)	2.5 (1.6)	3.5 (2.9)	2.81 (1.17)	2.65 (1.61)

Table 14 Baseline characteristics of included non-randomised studies

Study reference	Number of patients (eyes)	Age (years), mean ± SD (range)	Female, n (%)	CNV location, n (%)	Patients received prior vPDT, n (%)	Refractive error (D), mean ± SD (range)	BCVA, mean ± SD	CFT, CMT or CRT (µm), mean ± SD (range)
REPAIR Phase II trial	65 (65)	55.5 ± [redacted]	[redacted] (70.8)	Subfoveal: [redacted] (66.2) Juxtafoveal [redacted] 26.2) Probably subfoveal or juxtafoveal [redacted] (7.7)	None – were excluded if had prior treatment	Not reported	59.5 ± 13.6 letters	384.7 ± 130.8
Calvo-Gonzalez 2011[31]	67 (67)	59 ± 13	50 (74.6)	Subfoveal: 40 (59.7)	42 (62.7)	−11.1 ± 3.3	53.4 ± 12.4 letters	308.5 ± 87.4
Lalloum 2010[32] [a]Median	32 (32)	57[a] (26–86)	25 (78.1)	Subfoveal: 28 (87.5) Juxtafoveal: 4 (12.5)	13 (40.6)	−13.5 (−6 to −23)	0.2 logMAR[a] (SD NR)	336[a] (179−663)
Ouhadj 2010[33]	40 (40)	40 ± 11 (20–55)	33 (82.5)	Subfoveal: 21 (52.5) Juxtafoveal: 19 (42.5)	NR	−14.1 ± 4.7	NR (range 20/400 to 20/50 Snellen)	NR
Silva 2010[34]	32 (34)	54 ± 17	20 (62.5)	NR	13 (38.2)	NR	51.8 ± 18.1 letters	307.6 ± 79.2
Vadala 2011[35]	39 (40)	53 ± 13 (32–80)	27 (69.2)	Subfoveal: 29 (72.5) Juxtafoveal: 11 (27.5)	15 (37.5)	−13.5 ± 6.5 (−6 to −28)	0.7 ± 0.3 logMAR; 21 ± 16 letters	218.9 ± 7.0

Table 15 Summary of efficacy results for non-RCTs

Reference	N (eyes)	Time point at which efficacy assessed or mean ± SD (range) duration of follow up	Number of injections, mean± SD	Change in BCVA (letters), mean ± SD (range)	Gained ≥ 15 letters at follow up, %
REPAIR	65 (65 eyes)	12 months	3.6 [redacted]	13.76 [redacted]	37%
Calvo-Gonzalez 2011[31]	67 (67 eyes)	12 months (59 eyes), SD and range NR 16 (6−27) months, SD NR	3.9 ± 1.1 4.2 ± 1.7	12.4 ± 13.0* range not reported 12.0 ± 14.6*	40%
Lalloum 2010[32]	32 (32 eyes)	17 (7−29)[a] months	3.0 (1–12)[a]	9.5*** SD and range not reported	47%
Ouhadj 2010[33]	40 (40 eyes)	8 (3–15) months, SD not given	2.2, SD NR	15.0 (5–45) SD not reported	Not reported
Silva 2010[34]	32 (34 eyes)	12 months, SD and range not given	3.6 ± 1.8	8.0** SD and range not reported	24%
Vadala 2011[35]	39 (40 eyes)	13 ± 2 (12−18) months	2.8 ± 1.2	14.5 (5–40)[a] for 32 eyes with improvement	60% for 32 eyes with improvement

[a]Median (range); *p < 0.05; **p < 0.001;***p < 0.0001 vs baseline

Comparison of vPDT against placebo

The manufacturer found one trial for the comparator vPDT versus placebo and presented the results of the Verteporfin PhotoDynamic therapy (VIP) trial.[3] Data from the VIP trial months 3-12 were used in the economic model (see Chapter 5), as vPDT monotherapy within the Novartis phase III trial stopped at 3 months.

The VIP trial was a study of vPDT versus placebo for 120 patients with CNV secondary to PM specifically with subfoveal lesions. Patients were followed for 24 months and the primary outcome was categorical change in BCVA (loss of less than 8 letters from baseline at 12 months). Secondary outcomes included median change in BCVA and the proportion of patients gaining 15 letters or more in BCVA from baseline.

Stable BCVA was shown for the vPDT at 3 and 12 months, but by 24 months the proportion stable was not significantly different to those who had received placebo (Table 16).

Table 16 Summary of visual acuity results from the VIP 2001 trial[3]

Follow up, months	Patients with stable BCVA, %		Change in median BCVA, letters		Patients gaining ≥ 15 letters, n (%)	
	vPDT n = 81	Placebo n = 39	vPDT n = 81	Placebo n = 39	vPDT n = 81	Placebo n = 39
0	–	–	–	–	–	–
3	77*	56	0	−5	2 (2.5)**	0
12	72**	44	1**	−9	5 (6.2)**	1 (2.6)
24	64	49	1*	−8	10 (12.3)*	0

*p < 0.05; **p < 0.01 versus placebo.

Adverse Events

No studies were identified by the manufacturer that reported safety data specifically but the Novartis phase III trial provided detailed safety data. Some additional safety data were available from the Iacono 2012 and Gharbiya 2010 trials and from the non-RCTs. The adverse event (AE) data from all the sources are summarised below.

Novartis phase III trial

Any ocular AE occurred in [redacted] of ranibizumab disease activity patients, [redacted] ranibizumab stabilisation and [redacted] of vPDT patients (Table 17) from baseline to three months. None of these were classified as severe AEs. [redacted]

Table 17 details the adverse events in the first 3 months of the trial. Ocular AEs related to study medication or ocular injection occurred in [redacted]. The most common of these was again [redacted]. [redacted]

Table 17 **Summary of AEs in the Novartis phase III study reported in at least two patients in any treatment group and all AEs related to ocular safety concerns: baseline to month 3**

	AEs, n (%)		
	Ranibizumab disease activity (N = 118)	**Ranibizumab disease stabilisation (N = 106)**	**vPDT (N = 53)**
Ocular AEs, n (%)[a]			
Any	[redacted]	[redacted]	[redacted]
Severe	[redacted]	[redacted]	[redacted]
Conjunctival haemorrhage	[redacted]	[redacted]	[redacted]
Punctate keratitis	[redacted]	[redacted]	[redacted]
Intraocular pressure increased	[redacted]	[redacted]	[redacted]
Eye pain	[redacted]	[redacted]	[redacted]
Dry eye	[redacted]	[redacted]	[redacted]
Cataract	[redacted]	[redacted]	[redacted]
Ocular AEs related to study medication or ocular injection, or both, n (%)			
Any, n (%)	[redacted]	[redacted]	[redacted]
Conjunctival haemorrhage	[redacted]	[redacted]	[redacted]
Punctate keratitis	[redacted]	[redacted]	[redacted]
Eye pain	[redacted]	[redacted]	[redacted]
Intraocular pressure increased	[redacted]	[redacted]	[redacted]
Conjunctival oedema	[redacted]	[redacted]	[redacted]
Corneal erosion	[redacted]	[redacted]	[redacted]
Retinal tear	[redacted]	[redacted]	[redacted]
Vitreous floaters	[redacted]	[redacted]	[redacted]
Vitreous prolapse	[redacted]	[redacted]	[redacted]
Conjunctival hyperaemia	[redacted]	[redacted]	[redacted]
Injection site haemorrhage	[redacted]	[redacted]	[redacted]
Intracranial pressure increased	[redacted]	[redacted]	[redacted]
Uveitis	[redacted]	[redacted]	[redacted]
Non-ocular AEs, n (%)[b]			
Any	[redacted]	[redacted]	[redacted]
Severe	[redacted]	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]	[redacted]

Headache			
Intervertebral disc protrusion			
Pharyngitis			
Upper respiratory tract infection			
Back pain			
Hypertension			
Fatigue			
Haemorrhoids			
Tooth disorder			
Migraine			
Pain in extremity			
Hypercholesterolaemia			
Urinary tract infection			
Bronchitis			
Serious AEs, n (%)			

AE, adverse event; CI, confidence interval; NA, not applicable; NR, not reported; OR, odds ratio; RR, risk ratio; vPDT, verteporfin photodynamic therapy

[a]Reported in at least 2 patients in any treatment group and all AEs related to ocular safety concerns; [b]Reported in at least 2 patients in any treatment group

Source: table 40 of manufacturer submission

Table 18 Summary of ocular AEs of the study eye and non-ocular AEs in the Novartis phase III study reported in at least two patients in any treatment group and all AEs related to ocular safety concerns: baseline to months 6 and 12 (Safety set)

	Baseline to month 6				**Baseline to month 12**			
	Ranibizumab disease activity, N = 118	**Ranibizumab disease stabilisation, N = 106**	**vPDT + ranibizumab, N = 34**	**vPDT, N = 19**	**Ranibizumab disease activity, N = 118**	**Ranibizumab disease stabilisation, N = 106**	**vPDT + ranibizumab, N = 38**	**vPDT, N = 15**
Ocular AEs, n (%)[a]								
Any	[redacted]	[redacted]	[redacted]	[redacted]	44 (37.3)	46 (43.4)	16 (42.1)	4 (26.7)
Severe	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Conjunctival haemorrhage	[redacted]	[redacted]	[redacted]	[redacted]	12 (10.2)	12 (11.3)	2 (5.3)	0
Punctate keratitis	[redacted]	[redacted]	[redacted]	[redacted]	3 (2.5)	8 (7.5)	2 (5.3)	0
Intraocular pressure increased	[redacted]	[redacted]	[redacted]	[redacted]	7 (5.9)	3 (2.8)	4 (10.5)	0
Eye pain	[redacted]	[redacted]	[redacted]	[redacted]	4 (3.4)	4 (3.8)	1 (2.6)	1 (6.7)
Dry eye	[redacted]	[redacted]	[redacted]	[redacted]	2 (1.7)	4 (3.8)	0	1 (6.7)
Injection site haemorrhage	[redacted]	[redacted]	[redacted]	[redacted]	3 (2.5)	3 (2.8)	2 (5.3)	0
Vitreous floaters	[redacted]	[redacted]	[redacted]	[redacted]	1 (0.8)	5 (4.7)	0	0
Retinal tear	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Conjunctivitis allergic	[redacted]	[redacted]	[redacted]	[redacted]	5 (4.2)	1 (0.9)	1 (2.6)	0
Metamorphopsia	[redacted]	[redacted]	[redacted]	[redacted]	3 (2.5)	0	0	0
Retinal haemorrhage	[redacted]	[redacted]	[redacted]	[redacted]	3 (2.5)	1 (0.9)	0	0
Blepharitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Conjunctivitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eyelid oedema	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cataract	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocular hyperaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visual impairment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocular AEs related to study medication or ocular injection, or both, n (%)								
Any, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Conjunctival haemorrhage	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Punctate keratitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eye pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Intraocular pressure increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Conjunctival oedema	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Corneal erosion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Retinal tear	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vitreous floaters	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vitreous prolapse	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Conjunctival hyperaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Injection site haemorrhage	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Intracranial pressure increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Uveitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocular hyperaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Iridocyclitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug hypersensitivity	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Injection site pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adenoviral conjunctivitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eye irritation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Metamorphopsia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cataract	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visual impairment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-ocular AEs, n (%)[b]								
Any	[redacted]	[redacted]	[redacted]	[redacted]	51 (43.2)	48 (45.3)	19 (50.0)	5 (33.3)
Severe	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]	[redacted]	[redacted]	12 (10.2)	12 (11.3)	1 (2.6)	2 (13.3)
Headache	[redacted]	[redacted]	[redacted]	[redacted]	11 (9.3)	8 (7.5)	1 (2.6)	0
Intervertebral disc protrusion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pharyngitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]	[redacted]	[redacted]	4 (3.4)	3 (2.8)	1 (2.6)	0
Back pain	[redacted]	[redacted]	[redacted]	[redacted]	4 (3.4)	2 (1.9)	0	0
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]	5 (4.2)	3 (2.8)	3 (7.9)	0
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Haemorrhoids	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Tooth disorder	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Migraine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pain in extremity	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypercholesterolaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]	[redacted]	[redacted]	3 (2.5)	3 (2.8)	0	0
Bronchitis	[redacted]	[redacted]	[redacted]	[redacted]	4 (3.4)	1 (0.9)	1 (2.6)	0
Influenza	[redacted]	[redacted]	[redacted]	[redacted]	4 (3.4)	2 (1.9)	1 (2.6)	0
Tendonitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]	[redacted]	[redacted]	1 (0.8)	3 (2.8)	0	0
Bacteriuria	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diabetes mellitus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Osteoporosis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Toothache	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cough	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cystitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sciatica	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dental caries	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hyperglycaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hyperlipidaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Seasonal allergy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Tinnitus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Urticaria	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Serious AEs, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	**6 (5.1)**	**7 (6.6)**	[redacted]	[redacted]

[a]Reported in at least 2 patients in any treatment group and all AEs related to ocular safety concerns; [b]Reported in at least 2 patients in any treatment group.

Following clarification, the ERG was provided with AE information for the vPDT/ranibizumab and vPDT only group for baseline to 6 months and baseline to 12 months (Table 18). Over the course of the 12 months, any ocular AE was seen in 37.3% of the ranibizumab disease activity group, 43.4% of ranibizumab disease stabilisation group, 42.1% in vPDT/ranibizumab and 26.7% in vPDT only. Only two serious ocular AEs were reported during the trial, one [redacted] ([redacted]. [redacted]. The most common ocular AE was conjuctival haemorrhage with 10.2%, 11.3%, 5.3%, 0% in each of the four groups, respectively. [redacted]. [redacted] Non-ocular AEs occurred in 43.2%, 45.3%, 50.0% and 33.3%, respectively, in each of the groups described.

Other Safety data

Limited safety data were available for the two other RCTs (comparing ranibizumab to bevacizumab) and for the four non-RCTS. Iacono 2012 reported that 'no significant adverse ocular or systemic effects were registered over the entire course of the follow up in either group'.[2] Gharbiya 2010 reported that none of the patients experienced systemic complications related to intravitreal ranibizumab and bevacizumab.[1] They also reported that no major ocular injection-related adverse events were observed during the follow up in either group. Calvo-Gonzalez 2011 reported that two eyes developed anterior uveitis after the second and third injections but these AEs responded well to appropriate treatment.[31] No other ocular or systemic complications were recorded. The four non-RCTs reported that no ocular or systemic AEs were observed.

The REPAIR study provided detail on AEs and these are described in Table 19. [redacted]

Table 19 Summary of adverse events reported in ≥ 2 patients in the REPAIR study

Adverse event	**Number (%) of patients (N = 65)**
Any adverse event	[redacted]
Any ocular adverse event	[redacted]
Eye pain	7 (10.8)
Conjunctival hemorrhage	4 (6.2)
Vitreous floaters	4 (6.2)
Foreign body sensation in eyes	[redacted]
Intraocular pressure increased	[redacted]
Metamorphopsia	[redacted]
Vision blurred	[redacted]
Visual acuity reduced	[redacted]
Any non-ocular adverse events	[redacted]
Nasopharyngitis	6 (9.2)
Lower respiratory tract infection	5 (7.7)
Back pain	4 (6.2)
Cough	4 (6.2)
Fall	4 (6.2)
Headache	4 (6.2)
Hypertension	[redacted]
Arthralgia	[redacted]
Dizziness	[redacted]
Gout	[redacted]
Influenza	[redacted]
Migraine	[redacted]
Musculoskeletal pain	[redacted]
Procedural nausea	[redacted]
Sinusitis	[redacted]
Tooth extraction	[redacted]
Upper respiratory tract infection	[redacted]

4.3 Critique of submitted evidence

Use of LOCF within Novartis phase III trial

The Novartis phase III trial used a modified last observation carried forward (mLOCF) approach. This was defined for a missing observation as the average of the observation immediately prior and the one immediately after. If both these observations were not measured, then the traditional LOCF was employed where possible, but baseline values were not carried forwards. The ERG requested the equivalent of Table 20 in the manufacturer submission (results for main outcomes), but for observed data only. It was found that the results using observed data did not substantially differ from that using mLOCF and therefore the ERG is not concerned by the use of this method.

Exclusion of Bevacizumab as a comparator

The manufacturer did not include studies of bevacizumab where ranibizumab was not present and the reasons surrounding this have been discussed earlier in this report. The ERG deemed it appropriate to search for and present the main characteristics of the studies assessing the effects of bevacizumab (see section 4.5), but due to time constraints did not conduct any formal evaluation of these studies.

Table 20 Results of the two head to head trials of bevacizumab versus ranibizumab

	Gharbiya 2010[1] (n = 16) 6 months		**Iacono 2012[2] (n=23) 18 months**	
	Bevacizumab	**Ranibizumab**	**Bevacizumab**	**Ranibizumab**
Mean (SD) change from baseline in BCVA letters	15.87 (8.41)	17.31 (11.1)	8.5 (1.25)	9 (NR)
Patients gaining ≥ 10 letters n (%)	13 (81.2)	12 (75)	NR	NR
Patients gaining ≥ 15 letters n (%)	10 (62.5)	9 (56.2)	11 (44.0)	7 (30.4)
Mean (SD) change from baseline in CRT	52 (NR)	-45 (NR)	NR	NR
Mean (SD) number of injections	2.44 (0.89)	2.81 (1.17)	4.72 (2.24)	2.65 (1.61)

The manufacturer did include two randomised trials of ranibizumab versus bevacizumab.[1,2] However, data related to the bevacizumab arms of these two trials were not provided in the current submission. The ERG considers these data useful and presents them in Table 20. Gharbiya 2010 did not find any significant differences between bevacizumab and ranibizumab for the outcomes described at six months. Similarly, Iacono 2012 did not find any significant differences between treatment groups at 18 months.

Despite their different primary endpoints, data were available to undertake a meta-analysis of six month outcomes as Iacono 2012 provided these data within their publication. The data were in the logMAR format and were combined in a recent systematic review conducted by Wang et al 2013.[23] Nevertheless, the manufacturer chose not to present one.

Use of three months as primary endpoint

The manufacturer has chosen three months as the primary endpoint for clinical effectiveness within the Novartis phase III trial of ranibizumab versus vPDT. Other studies in this clinical area have typically used 12 months and the ERG clinical opinion is that 12 months should be regarded as the bare minimum. The ERG is concerned at the choice of 3 months as the primary endpoint because this is unlikely to reflect the longer term efficacy of the treatment and will not provide accurate information on the number of treatments required to control the disease. For instance, the statistically significant difference observed in the primary outcome at three months between vPDT and placebo groups in the VIP trial, which evaluated a similar group of patients with CNV and pathological myopia to those participating in the Novartis phase III trial, were no longer observed at longer term (24 months). This seemed to relate to an increased proportion of patients in the vPDT arm experiencing deterioration in visual acuity (> 8 letter loss) over time (from 3 months to 24 months). A similar phenomenon could occur following ranibizumab. Furthermore, the ERG believes it is unlikely that such a short-term follow up (3 months) would provide adequate information about potential deleterious effects of the anti-VEGF treatment.

Using three months as the primary endpoint and allowing patients in the vPDT arm to receive ranibizumab after 3 months meant the manufacturer did not have any efficacy data for vPDT from the Novartis phase III trial to populate the economic model (see Chapter 5 for details). Instead they opted to use the data from the vPDT arm within the VIP trial for months 3 to 12. The implications of this are discussed in Chapter 5.

Lack of data on atrophy

Concerns have been raised with regards to the potential effect of anti-VEGF therapies in the development of retinal pigment epithelial (RPE) atrophy in the context of age-related macular degeneration .[36,37] RPE cells at the macula are required for normal visual functioning; if atrophy ensues, RPE cells are lost and visual loss follows. VEGF appears to be an essential factor for the maintenance of the RPE and choriocapillaris, [38,39] the latter being the layer of the retina that nourishes the RPE. Blocking the VEGF could therefore potentially have a detrimental effect in these retinal layers. In the CATT and IVAN trials of AMD patients, atrophy was most commonly observed in those patients who received monthly treatments when compared with those on pro re nata regimens, supporting the notion that anti-VEGF therapy may have an unwanted effect in the chorioapillaris-

RPE. Retinal pigment epithelial atrophy is a common feature in eyes with pathological myopia. It is likely that deleterious effects of anti-VEGF therapy on the RPE in pathological myopia, similar to those observed in eyes with AMD, may occur.

Unfortunately, the manufacturer did not consider atrophy among the potential adverse events of ranibizumab. Following clarification, the manufacturer explained that areas of RPE atrophy were not specifically measured during the course of the Novartis phase III trial. They maintain, however, that post-baseline assessments of morphological changes in colour fundus and OCT images did not seem to suggest that atrophy occurred during the 12-month treatment with ranibizumab. Further evaluation of the long-term efficacy and safety in subjects with CNV secondary to pathological myopia is planned by the manufacturer in a future 3-year observational study.

4.4 Critique of indirect and mixed treatment comparisons

The manufacturer did not present an indirect comparison of ranibizumab with other treatments. Their reason was that there was a head to head trial of ranibizumab versus vPDT, the only comparator considered in the submission. As bevacizumab was not included as a comparator they felt it unnecessary to undertake a network meta analysis. The manufacturer did present within Appendix 16 a preliminary network analysis including a number of treatments (observation, vPDT, ranibizumab, bevacizumab, laser). However, following clarification, they confirmed it was inappropriate given the heterogeneous nature of the study populations and the differing length of follow ups. Therefore, within the main submission, a network meta analysis of ranibizumab with treatments other than vPDT was not presented.

4.5 Additional work carried out by the ERG

The literature searching undertaken by the manufacturer for the clinical effectiveness review did not include any intervention or comparator terms hence it is very likely that any relevant trials of bevacizumab would not have been retrieved by the search. However, due to resource constraints, the ERG did not screen the replicated searches but rather undertook an independent search. This was more focused, primarily to identify any relevant RCTs, and was carried out on a restricted range of databases: MEDLINE, MEDLINE In-Process, EMBASE and CENTRAL. These searches were performed in June 2013 and so will have captured additional studies which had been added to the databases after the manufacturer's search in November 2012. The searches are detailed in Appendix 1.

After de-duplication and exclusion of the studies already included in the manufacturer's submission, 214 titles and/or abstracts were retrieved and screened.

Additional studies involving bevacizumab identified by the ERG

Table 21 shows the main characteristics of the potentially relevant randomised and non-randomised studies of bevacizumab identified by the additional literature search conducted by the ERG. Table 22 presents the details of the potentially relevant bevacizumab and ranibizumab efficacy studies further identified by the ERG.

Table 21 Characteristics of additional relevant randomised and comparative non-randomised studies identified by the ERG

Study	Design	Age Mean (SD)	Lesion location	Treatment (Dose)	No of eyes	Visual acuity Baseline Mean (SD)	Visual acuity Final Mean (SD)	Length of follow up
RCTs								
Liu 2013[40] (full text not available)	RCT	NR	NR	bevacizumab + fufangzueshuantong (dose NR) fufangzueshuantong only (dose NR)	22 20	NR	NR	12 months
Parodi 2010[41]	RCT	47.9	Juxtafoveal	bevacizumab (1.25mg) vPDT laser therapy	19 18 17	0.61 (0.30)[a] 0.52 (0.24)[a] 0.45 (0.27)[a]	0.42[ab] 0.72[ab] 0.56[ab]	24 months
Parodi 2006[42] (conference abstract)				vPDT vs laser therapy	NR	NR	NR	12 months
Non-randomised comparative studies								
Dethorey 2012[43] (full text not available)	Retrospective comparative	NR	NR	ranibizumab vPDT	18 27	20/160 20/80	20/63[c] 20/80[c]	12 months
El Matri 2011[44]	Retrospective comparative	54.4 (12.9)	Subfoveal, juxtafoveal	bevacizumab (1.25mg) vPDT	40 40	0.90 (0.85)[a] 0.88 (0.45)[a]	0.6[ab] 0.90 (0.54)[a]	12 months

Study	Design	Age Mean (SD)	Lesion location	Treatment (Dose)	No of eyes	Visual acuity Baseline Mean (SD)	Visual acuity Final Mean (SD)	Length of follow up
Baba 2010[45]	Retrospective comparative	62.6 (7.8)	Subfoveal, juxtafoveal	bevacizumab (1.25mg) vPDT	12 12	0.75 (0.25)[a] 0.77 (0.25)[a]	0.50 (0.38)[a] 0.78 (0.24)[a]	24 months
Ikuno 2010[46]	Retrospective open-label interventional case series	67.0 (7.0)	Subfoveal, juxtafoveal	bevacizumab (1mg) PDT	11 20	0.68 (0.29)[a] 0.74 (0.20)[a]	0.56 (0.34)[a] 0.92 (0.24)[a]	24 months
Hayashi 2009[47] Hayashi 2008[48]	Prospective open-label consecutive interventional case series	56.5 (13.8)	Subfoveal, juxtafoveal, extrafoveal	bevacizumab (1.25mg) vPDT vPDT	43 44 43	0.68 (0.29)[a] 0.61 (0.43)[a] 0.59 (0.42)[a]	0.45 (0.35)[a] 0.54 (0.40)[a] 0.56 (0.41)[a]	12 months Mean (SD) 15 (7) months
Chen 2011[49]	Retrospective comparative	51.4	Subfoveal	bevacizumab (1.25mg) bevacizumab (1.25mg) + vPDT	7 4	2 lines[d] 2.3 lines[d]		12 months
Lai 2012 [27]	Retrospective comparative	57.3 (13.0)	Subfoveal	bevacizumab (1.25mg) ranibizumab (0.5mg)	22 15	0.73 (0.39)[a] 1.04 (0.43)[a]	0.41 (0.32)[a] 0.49 (0.37)[a]	12 months
Yoon 2010[50]	Retrospective comparative	44.9 (13.8)	Subfoveal, juxtafoveal, extrafoveal	bevacizumab (1.25mg) or ranibizumab (0.5mg) vPDT	63 28	0.57 (0.46)[a] 0.54 (0.46)[a]	0.33 (0.34)[a] 0.60 (0.48)[a]	12 months

Study	Design	Age Mean (SD)	Lesion location	Treatment (Dose)	No of eyes	Visual acuity Baseline Mean (SD)	Visual acuity Final Mean (SD)	Length of follow up
Wakabayashi 2009[51]	Retrospective comparative	51.2 (15.2)	Subfoveal, juxtafoveal	bevacizumab (1mg)	34	0.34 (0.25)[a]	0.18 (0.24)[a]	12 months
				sub-Tenon triamcinolone acetonide	20	0.33 (0.27)[a]	0.32 (0.33)[a]	

[a] mean logMAR BCVA; [b] SD for follow up not reported; [c] median VA (units not reported) [d] Mean gain baseline to final; NR Not reported

Table 22 Further relevant bevacizumab and ranibizumab efficacy studies

Study	Intervention(s)	Design
Efficacy studies: bevacizumab		
Parodi 2013[52]	bevacizumab	Prospective open-label interventional
Sabry 2013[53]arodi 2013	bevacizumab	Prospective non-randomised interventional case series
Gharbiya 2012[54] Gharbiya 2009[55] Gharbiya 2010[56]	bevacizumab	Prospective non-randomised interventional case series
Hayashi 2012[57]	bevacizumab	Prospective open-label consecutive interventional case series
Macky 2012[58]	bevacizumab	Prospective non-randomised interventional case series
Niwa 2012[59]	bevacizumab	Retrospective review
Peiretti 2012[60]	bevacizumab	Retrospective consecutive non-randomised interventional case series
Ruiz-Moreno 2012[61] Ruiz-Moreno 2011[62] Ruiz-Moreno 2010[63] Ruiz-Moreno 2010[64] Ruiz-Moreno 2009[65] Ruiz-Moreno 2009[66]	bevacizumab	Retrospective non-randomised multicentre consecutive interventional case series
Uemoto 2012[67]	bevacizumab	Retrospective case series
Chen 2011[68]	bevacizumab	Prospective non-randomised interventional case series
Iacono 2011[69]	bevacizumab	Prospective single centre non-comparative consecutive case series
Kuo 2011[70]	bevacizumab	Consecutive case series
Nakanishi 2011[71]	bevacizumab	Retrospective non-randomised case series
Wakabayashi 2011[72]	bevacizumab	Retrospective review
Coppens 2010[73]	bevacizumab	Retrospective interventional case series
Scupola 2010[74]	bevacizumab	Prospective interventional case series
Voykov 2010[75]	bevacizumab	Retrospective interventional case series
Chan 2009[76]	bevacizumab	Prospective interventional case series
Dithmar 2009[77]	bevacizumab	Prospective interventional case series
Hayashi 2009[78]	bevacizumab (after vPDT)	Prospective interventional case series

Ikuno 2009[79]	bevacizumab	Retrospective case series
Spielberg 2009[80]	bevacizumab	Retrospective interventional case series
Wu 2009[81]	bevacizumab	Prospective consecutive case series
Yodoi 2009[82]	bevacizumab	Prospective interventional case series
Arias 2008[83]	bevacizumab	Prospective consecutive case series
Nguyen 2008[25]	bevacizumab	Prospective non-randomised comparative open-label
Rheaume 2008[84]	bevacizumab	Retrospective review
Rensch 2008[85]	bevacizumab	Retrospective review
Chan 2007[86]	bevacizumab	Prospective consecutive non-randomised interventional case series
Hernandez-Rojas 2007[87]	bevacizumab	Prospective interventional case series
Mandal 2007[88]	bevacizumab	Prospective non-comparative consecutive interventional case series
Sakaguchi 2007[89]	bevacizumab	Prospective non-randomised interventional case series
Yamamoto 2007[90]	bevacizumab	Retrospective review
Efficacy studies: ranibizumab		
Ellabban 2012[91]	ranibizumab	Prospective case series
Franqueira 2012[92]	ranibizumab	Retrospective non-randomised interventional case series
Troutbeck 2012[93]	ranibizumab	Prospective case series
Wu 2012[94]	ranibizumab	Retrospective review
Gedik 2011[95]	ranibizumab	Retrospective review
Lorenzo 2011[96]	ranibizumab	Retrospective case series
Qureshi 2011[97]	ranibizumab	Retrospective review
Varano 2010[98]	ranibizumab	Retrospective review
Konstantinidis 2009[99]	ranibizumab	Prospective consecutive interventional
Lai 2009[100]	ranibizumab	Retrospective review
Mones 2009[101]	ranibizumab	Prospective consecutive non-randomised interventional case series

4.6 Conclusions of the clinical effectiveness section

In summary, the Novartis phase III trial of ranibizumab versus vPDT found the following:

- Mean average change in BCVA from baseline (for months 1 to 3) was significantly higher in the two ranibizumab arms compared to vPDT.
- The proportion of patients gaining 15 or more letters at 3 months compared to baseline was significantly greater for the two ranibizumab arms compared to vPDT.

- Within subgroup analyses, the benefits of ranibizumab compared to vPDT at three months were evident regardless of age, sex, race, baseline visual acuity of CNV location.
- The most common ocular adverse event in the ranibizumab groups was conjunctival haemorrhage occurring in [redacted] had a conjuctival haemorrhage during the first 3 months.

Two additional RCTs were provided by the manufacturer comparing ranibizumab with bevacizumab and the manufacturer presented information for the ranibizumab arms only. Each study showed a benefit of ranibizumab but also found no difference between ranibizumab and bevacizumab.

The above summary conclusions should be considered against the following concerns of the ERG:

- the exclusion of bevacizumab as a comparator, and therefore lack of any formal meta-analysis or network meta-analysis including the different treatment options
- the choice of 3-month assessment as the primary endpoint to evaluate the efficacy and safety of ranibizumab

5 COST EFFECTIVENESS

5.1 ERG comment on manufacturer's review of cost-effectiveness evidence

Description of manufacturer's search strategy and critique

The disease-specific searches undertaken for the clinical effectiveness review were used to identify the cost-effectiveness studies. As well as the clinical databases, the appropriate health economic sources were searched and included EconLit and NHS EED. The manufacturer undertook additional, less focussed searches of MEDLINE and EMBASE for any economic evaluations associated with degenerative or pathological myopia without reference to CNV. The facets for the search (myopia and economic evaluation) were correctly constructed, using the relevant text and controlled vocabulary terms, and were combined correctly with Boolean operators. These are reproduced in Appendix 10.10 of the manufacturer's submission. Reference lists of eligible studies and recent reviews were checked for additional studies. This overall approach was considered by the ERG to be robust and likely to have retrieved the relevant articles.

Inclusion and exclusion criteria

Economic evaluations of patients undergoing any treatment for PM or CNV secondary to PM (including patients refractory to other therapies) were eligible for inclusion. Relevant outcomes included total, direct and indirect costs, summary health outcomes, utility values, cost-effectiveness ratios and number of cases of blindness.

Results and conclusions

The manufacturer's search identified one relevant study - Sharma and Bakal, 2002,[102] a cost-utility study based on data from the VIP trial. The Sharma and Bakal study considered cost-effectiveness of vPDT from the patient and insurer perspective in the United States and was based on costs for one year. The manufacturer judged that the study did not sufficiently address the ranibizumab decision problem and, therefore, developed a de novo Markov model.

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[a].
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 bevacizumab with vPDT uses data from the phase III trial and the VIP trial[b].
Outcome measure	Quality adjusted life years	Yes.

Superseded – see erratum

[a] 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.

[b] 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
Health states for QALY	Described using a standardised and validated instrument	No. The base case uses the Czoski-Murray utility function from the literature. This was an experimental study that temporarily reduced the BCVA of respondents using contact lenses. EQ-5D was administered during the phase III trial, but is not used. Novartis has used EQ-5D data in previous submissions for ranibizumab, but argues within this submission that EQ-5D is not appropriate for vision related quality of life.
Benefit valuation	Time trade-off or standard gamble	The Czoski-Murray utility function used for the base case analysis uses time trade-off.
Source of preference data for valuation of changes in HRQL	Representative sample of the public	No. The Czoski-Murray study was among 108 members of the UK general public.
Discount rate	An annual rate of 3.5% on both costs and health effects	Yes.
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes.

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.

Superseded – see erratum

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 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 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]

Superseded – see erratum

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, which occurred in more than 5% of the patients 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.

Perspective, time horizon and discounting

These are as per the NICE reference case.

The perspective for costs is that of the NHS and PSS. The perspective for benefits is that of the patient. The time horizon is 50 years, which is effectively a lifetime horizon given the baseline age of 55 years. Costs and benefits are discounted at an annual 3.5% rate.

Treatment effectiveness and extrapolation

Treatment effectiveness

For the ranibizumab arm, treatment effectiveness for the first four quarters of the model is based upon transition probability matrices (TPMs) between the 8 health states, the 64 cells of which are populated with patient level data drawn directly from the Novartis phase III trial.

For the vPDT arm, treatment effectiveness for the first quarter of the model is also based upon a TPM which is populated with patient level data drawn directly from the Novartis phase III trial. The treatment effectiveness for the second, third and fourth quarters is based upon TPMs which are populated with patient level data drawn directly from the VIP trial.

Bilateral involvement at baseline and incidence over time

Bilateral involvement only affects costs within the modelling. A baseline rate of bilateral involvement of 15% was drawn from two studies within the literature: one conducted in the USA on 269 patients, which reported bilateral Fuchs' spots in 17%, and a second conducted in France on 225 patients referred to tertiary care, which reported bilateral lesions among 14% of those with confirmed CNV secondary to PM. The model assumes zero incidence of CNV secondary to PM subsequent to baseline.[17,103]

Note that page 33 of the submission cites Ohno-Matsui et al[21] as estimating an annual incidence of myopic CNV of 0.98% per year, and an annual incidence of bilateral disease of 5.5%.

Ohno-Matsui et al followed 218 Japanese patients and 325 eyes with high myopia for the development of myopic CNV.[21] The follow up period ranged from 36 to 314 months, with an average of 130 months. Myopic CNV eventually developed in 33 of 325 eyes (10.2%, 32 patients). Among the 33 eyes that developed myopic CNV, 16 eyes (48.5%) were the fellow eyes of patients with pre-existing myopic CNV.

However, Ohno-Matsui et al did not follow patients with myopic CNV in one eye to estimate the rate of bilateral involvement in the fellow eye.[21] They also only studied eyes with pre-existing high

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) were included within the modelling. Therefore, adverse events such as retinal tears were not included. 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.

Superseded

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.

see erratum

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

proportion of the [redacted] who had their BSE treated at baseline. In this example, this applies to about [redacted] of the patients who had what was their BSE at baseline treated.

A similar effect applies if a proportion of these patients are modelled as improving to, say, HS02 with a BCVA of 76 letters to 85 letters. [redacted] of these patients are modelled as having their BSE treated. In effect, the improvement in the BCVA of the treated eye causes it to cross-over to become the BSE for a proportion of the [redacted] who had their WSE treated at baseline. In this example, this applies to about [redacted] of the patients who had what was their WSE at baseline treated.

This cross-over affects the calculation of both QALYs and the costs of blindness.

Extrapolation

The manufacturer submission identifies seven papers which include data on the rate of visual worsening over time, as summarised in Table 51 on page 162 of the submission. Table 51 is replicated below with some additional information.

Table 26 Natural history data for extrapolation

Study	Country	Mean age	Eyes	Follow up months	% BCVA decrease	BCVA loss/mth	% deteriorate per cycle
Hotchkiss (1981)[20]	USA	44	27	25.2	54%	2.90%	0.98%
Hampton (1983)[104]	UK	n.a.	42	40.8	71%	3.00%	1.02%
Secrétan (1997)[105]	France	41*	50	60.0	62%	1.60%	0.54%
Tabandeh (1999)[106]	USA	63	22	12.0	36%	3.70%	1.26%
Bottoni (2001)[107]	EU	44**	31	46.8	58%	1.90%	0.62%
Yoshida (2002)[6]	Japan	55***	47	86.4	51%	0.80%	0.28%
Kojima (2006)[108]	Japan	48****	54	60.0	85%	3.20%	1.07%

* Secrétan et al excluded patients over 60 years of age, and also only report the median age.

** Bottoni et al excluded patients over 55 years of age, and also only report the median age.

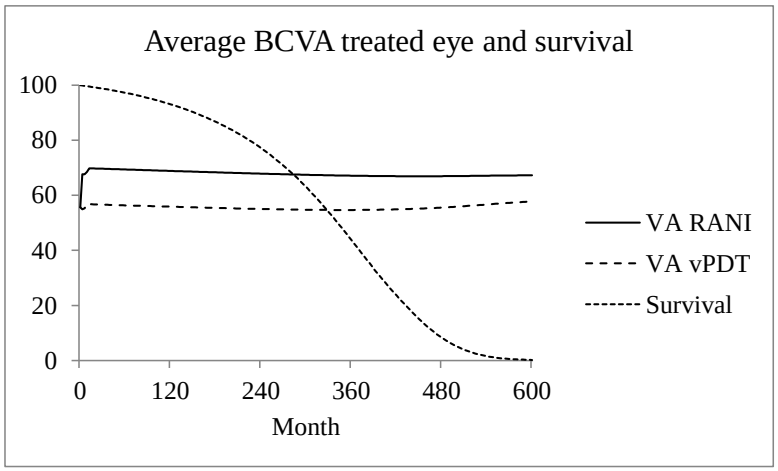
***Yoshida et al split their sample into those less than 40 years of age and those more than 40 years of age. Results here are reported for those of more than 40 years of age.

****Kojima et al split their sample into those less than 40 years of age and those more than 40 years of age. Results here are reported pooled across the patient population

The manufacturer model permits all of these papers or only a subset of these papers to be selected to provide a weighted average estimate for the quarterly rate of visual worsening that is used for extrapolation beyond year 1. The base case of the model selects only Yoshida et al because it has the longest duration of follow up.[6]

The base case assumes that, beyond the first year there is a quarterly 0.28% probability of worsening by one health state, as drawn from Yoshida et al.[6] The remaining 99.72% remain in their current health state for that quarter. This results in the following modelled evolution of visual acuity for the base case comparison of ranibizumab with vPDT.

Figure 3 Modelled evolution of visual acuity and survival: base case

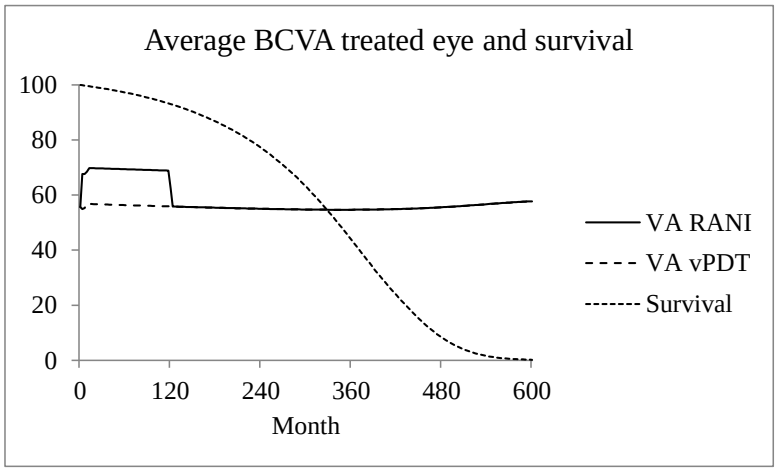


The literature searches undertaken by the manufacturer identified further six studies within the literature from which natural history estimates for extrapolation could be drawn. Yoshida et al provide the lowest estimate of the quarterly probability of worsening by one health state.[6] Including the results of all these studies, weighted by the number eyes studied, results in a quarterly 0.783% probability of worsening by one health state, based upon the manufacturer calculation.

Note that only the survival curve for the ranibizumab is given since for current purposes the survival curve for vPDT would be indistinguishable from it. But the slight rise in the average BCVA of the treated eye in the vPDT arm towards the end of the survival curve arises from the patients in the worse seeing health states being modelled as having a blindness mortality multiplier. As patients age and the general all-cause mortality risk increases, this effect begins to overtake that of the extrapolated visual decline as drawn from Yoshida et al.[6]

The model also has the facility to impose convergence after a given number of months. Figure 4 illustrates convergence at 10 years.

Figure 4 Modelled evolution of visual acuity: convergence at 10 years



The model also has the facility to model year 2 data as being drawn i) from the open label extension of ranibizumab as reported in Franqueira et al and ii) from the vPDT arm of the VIP trial.[3,92]

Table 27 Alternative extrapolation data for year 2

	Ranibizumab	vPDT
Gain ≤ 4 lines	0%	2%
Gain 2 to 4 lines	18%	15%
No change	76%	62%
Lose 2 to 4 lines	4%	18%
Lose ≥ 4 lines	2%	3%

Due to the higher proportion of patients worsening in the vPDT arm of the VIP trial, applying these values increases both the net patient gains and the net savings estimated for ranibizumab compared to vPDT.

Health related quality of life

Description of manufacturer's search strategies and critique

The manufacturer states that the search aimed to identify studies of utilities for patients with AMD or CNV due to AMD, because few studies were anticipated reporting utilities for patients with visual impairment due to CNV secondary to PM. The databases searched initially in April 2012 and again in November 2012 included MEDLINE, EMBASE, NHS EED, HEED, EconLit PROQOLID, CEA Registry and the HTA Database. The search structure combined the facets macular degeneration or CNV with quality of life terms. A comprehensive range of text and controlled vocabulary terms were used and were combined appropriately using Boolean logic. All these strategies were reproduced in Appendix 10.12 of the submission. The search strategies were considered fit for purpose and likely to be highly sensitive.

The base case uses HRQoL values for the BSE derived from Czoski-Murray et al.[4] A scenario analysis using values drawn from Brown et al[5] is also provided for within the model. The base case assumes a linear utility function for the WSE, with a HRQoL range of 0.1 from HS01 to HS08.

Table 28 Health state quality of life values

	Czoksi-Murray (2009)		Brown (1999)	
	BSE	**WSE**	**BSE**	**WSE**
HS01	0.850	0.850	0.920	0.920
HS02	0.758	0.836	0.880	0.906
HS03	0.685	0.821	0.770	0.891
HS04	0.611	0.807	0.755	0.877
HS05	0.537	0.793	0.670	0.863
HS06	0.464	0.779	0.665	0.849
HS07	0.390	0.764	0.645	0.834
HS08	0.353	0.750	0.510	0.820

Adverse events quality of life values

The estimates for the duration and quality of life impacts of adverse events are derived from the literature.

Table 29 Adverse events durations and quality of life values

				Ranibizumab		vPDT	
	Months	**Disutility**	**QALYs**	**%**	**Average**	**%**	**Average**
Conjunct. haemorrhage	1.000	-0.020	-0.002	8.50%	-0.000142	[redacted]	
IOP increased	0.030	-0.010	0.000	4.20%	-0.000001	[redacted]	
Visual Disturbance	0.000	0.000	0.000	0.00%		[redacted]	[redacted]
Injection site AEs	0.270	-0.134	-0.003	0.00%		[redacted]	[redacted]
Total QALYs					-0.000143		[redacted]

As shown in Table 29, the quality of life impacts from adverse events have minimal impact upon the modelling.

Resources and costs

Treatments, treatment visits and monitoring visits

The 3.5 ranibizumab treatments in year 1 is drawn from the Novartis phase III trial, while the 3.4 vPDT treatments in year 1 is drawn from the VIP trial. Only 1 ranibizumab treatment is assumed for

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, which reproduces Table 60 on page 184 of the submission, assumes that the monthly monitoring visits during the first year within the ranibizumab arm could double as treatment visits. However, treatment visits for vPDT are assumed to be in addition to the quarterly monitoring visits of the VIP trial.

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

Superseded – see erratum

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]

The costs of blindness

The cost of blindness in the incident year estimate is £17,326, with an annual cost estimate of £17,245 thereafter. This cost is applied to the proportion of patients modelled as having their BSE fall into either HS07 or HS08.

Cost effectiveness results

Deterministic results

Table 32 shows the results for the base case presented in section 7.7.6 of the submission.

Table 32 Deterministic results: ranibizumab versus vPDT

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

Probabilistic results

Table 33 shows the results of the probabilistic modelling run over 1,000 simulations.

Table 33 Probabilistic results: ranibizumab vs vPDT

	Ranibizumab	vPDT	net
Total costs	£9,580	£12,351	-£2,770
QALYs	12.98	12.56	0.41
ICER	Dominant	Dominated	..

Over the 1,000 simulations, only 9 iterations do not result in a cost-saving for ranibizumab, while all 1000 iterations estimate that ranibizumab results in QALY gains. Consequentely, ranibizumab is estimated to have a likelihood of being cost effective that is indistinguishable from 100% for all willingness to pay values.

Sensitivity analyses

Table 34, which replicates Table 77 on page 203 of the submission, illustrates the range of univariate sensitivity analyses performed by the manufacturer. The net health benefits relate to a willingness to pay of £20,000 per QALY

Table 34 Univariate sensitivity analyses

	Low value			High value		
	Δ £	Δ Q	NHB	Δ £	Δ Q	NHB
Ranibizumab injection frequency Y1 (0–12)	-£5,148	0.43	£13,787	£3,108	0.43	£5,531
Ranibizumab injection frequency Y2 (0–12)	-£3,307	0.43	£11,946	£4,538	0.43	£4,101
vPDT injection frequency Y1 (0–12)	£1,127	0.43	£7,512	-£12,647	0.43	£21,287
vPDT injection frequency Y2 (0–12)	-£1,007	0.43	£9,647	-£14,144	0.43	£22,784
Ranibizumab monitoring frequency Y1 (0–12)	-£4,420	0.43	£13,059	-£2,063	0.43	£10,703
Ranibizumab monitoring frequency Y2 (0–12)	-£3,506	0.43	£12,145	-£1,240	0.43	£9,880
vPDT monitoring frequency Y1 (0–12)	-£1,965	0.43	£10,604	-£4,322	0.43	£12,961
vPDT monitoring frequency Y2 (0–12)	-£1,996	0.43	£10,635	-£4,261	0.43	£12,900
Cost of monitoring visit (£0–1,500)	-£4,345	0.43	£12,984	£9,325	0.43	-£685
Cost of ranibizumab administration (£0–1,500)	-£4,124	0.43	£12,763	£8,097	0.43	£543
Cost of vPDT administration (£0–1,500)	-£1,233	0.43	£9,872	-£14,251	0.43	£22,890
Unit cost of ranibizumab (£0–3,000)	-£6,379	0.43	£15,018	£18,062	0.43	-£9,423
Unit cost of vPDT (£0–3,000)	£4,626	0.43	£4,013	-£21,410	0.43	£30,049
Cost of blindness (multiplier: 0.5–2)	-£2,477	0.43	£11,116	-£3,298	0.43	£11,937
Starting age (35 – 95)	-£3,295	0.50	£13,201	-£1,334	0.10	£3,337
Rate of recurrence (0–12%)	-£2,285	0.43	£10,924	-£3,217	0.43	£11,856
Baseline prevalence of bilateral disease (0–30%)	-£2,511	0.43	£11,151	-£2,989	0.43	£11,649
Probability study eye is the BSE (multiplier: 0.5–2)	-£2,486	0.39	£10,271	-£3,272	0.51	£13,557
Discount rate – costs (0–5.50%)	-£3,565	0.43	£12,205	-£2,478	0.43	£11,118
Discount rate – benefits (0–5.50%)	-£2,751	0.77	£18,168	-£2,751	0.33	£9,385
Utility curve for BSE (multiplier: 0.3–1.3)	-£2,751	0.32	£9,248	-£2,751	0.62	£15,099
Utility curve for WSE (0.05–0.60)	-£2,751	0.29	£8,660	-£2,751	1.83	£39,284
Ranibizumab TPMs – C1 (multiplier: 0.5–2)	-£2,351	0.35	£9,408	-£2,968	0.47	£12,464
Ranibizumab TPMs – C2 (multiplier: 0.5–2)	-£2,351	0.35	£9,449	-£3,038	0.50	£13,075
Ranibizumab TPMs – C3 (multiplier: 0.5–2)	-£2,669	0.39	£10,414	-£2,812	0.47	£12,280
Ranibizumab TPMs – C4 (multiplier: 0.5–2)	-£2,750	0.41	£10,937	-£2,752	0.47	£12,056
vPDT TPMs – C1 (multiplier: 0.5–2)	-£3,005	0.54	£13,733	-£2,544	0.33	£9,181
vPDT TPMs – C2 (multiplier: 0.5–2)	-£2,921	0.49	£12,781	-£2,561	0.37	£9,873
vPDT TPMs – C3 (multiplier: 0.5–2)	-£2,935	0.52	£13,267	-£2,591	0.35	£9,645
vPDT TPMs – C4 (multiplier: 0.5–2)	-£3,384	0.52	£13,862	-£2,228	0.34	£9,035
Natural progression (multiplier: 0.5–2)	-£2,555	0.43	£11,199	-£3,096	0.43	£11,694

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%.

Superseded

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.

Model validation and <u>face validity check</u>

see erratum

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.

The source of the discrepancy in the vPDT arm at 3 months is not known, but this should be read in conjunction with the section on patient level data and the transition probability matrices in section 5.3 below.

5.3 ERG cross check and critique

The ERG has rebuilt the deterministic model structure, though without a minor error relating to the manufacturer model mixing quantities that have half cycle correction with quantities that do not have half cycle correction. Both the net costs and the net QALYs of this rebuild cross check to within 1% of those of the manufacturer submission.

Base case results

The base case results cross check with those of the submission.

Data Inputs: Correspondence between written submission and sources cited

Quarterly rate of worsening used for extrapolation beyond year 1

In general, it appears that the rate of worsening increases with age. As a consequence, both the duration of follow up and the average age need to be considered when deciding which studies and relationships are most appropriate to include within the modelling. This is also in the context of the base case modelling a 55 year old patient.

It should be noted that it is typically unclear which papers measure changes in the best corrected visual acuity and which measure changes in the uncorrected visual acuity.

Yoshida et al compared the long term visual prognosis among 41 patients of 40 years or more with that among 22 patients of less than 40 years of age. Seventy seven percent had subfoveal involvement and 23% juxtafoveal involvement.[6] Their main finding was that while the younger patient group did not have a significant worsening in their LogMAR, the older patient group did. The patient data for the model relates to the 41 patients of 40 years or more, among whom 47 eyes were studied. During the mean follow up period of 86 months among the 47 eyes studies, 8 (17%) improved by two lines or more, 15 (32%) were stable and 24 (51%) worsened by two lines or more. Not taking into account the proportion that improves will overestimate the average rate of worsening over time.

While their follow up period is shorter than the mean 86 months of Yoshida et al,[6] both Kojima et al[108] and Secrétan et al[105] have quite long follow up of 60 months.

Kojima et al[108] estimate a function for the BCVA 5 years from onset of PM from CNV, based upon:

- a patient's age and initial BCVA for the pooled patient population; and,

- a patient's initial BCVA for the subset of patients aged over 40 years at onset.

It is not clear how the manufacturer has translated this data into the 85% estimate of the proportion of patients who lost at least 2 lines by year 5. Given the patient numbers cited, it also appears likely that the pooled regression was employed rather than the regression specific to the older age group subset.

Secrétan et al[105] excluded patients of over 60 years of age, resulting in a median age of 41 years. The aim of the study was to compare the effectiveness of laser treatment with no treatment, with 50 eyes being retrospectively selected for each group. It should be noted that Secrétan et al also supply scatter plots of initial visual acuity against the visual acuity for 50 natural history eyes at 5 years, for 41 natural history eyes as 8 years and for 13 natural history eyes at 10 years. Regression equations, split into three subgroups based upon their initial visual acuity, are also presented at 2 years, 5 years and 8 years. The 8 year follow up retained 82% of the natural history eyes and, as a consequence, Secrétan et al could be a source of follow up longer than that of the mean 86 months of Yoshida et al.[6] However, there is no easy link from Secrétan et al to the rate of visual deterioration estimated by the manufacturer.

Bottoni et al[107] excluded patients over 55 years of age, resulting in a median age of 44 years. The data cited by the manufacturer corresponds with the paper, though it should be noted that in addition to 58% worsening by at least two lines, 16% improved. These improvements were concentrated among those with juxtafoveal CNV with 4 patients out of 9 improving, compared to only 1 patient out of 22 with subfoveal CNV improving.

Hotchkiss et al[20] recruited 81 patients with severe myopia, with 33 of these patients having CNV, and four of these having CNV in both eyes. Follow up information was obtained for 23 patients and 27 of these eyes, with an average follow up of 25.5 months. This does not appear to cross check with the data used by the manufacturer. The ERG has not been able to derive the likelihood of worsening by two lines that the manufacturer estimates from Hotchkiss et al.

Hampton et al[104] recruited 42 patients, with around 18% being under 30 years, 50% being 30 to 55 years and 32% being older than 55 years. In contrast to the other papers, in Table 6 and in the text, Hampton notes that "*there was no statistically significant difference related to the length of follow up confirming that acuity is stable after initial loss*". Whether this result carries over to the older aged subgroup is not known. The ERG has not been able to derive the likelihood of worsening by two lines that the manufacturer estimates from Hampton et al. Similarly, the ERG has not been able to derive the likelihood of worsening by two lines that the manufacturer cites from Tabandeh et al.[106]

In the light of the above, Yoshida et al[6] and Kojima et al[108] appear to be reasonable sources based upon the patient ages. Secrétan et al[105] also appears to be a reasonable source, even though the exclusion of those over 60 years of age may be a concern.

The methods used to derive the estimates from Kojima et al[108] and Secrétan et al[105] are, however, not clear. Any estimates drawn from Kojima et al should also be specific to the older patient subgroup, but this may not be the case for the estimate of the manufacturer.

HRQoL data

The HRQoL values drawn from Czoski-Murray et al[4] for the modelling cross check with those of the rapid review of ranibizumab for diabetic macular oedema. It should be noted that the function of Czoski-Murray et al adjusts for age, and that the baseline age for the current modelling is 55 years compared to the 65 years of the rapid review of ranibizumab for diabetic macular oedema. This age effect has minimal impact upon the slope of the curve, but shifts it upwards by around 0.01.

For the sensitivity analysis that draws values from Brown et al[5] there may be some discrepancies. The ERG has not been able to source the manufacturer HRQoL values for Brown et al. Brown et al subdivided the BSEs into 12 BCVA groups, with TTO suggesting the HRQoL values presented in Table 36.

Table 36 HRQoL by BCVA in BSE: Brown et al 1999

BCVA in BSE	**ETDRS***	**n**	**TTO**
20/20	100	32	0.920
20/25	80	50	0.870
20/30	75	44	0.840
20/40	70	54	0.800
20/50	65	31	0.770
20/70		40	0.740
20/100	50	18	0.670
20/200	35	16	0.660
20/300	25	13	0.630
BCVA in BSE	ETDRS*	n	TTO
20/400	20	9	0.540
≤20/800 (CF)	5	12	0.520
≤20/1600 (HM/NLP)		6	0.350
*Some ETDRS letters are approximate; e.g. 25 letters is 20/320			

It appears that the BCVAs stated in Brown et al[5] form the upper bound of the range and extend down to the upper bound of the next best range. The ERG has assumed that there is not an exact mapping between the categories and for both HS01 and HS02, though a value of 0.920 could be used for both. Similarly, given that patients move into blindness within the modelling the most appropriate value for HS08 might be 0.540.

Table 37 HRQoL by BSE: TTO Czoski-Murray and, Brown 1999

			Manufacturer values		ERG values	
State	**ETDRS**	**Snellen**	**Czoski-M**	**Brown 99**	**Czoski-M**	**Brown 99**
HS01	86-100	>20/20	0.850	0.920	0.860	0.920
HS02	76-85	>20/32 to ≤20/20	0.758	0.880	0.768	0.920
HS03	66-75	>20/50 to ≤20/32	0.685	0.770	0.695	0.840
HS04	56-65	>20/80 to ≤20/50	0.611	0.755	0.621	0.770
HS05	46-55	>20/125 to ≤20/80	0.537	0.670	0.547	0.740
HS06	36-45	>20/200 to ≤20/125	0.464	0.665	0.474	0.670
HS07	26-35	>20/320 to ≤20/200	0.390	0.645	0.400	0.660
HS08	0-25	≤20/320	0.353	0.510	0.363	0.540

The costs of blindness

The annual cost of blindness is given as £17,245 referencing the ERG STA report for dexamethasone for retinal vein occlusion by Shyangdan et al.[109] The main elements within Shyangdan et al were the cost of residential care at an annual cost of £16,999 and the cost of community care at an annual cost of £6,708. The manufacturer estimates these as £51,090 and £10,006 respectively. The manufacturer also estimates a somewhat higher annual cost of depression: £2,291 compared to £500.

Shyangdan et al[109] drew a weekly cost for private residential care of £467 from the 2009 PSSRU unit costs of health and social care. This £467 was the residential care home fees, but excluded the other NHS and PSS costs and the personal living expenses within the PSSRU costing. The weekly £467 is equivalent to an annual £24,284, which was further qualified by 30% being privately funded as drawn from the Colquitt et al,[110] so resulting in an average annual cost to the NHS and PSS of £16,999. Shyangdan et al[109] noted that the £16,999 corresponded reasonably closely with the original Colquitt et al[110] reference of £15,750 in 2009 prices (£13,577 in 2005 prices). Including the other NHS and PSS costs and 70% of the personal living expenses within the PSSRU costing would increase it from £16,999 to £18,716.

The manufacturer drew a weekly cost for health authority residential care for older people of £983 from the 2011 PSSRU unit costs of health and social care, excluding the personal living expenses

within the PSSRU costings. This is equivalent to an annual cost of £51,090 and has not been qualified for the 30% being privately funded, which would reduce the £51,090 to £35,763.

The 2011 PSSRU unit costs of health and social care also list a weekly cost of £497 for private sector residential care for older people. This would suggest an annual cost of £25,844 which comes down to £18,091 when adjusting for the 30% who are privately funded. It appears that the vast majority of residential care is now provided by the private sector. The original Meads et al study[111] upon which Colquitt et al is based also used the PSSRU the cost of private residential care for elderly people.

It appears that Shyangdan et al[109] indexed the cost of community care by the HCHS to arrive at their estimate. However, as the manufacturer notes, the 2011 PSSRU unit costs of health and social care suggests a typical care home package of 12.4 hours per week. Given the items preceding this in the table of section 11.6 of the 2011 PSSRU unit costs of health and social care, the ERG interprets this as the amount worked rather than the amount of face to face contact, with face to face contact costing an additional 25%. There is some confusion within the table of section 11.6, but calculating an average cost per hour appears to be based upon an "average" working day of 7.86 hours. This is split between 6.6 hours during the weekday, 0.16 hours during the weekday evening, 0.55 hours on Saturday and 0.55 hours on Sunday at hourly costs of £18, £22, £27 and £36 respectively, yielding an average hourly cost of £20. For the typical care home package of 12.4 hours per week this amounts to £247, or £12,877 per year.

Meads et al[111] base their estimate upon the 2000 PSSRU unit costs of health and social care. Unfortunately, this is not available electronically, the earliest electronic copy that is available being the 2001 PSSRU unit costs of health and social care. This gave a somewhat shorter typical homecare package of only 5 hours per week and appears likely to be the main source of the difference between Shyangdan et al[109] and the manufacturer's submission.

The manufacturer estimates a cost for depression of £2,291 from McCrone et al,[112] this being a £2000 2006 cost inflated to 2011 using the HCHS index. McCrone et al was a substantial Kings Fund study of the costs of mental health care in England. The cost used is specific to depression. Within Meads et al,[111] the cost of depression was drawn from Knapp et al,[113] a study among people with affective disorders who had been recently discharged from a long stay psychiatric hospital in the UK. The sample was small (n=28) with average age of 62 years, and Meads et al[111] recognised that it would not closely mirror the population suffering visual loss in AMD. Given this, the estimate from McCrone et al[112] seems to be preferable. Note that around 10% of the total cost was for residential care. This should perhaps be excluded in order to avoid double counting, suggesting a slightly lower annual average cost of £2,062.

Applying the annual costs of £18,091 for residential care, £12,877 for community care and £2,062 for depression results in the estimates reported in Table 38.

Table 38 Revised costs of blindness

	%	Manufacturer		ERG
		Original	Revised	
Residential care	30.0%	£51,090	£35,763*	£18,091
Community care	6.0%	£10,006	£10,006	£12,877
Depression	38.6%	£2,291	£2,291	£2,062
Hip replacement	5.0%	£6,617	£6,617	£6,617
Low vision aids	33.0%	£167	£167	£167
Low vision rehabilitation	11.0%	£426	£426	£426
Blind registration	94.5%	£86	£86	£86
Initial cost		£81	£81	£81
Subsequent annual cost		£17,245	£12,647	£7,429
* revised to take into account 30% privately funded				

Note that in the above the ERG has not cross checked the other elements as these either contribute relatively little to the total cost or are broadly in line with the estimates within Shyangdan et al.[109]

Blindness mortality multipliers

The visual impairment mortality multipliers as applied within the model increase the net gains from ranibizumab from 0.354 QALYs to the 0.432 QALYs of the base case, a 22% increase. Given the base case annual cost of blindness of £17,326 the visual impairment mortality multipliers as applied within the model also increase the costs offset from the costs of blindness. However, the increase is only by £62 or around 11% of blindness cost offsets or 2% of the overall cost saving estimated from ranibizumab in the base case. The more muted impact upon the costs of blindness may be due to the visual impairment mortality multipliers of the model being applied to states other than blindness, coupled with the less effective arm having a higher mortality rate which may tend to reduce its total costs.

The manufacturer notes that the STA of dexamethasone for retinal vein occlusion also applied a mortality multiplier, as did the MTA of ranibizumab and pegaptanib for the treatment of age-related macular degeneration.

- The dexamethasone STA applied the 1.54 mortality multiplier for severe visual impairment of Christ et al[114], but it did not apply the 1.23 mortality multiplier for some visual impairment.

- The macular degeneration MTA appears to have applied a 1.50 mortality multiplier for visual impairment of worse than 6/60. It appears this was by assumption, the assumption being drawn from the manufacturer submission for ranibizumab.

The manufacturer modelling for the STA of ranibizumab for macular oedema secondary to retinal vein occlusion also drew visual impairment mortality multipliers from Christ et al,[114] apparently applying the same mortality multipliers as are applied for the BSE within the current submission. The manufacturer modelling for the STA of ranibizumab for diabetic macular oedema does not appear to include any visual impairment mortality multipliers.

Christ et al[114] is a study of a sample of adult respondents to the US National Health Interview Survey (NHIS). The paper is not clear about the number of respondents who had their data analysed. It notes that the NHIS includes a sample of 135,581 respondents. But it goes on to note that the sample analysed comprised those who provided sufficient data to enable linkage between the NHIS and the National Death Index and who were among the sixth of NHIS respondents selected to complete the visual impairment module.

Severe visual impairment was defined as respondent reported blindness in both eyes. Legal blindness in the US is also defined as a BCVA of 20/200 or less in the better eye; i.e. the BSE being in HS07 or HS08.

Some visual impairment was defined across a range of scenarios, though again the text is slightly ambiguous about this:

- Respondent reported visual impairment in both eyes, with one in blindness and one with visual impairment.
- Respondent reported visual impairment in one eye only, with the other eye having good vision or not being mentioned.

There may be some ambiguity in the definition of visual impairment in the US, but a BCVA of less than 20/60 appears the most reasonable definition for current purposes. Based upon the midpoint of the health states' BCVAs would seem to require the eye under consideration to be in HS04 or worse.

Two models are fitted by Christ et al[114]: a Cox proportional hazards model and a structured event equation model (SEM). The SEM not only takes into account the impact of vision, but also respondents' self-reported health and disability, the latter being measured as a latent variable with the indicators of bed days during the past fortnight and reduced activity days during the past fortnight.

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.

Superseded – see erratum

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 increases 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

above. Nevertheless, a literal reading of Christ et al[114] might argue for the 2nd alternative interpretation. This increases the gain from ranibizumab from the 0.432 QALYs of the base case to 0.511 QALYs and also causes the net cost savings to fall slightly from £2,751 to £2,710.

Christ et al[114] note the potential for misclassification in respondents' reported visual impairment. It is also unclear whether some visual impairment related to best corrected vision or uncorrected vision. Given these uncertainties, this might further argue for the 3rd alternative interpretation, as used in previous models submitted to NICE. Applying only the 1.54 mortality multiplier for the BSE and assuming no mortality multiplier for the WSE, reduces the gain from ranibizumab from the 0.432 QALYs of the base case to 0.369 QALYs. Further restricting the mortality multiplier to 1.48, to control for the effects of smoking, reduces the gain to 0.368 QALYs.

Data Inputs: Correspondence between written submission and electronic model

Transition probability matrices and patient level data

The patient numbers supplied in response to the ERG clarification question B6 appear to imply different transition probability matrices (TPMs) than those of the electronic model. This mainly applies to the patient numbers and TPMs in the ranibizumab arm, as outlined in greater detail in Appendix 3 of this report.

The impact upon the model of using the TPMs that seem to be implied by the patient numbers supplied in response to the ERG clarification question B6, this can first be assessed using the short term model outputs validation data.

Table 40 Alternative data sources for model TPMs for ranibizumab

	Original model		**Patient numbers**		**Trial**
	BCVA	**change**	**BCVA**	**change**	**change**
Baseline	55.6		55.6		
Month 3	67.6	12.0	68.1	12.5	12.5
Month 6	67.6	12.0	68.2	12.6	12.7
Month 12	69.8	14.2	70.2	14.6	14.4

Results are perhaps more in line with the trial for month 3 and month 6 when the patient numbers supplied in response to the ERG clarification question B6 are used. However, this then moves into a slight over prediction of the change from baseline for ranibizumab, compared to the original model which results in a similar slight under prediction.

Applying the TPMs that appear to be implied by the patient numbers provided in response to the ERG clarification question B6 suggests slightly larger QALY gains from ranibizumab of perhaps around 0.46 QALYs and slightly larger cost savings of around £3,141 due to larger savings in the costs of blindness compared to the base case.

As a consequence, there is a lack of clarity around what patient data set has been used to calculate the transition probabilities of the base case.

ERG commentary on model structure, assumptions and data inputs

Novartis phase III trial and VIP trial data

A key assumption underlying the modelling is that it is appropriate to bolt months 3 to 12 of the vPDT arm of the VIP trial[3] onto months 0 to 3 of the vPDT arm of the Novartis phase III trial.

Table 41 Proportions of patients with subfoveal, juxtafoveal and extrafoveal lesions

	Novartis phase III trial		**VIP trial**	
	Ranibizumab	**vPDT**	**vPDT**	**placebo**
Subfoveal	70%	69%	62%	69%
Probably subfoveal			19%	18%
Juxtafoveal	21%	29%		
Extrafoveal	3%	2%		
	Novartis phase III trial		**VIP trial**	
	Ranibizumab	**vPDT**	**vPDT**	**placebo**
Not subfoveal			14%	8%
Total juxta, extra and not subfoveal	**24%**	31%	**14%**	8%
No CNV/cannot grade	[redacted]	[redacted]	6%	5%
Not applicable	[redacted]	[redacted]	..	..
Missing	[redacted]	[redacted]	..	..

For months 3 to 12 of the modelling, the ranibizumab arm of the Novartis phase III trial with a total of juxtafoveal, extrafoveal and not subfoveal of 24% is being compared with a total of only 14% in the vPDT arm of the VIP trial.

As observed, for example, in Bottoni et al,[107] juxtafoveal CNV has a better functional prognosis than subfoveal CNV. Of 9 eyes with juxtafoveal CNV, 7 had a final visual acuity of ≥ 20/40 after a median follow up of 4 years. Of 22 eyes with subfoveal CNV only 2 had a final visual acuity of ≥ 20/40 with a median of 20/100 after a median follow up of only 2.5 years.

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.

Superseded see erratum

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.

Treatment and monitoring visits

No justification has been offered for the apparent assumption that monitoring visits can double as treatment visits for ranibizumab but not for vPDT. It may be argued that some patients may receive one stop treatment and other patients two stop treatment, with the proportions differing between ranibizumab and vPDT. However, the base case assumption is the most extreme that can be made and is to the benefit of ranibizumab.

In the absence of any consideration of the proportions receiving one stop and two stop treatment, it seems most reasonable to assume either that monitoring visits can double as treatment visits for both arms or that monitoring visits cannot double as treatment visits for both arms.

Calculation of quarterly rate of worsening for extrapolation

As acknowledged in the manufacturer's response to the ERG clarification question B17, there is an error in the calculation of the quarterly rate of worsening used for extrapolating beyond the first year. Correcting this reduces the net gain of the base case from 0.432 QALYs to 0.358 QALYs (a reduction of 17%). However, the cost saving that is modelled increases from £2,751 to £3,805.

This correction increases the importance of the rate of visual worsening. Applying the manufacturer weighted average across all seven papers rather than selecting only the results of the Yoshida et al[6] study resulted in a net gain of 0.426 QALYs and a net saving of £3,330. With the correction the net gain falls to only 0.186 QALYs, a reduction of 56%. The cost saving also falls from £3,330 to £2,806 which is roughly in line with the £2,751 of the original base case.

It worth noting that the papers, such as Yoshida et al[6], report the proportion of patients worsening by two lines or more during follow up. The manufacturer calculation, in effect, assumes an exponential survival curve to estimate the proportion of those that worsen each month. However, this may over-estimate the monthly rate of worsening since the estimate is, in effect, compounded for those modelled as worsening relatively early. In other words, the exponential rate is, in a sense, re-applied each month among all patients including those who have already been modelled as worsening by two lines. The effect of this will be counterbalanced, to some extent, by the data from Yoshida et al relating to a loss of at least two lines.

HRQoL data sourced from the literature

Czoski-Murray et al[4] explored the feasibility of using contact lenses to simulate the severity of three different BCVAs of AMD: LogMARs of 0.6 from Lens1, 1.0 from Lens2 and 1.4 from Lens3. 108 respondents were recruited to the study: 107 had a BSE BCVA of LogMAR≤30 (≥20/40) and 104 wore all three sets of contact lenses. HRQoL was measured using TTO, with this being anchored at full health and immediate death. Given patient characteristics this enabled the mean HRQoL to be estimated over four ranges of BCVA in the BSE as shown in Table 42.

Table 42 Czoski-Murray HRQoL values

	Lens1		Lens2		Lens3		Overall	
LogMAR	**n**	**HRQoL**	**n**	**HRQoL**	**n**	**HRQoL**	**n**	**HRQoL**
≤0.3	18	0.778	23	0.649	0		41	0.706
0.31-0.60	40	0.731	40	0.649	9	0.603	89	0.681
0.61-1.30	46	0.653	41	0.486	38	0.366	125	0.511
≥1.31	0		0		56	0.314	56	0.314
Total	104	0.705	104	0.585	103	0.358	311	0.550

This resulted in two regression equations, one controlling for age and the other not. These were also compared with similar regression equations derived from a patient survey among AMD patients undertaken by Espallargues et al,[115] whose colleagues included Czoski-Murray. Espallargues measured TTO, HU13 and EQ-5D among 209 UK AMD patients and related these to the VA of the BSE. Valuation of the EQ-5D data was based upon the UK social tariff, while valuation of the HU13 index was apparently based upon the VAS and standard gamble conducted among a sample of the Canadian public. Note that the regression models reported below are only reported in Czoski-Murray.[4]

Table 43 Czoski-Murray HRQoL models

	Lens study		**Survey of AMD patients**					
Method	**TTO**		**TTO**		**HUI3**		**EQ-5D**	
Models	**coef**	**s.e.**	**coef**	**s.e.**	**coef**	**s.e.**	**coef**	**s.e.**
Not controlling for Age								
Constant	0.828	0.039	0.753	0.038	0.479	0.033	0.745	0.027
VA LogMAR	-0.359	0.045	-0.087	0.031	-0.140	0.027	-0.027	0.023
Adjusted R^2	0.171		0.032		0.110		0.002	

	Lens study		**Survey of AMD patients**					
Method	**TTO**		**TTO**		**HUI3**		**EQ-5D**	
Models	**coef**	**s.e.**	**coef**	**s.e.**	**coef**	**s.e.**	**coef**	**s.e.**
Controlling for Age								
Constant	0.860	0.068	1.737	0.217	1.078	0.198	0.753	0.164
VA LogMAR	-0.368	0.046	-0.036	0.032	-0.109	0.028	-0.027	0.024
Age	-0.001	0.002	-0.013	0.013	-0.008	0.003	0.000	0.002
Adjusted R^2	0.172		0.121		0.147		0.003	

Czoski-Murray[4] noted that the coefficient from TTO values obtained from the lenses study within the model not correcting for age was "*over four times the size of the patients' own TTO coefficients and 13 times the coefficient for the EQ-5D*" and that controlling for age "*increased the differences between the coefficients on the VA for the TTO values*". They further argued that "*By comparing our sample with a patient sample, we have drawn attention to the potential use of a simulation method; however, the nature of the sample and the problems encountered with the lenses themselves makes any true comparison impossible at this stage*", and that "*Our sample was considerable younger than the patient study and therefore comorbidities in the older population may be an issue*". They concluded that "*Further validation work comparing or combining vignettes and contact lens simulation methods may make it possible to use this method in the future to obtain general population values for an important health condition*".

Brown et al[5] employed Time Trade Off (TTO) and Standard Gamble (SG) to assess the HRQoL among 325 US patients with impaired vision of at least 20/40 in at least one eye. This enabled Brown et al to split the sample by the BCVA of their BSE into a reasonably fine gradation while retaining reasonable patient numbers within each gradation for the estimation of the mean value, as has been previously outlined in Table 36.

Neither Czoski-Murray or Brown are entirely in line with the NICE TAPs methods. Brown has the advantage of using patient level data measured over a wide range of BCVAs. There may be some concerns that the relatively brief period of time Czoski-Murray respondents spent being visually impaired, and the limited number of tasks they were required to complete during this time, may not fully reflect the experience of severe visual impairment and possible acclimatisation to it over the longer term.

Novartis phase III trial EQ-5D data

The Novartis phase III trial collected EQ-5D data. The pooled HRQoL values using the UK social tariff are supplied by the manufacturer in response to the ERG clarification questions B12 and B13. The response to B12 gives the EQ-5D values split by arm and time point (Table 44).

Table 44 Mean EQ-5D split by arm and time point

	Month 0	Month 3	Month 6	Month 12
Ranibizumab				
mean	0.811	0.856	0.828	0.855
s.e.	0.019	0.014	0.020	0.017
Δ baseline	..	0.045	0.017	0.044
vPDT				
mean	0.832	0.831	0.855	0.862
s.e.	0.027	0.027	0.027	0.022
Δ baseline	..	-0.001	0.023	0.029

The response to B13 gives the EQ-5D values pooled across arms and time points but split by BCVA (Table 45).

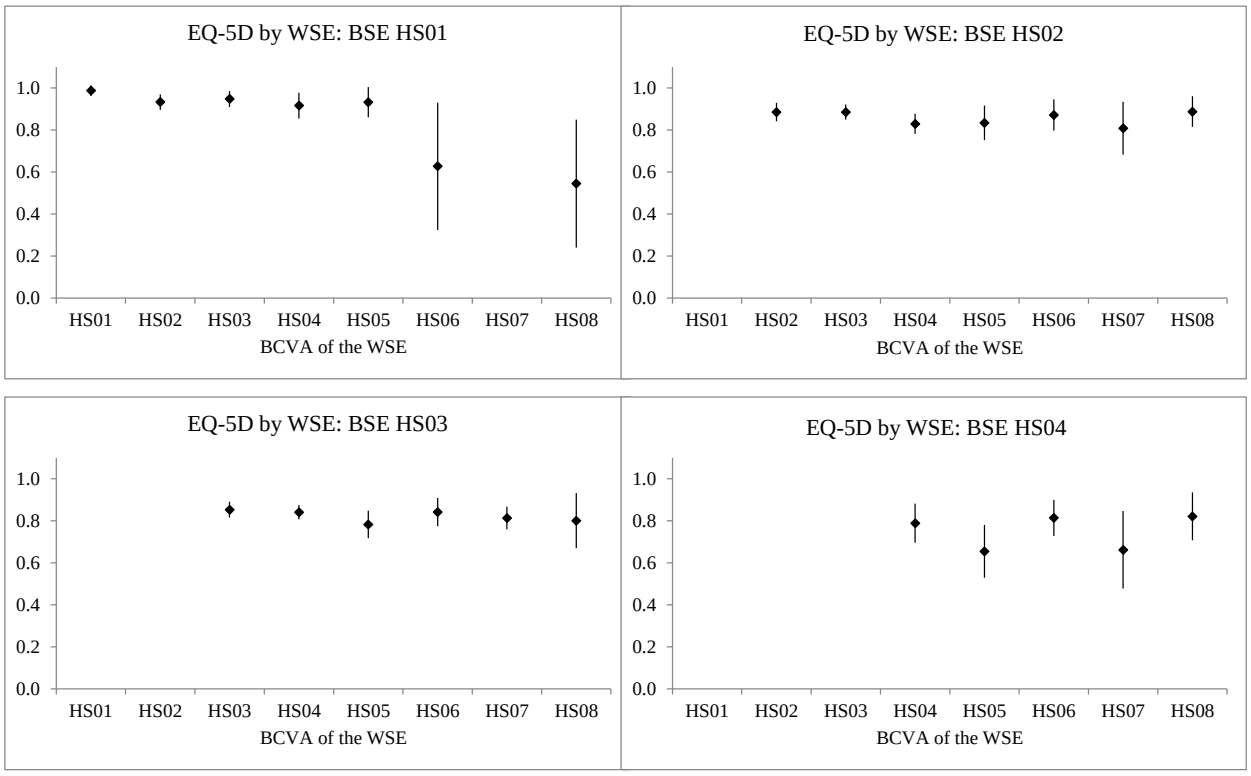
Table 45 Mean EQ-5D split by BCVA

		BSE BCVA						
		HS01	**HS02**	**HS03**	**HS04**	**HS05**	**HS06**	**HS07**
WSE BCVA	**HS01**	0.987						
	HS02	0.933	0.885					
	HS03	0.947	0.885	0.853				
	HS04	0.915	0.829	0.840	0.788			
	HS05	0.932	0.833	0.782	0.654	0.750		
	HS06	0.627	0.871	0.841	0.814	0.708	0.843	
	HS07	0.585	0.808	0.813	0.661	0.702	0.792	0.938
	HS08	0.544	0.887	0.801	0.821	0.543	0.690	0.673

Trial EQ-5D data: WSE impacts

Coupling the above values with their standard errors, and assuming symmetric confidence intervals in the absence of other information, the impact of changes in the BCVA of the WSE can be graphed separately for patients whose BSE is in HS01, HS02, HS03 and HS04 (Figure 5). The values for those whose BSE is in HS05, HS06 and HS07 are not presented graphically mainly due to the relatively small number of patients underlying many of the values.

Figure 5 Mean EQ-5D and confidence intervals split by BCVA: WSE plots



What is immediately striking in Figure 5 is the lack of any obvious relationship between HRQoL and the BCVA in the WSE.

This is also broadly in line with Brown et al[5] of whose 325 patients with impaired vision of at least 20/40 in at least one eye there were 78 patients with good vision of 20/20 to 20/25 in one eye. These patients were subdivided by the BCVA in the fellow eye into 5 groups with TTO and SG being applied to them (Table 46).

Table 46 HRQoL by BCVA in WSE among patients with good vision in BSE: Brown et al 1999

BCVA in WSE	n	TTO	SG
20/40-20/50	18	0.860	0.930
20/70-20/100	12	0.900	0.960
20/200-20/400	13	0.950	0.940
≤ 20/800 (CF)	28	0.880	0.920
≤ 20/1600 (HM/NLP)	7	0.810	0.950

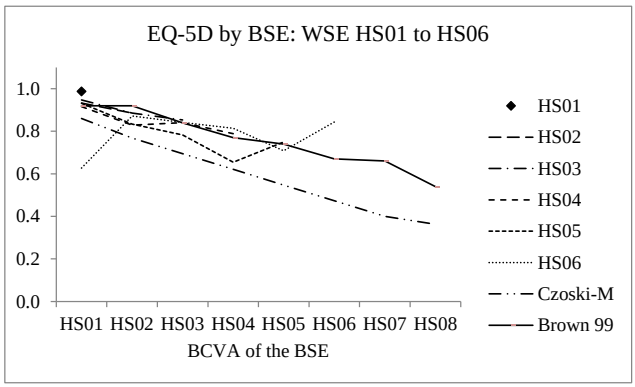
CF: Counting fingers
HM: Detecting hand movement
NLP: No light perception

No obvious pattern was observed between changes in the BCVA of the WSE and the average HRQoL measured by TTO or standard gamble.

Trial EQ-5D data: BSE impacts

Similarly, the impact of changes in the BCVA of the BSE upon HRQoL, can be presented separately for those patients whose WSE is in HS01, HS02, HS03, HS04, HS05 and HS06. These can also be presented graphically alongside the ERG Czoski-Murray et al BSE HRQoL curve[4] and the ERG Brown BSE HRQoL curve.[5]

Figure 6 Mean EQ-5D intervals split by BCVA: BSE plots



Given the previous exploration of the impact of changes in the BCVA of the WSE, the curves in Figure 6 largely overlap one another (i.e. there is not a clear vertical separation between the curves as the BCVA WSE of the fellow eye worsens).

It is not clear whether the curves more closely follow the Czoski-Murray et al curve or the Brown et al curve. A casual visual inspection might suggest that the BSE EQ-5D curve for patients whose fellow WSE is in HS05 more closely follows the Czoski-Murray et al curve, while the remainder of the BSE EQ-5D curves more closely follow the Brown et al curve.

HRQoL WSE in the model

A change in the BCVA of the WSE from HS01 to HS08 is assumed to result in a 0.100 worsening in HRQoL. The Czoski-Murray et al[4] HRQoL function of the BSE ranges from 0.850 for HS01 to 0.353 for HS08, a span of 0.497.

In other words, for the base case the manufacturer assumes that a change in the BCVA of the WSE has approximately 20% of the HRQoL impact of the same change in the BCVA of the BSE.

For the sensitivity analysis using the Brown et al[5] HRQoL functions, the manufacturer assumes that a change in the BCVA of the WSE has approximately 25% of the HRQoL impact of the same change in the BCVA of the BSE. A number of NICE assessments have, at the suggestion of the assessment committee, assumed that a change in the BCVA of the WSE has 30% of the HRQoL impact of the same change in the BCVA of the BSE. However, these percentages also need to be read in conjunction with the previous section examining the impact of changes in the BCVA of the WSE upon EQ-5D HRQoL values.

Adverse event quality of life impacts

It appears that the average per patient quality of life impacts have been divided by the cohort size, so further reducing them by a factor of 1,000. This has minimal impact upon the model outputs.

Cross-over, quality of life and the costs of blindness

The model combines the proportions having their BSE affected with the quality of life values associated with the BSE and the quality of life values associated with the WSE to arrive at a weighted average.

For the calculation of the QALYs associated with each health state, the simple weighted averages can be presented as below[c].

Table 47 QoL weighted average of BSE and WSE

		HRQoL		
State	**% BSE**	**BSE**	**WSE**	**Weighted**
HS01	[redacted]	0.850	0.850	[redacted]
HS02	[redacted]	0.758	0.836	[redacted]
HS03	[redacted]	0.685	0.821	[redacted]
HS04	[redacted]	0.611	0.807	[redacted]
HS05	[redacted]	0.537	0.793	[redacted]
HS06	[redacted]	0.464	0.779	[redacted]
HS07	[redacted]	0.390	0.764	[redacted]
HS08	[redacted]	0.353	0.750	[redacted]

With regard to Table 47, it is important to understand the underlying logic of a move between the health states. In moving from, say, HS02 to HS03 there are [redacted] of WSE patients who are assumed to remain as WSE patients and so go from a quality of life of 0.836 to a quality of life of 0.821. There are [redacted] of BSE patients who are assumed to remain as BSE patients and so go from a quality of life of 0.758 to a quality of life of 0.685. But there are [redacted] of BSE patients who are assumed to cross-over to be WSE patients and so have their quality of life go from 0.758 to 0.821 (i.e. to experience an improvement in their quality of life in spite of the worsening of the BCVA of their treated eye).

The results of this are that despite the move from HS02 to HS03 being associated with a QoL loss of 0.758 – 0.685 = -0.073 for BSE patients and a QoL loss of 0.836 – 0.821 = -0.014 for WSE patients, the weighted QoL loss is only [redacted]. Due to the cross-over effect, the weighted QoL loss is less than even the QoL loss for WSE patients. This is most clearly seen in the move from HS07 to HS08 which is actually associated with a QoL gain within the modelling.

For the costs of blindness, similar considerations will apply to the proportion of patients that should be modelled as crossing over from having their BSE treated to it becoming their WSE when it falls into blindness. For those whose treated eye was originally their BSE, some will be modelled as having this eye fall into HS07 or HS08. Suppose this occurs from HS06. The [redacted] in HS06 whose treated eye is their BSE falls to only [redacted] in HS07. In other words, an absolute [redacted] more patients are modelled as having their treated eye cross-over from being their BSE to be their WSE and as a consequence to not

[c] The impact of this can be explored by setting columns X:AE in the *Calculations* worksheet equal to zero, then each column equal to one in isolation and examining the *Tx_QALYs* worksheet.

incur the costs of blindness. For those moving from HS06 to HS07 whose BSE was treated, this cross-over to the WSE amounts to [redacted]

[redacted][d].

In the light of the above, the current economic model might be best seen as a model of the BSE or as a model of the WSE with an additional assumption of no cross-over[e].

Cross-over should, however, not be considered. So far, most STAs modelling has only considered single eye modelling and therefore the above errors have not occurred. Previous STAs have also implicitly assumed that there is no cross-over and that if the treated eye is at baseline the BSE (WSE), it remains the BSE (WSE) throughout the period of the modelling. The effect of correctly incorporating cross-over upon net QALYs is difficult to predict, but the effect upon net costs seems likely to be to reduce them due to a smaller net costs of blindness.

The likelihood of cross-over is difficult to assess, but can be speculatively assessed by examining the difference in the number of health states between the BCVA of the BSE and the BCVA of the WSE at baseline. This can be done for the two subgroups of those who had their WSE treated at baseline and those who had their BSE treated at baseline.

The likelihood of cross-over for those who had their WSE treated at baseline can be assessed by examining the proportions of patient gaining a sufficient number of letters within the ranibizumab arm of the Novartis phase III trial and the vPDT arm of the VIP trial at 12 months.

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[d] [redacted] Again, the impact of this can be explored by setting columns X:AE in the *Calculations* worksheet equal to zero, then either column AD or column AF equal to one and examining the *Tx_Costs* worksheet.

[e] Implemented by either setting cells D24:D31 of the *Inputs_(2)* worksheet to all be 100% or to all be 0%.

Table 48 Differences in baseline BCVAs of BSE and WSE: WSE treated at baseline

	BCVA BSE superiority over BCVA WSE at baseline						
	Same	**+1 HS**	**+2 HS**	**+3HS**	**+4 HS**	**+5 HS**	**+6 HS**
WSE treated	8.4%	29.0%	26.2%	23.8%	7.9%	3.7%	0.9%
	12 months letters gained required for cross-over						
Minimum letters gained	10	20	30	40	50	60	70
RANI phase III trial[f]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
vPDT VIP trial[g]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The above may suggest that cross-over from the treated eye being the WSE to becoming the BSE may be more likely among those treated with ranibizumab than among those treated with vPDT.

Table 49 Differences in baseline BCVAs of BSE and WSE: BSE treated at baseline

	BCVA BSE superiority over BCVA WSE at baseline						
	Same	**+1 HS**	**+2 HS**	**+3HS**	**+4 HS**	**+5 HS**	**+6 HS**
BSE treated	19.0%	31.7%	19.0%	15.9%	9.5%	4.8%	0.0%
	12 months letters lost required for cross-over						
Minimum letters lost	10	20	30	40	50	60	70
RANI phase III trial	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
vPDT VIP trial[h]	[redacted]	[redacted]	[redacted]	n.a.	n.a.	n.a.	n.a.

Unfortunately, the manufacturer's response to the ERG clarification question A6 provided the data in a format different from that of the manufacturer's response to the ERG clarification question A5. Apparently this was due to some confusion when the manufacturer sought further clarification from the ERG about the desired format. Subsequent to the manufacturer response, the ERG highlighted this to NICE, and asked if it would be possible to request the data for the ERG clarification question A6 in the same format as the ERG clarification question A5. NICE declined to do this on grounds of it being outwith normal process. As a consequence, it was not possible to assess the relative likelihood of cross-over from the treated eye being the BSE to becoming the WSE between the arms.

However, the above is only presented for those whose BSE was treated at baseline across the pooled patient population. It should also be borne in mind that, for modelling purposes, the most relevant cross-over aspect is the cross-over for patients whose treated BSE is likely to be modelled as falling into blindness, and so the affecting the likelihood of the costs of blindness being incurred.

[f] From Table 20 of the manufacturer's submission and response to ERG clarification question A6 table 7
[g] From response to ERG clarification question A5 table 5
[h] From response to ERG clarification question A5 table 6

The above should be read as a first exploration of the possibilities of cross-over. However, it is naïve as it uncritically directly compares data from the two trials, and therefore should be treated with caution.

All the above considerations around the likelihood of cross-over would be further complicated by bilateral involvement at baseline and its development over time, the associated treatment of the fellow eye and the resultant changes in its BCVA.

Populating the transition probability matrices and the probabilistic modelling of the TPMs

The TPMs are based upon 112 patients for ranibizumab, 56 patients for vPDT for baseline to month 3 and 82 patients for vPDT for 3 months to 12 months as this latter is drawn from the vPDT arm of the VIP trial. Given the 8 health states of the model, this is in the context of being required to populate TPMs with 64 entries. While the patient numbers are typically clustered around the principal diagonal of the TPM with zero probabilities for the more extreme transitions, this still results in quite a large number of probabilities being populated by relatively few patients. Based upon the patient numbers supplied in response to the ERG clarification questions, the empty columns, the number of populated cells, the number of populated cells with only one patient, the number of unpopulated cells and the number of unpopulated cells that are “holes” in the TPMs, can be presented.

The “holes” in the TPMs refer to cells with a zero probability that are flanked by cells with non-zero probabilities. For instance, in the vPDT arm, among those in HS02 at baseline there is a 67% probability of them transferring to HS03, a 33% probability of them transferring to HS07 but a 0% probability of them transferring to HS04, HS05 or HS06. These 0% probabilities are the “holes” in the TPM.

Table 50 Population of the TPM cells

	Ranibizumab				**vPDT**			
TPM for months	0 to 3	3 to 6	6 to 9	9 to 12	0 to 3	3 to 6	6 to 9	9 to 12
Empty columns out of 8	2	1	1	1	1	3	1	1
Cells populated	20	21	19	20	21	19	22	18
of which populated by 1 patient	1	8	5	10	8	8	11	5
Cells not populated	44	43	45	44	43	45	42	46
of which "holes" in the TPM	1	3	0	0	4	0	1	1

The empty columns are health states which contained no patients at the beginning of the period. Empty columns are populated by the simplifying assumption that patients remain in their current health state for that period. As would be expected for months 0 to 3, the column for HS01 is empty in

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.

Superseded – see erratum

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[i].
- Assumed a two stop model for monitoring and dosing[j].

[i] Implemented within the *Cost_Inputs* worksheet by setting cell F30=1.7
[j] Implemented within the *Cost_Inputs* worksheet by setting cell E30=12, E31=4, G30=4 and G31=4

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

The impact of these changes is assessed for the ERG utility values[o], 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[p], 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

Superseded – see erratum

	Ranibizumab	vPDT	Incremental
Total costs	£10,743	£12,529	-£1,786
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			£8,673

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

	Ranibizumab	vPDT	Incremental
Total costs	£10,743	£12,529	-£1,786
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			£7,116

[k] Implemented within the *Mortality* worksheet cells H11:I18
[l] Implemented within the *Resource_Use* worksheet cells D19:D20
[m] Implemented within the *Natural_history* worksheet cells H25:H31
[n] Implemented within the *Tx_QALYs* worksheet and the *Comp_QALYs* worksheet by not dividing cell O11 by the cohort size
[o] Implemented within the *QoL* worksheet cells D86:K86 and D89:K89
[p] 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	-£1,786	0.344	£8,673
Duration of benefit			
1 year	-£1,107	0.078	£2,674
5 years (a)	-£1,178	0.143	£4,037
10 years	-£1,358	0.209	£5,530
20 years	-£1,676	0.296	£7,591
Proportion BSE			
0%	-£1,081	0.282	£6,714
100%	-£19,585	1.260	£44,785
All natural history studies (b)	-£1,342	0.189	£5,123
(a) and (b) together	-£1,276	0.065	£2,570
1 stop treatment	-£1,806	0.344	£8,692

Superseded – see erratum

Table 54 Sensitivity analyses: Czoski-Murray 2009 utility values

	Δ cost	Δ QALY	NHB
Base case	-£1,786	0.266	£7,116
Duration of benefit			
1 year	-£1,107	0.001	£1,118
5 years (a)	-£1,178	0.065	£2,481
10 years	-£1,358	0.131	£3,974
20 years	-£1,676	0.218	£6,035
Proportion BSE			
0%	-£1,081	0.282	£6,713
100%	-£19,585	1.478	£49,152
All natural history studies (b)	-£1,342	0.119	£3,728
(a) and (b) together	-£1,276	-0.005	£1,175
1 stop treatment	-£1,806	0.266	£7,136

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 50% and 60% 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.

Superseded – see erratum

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

changes in the BCVA of the WSE have little impact upon HRQoL. If so, this would tend to somewhat reduce the net patient gains.

ERG model revisions reduce the anticipated net patient gains and cost savings from ranibizumab over vPDT, but they typically do not reverse them. However, the ERG cannot address the effects of cross-over within the model or the differing proportions with non-subfoveal involvement. It has also not explored reducing the quality of life impacts from changes in the BCVA if the WSE, in part due to the possible problems in the modelling regarding cross-over.

Given the eight health states of the model there may be some issues around populating the sixty-four cells of the transition probability matrices given the patient numbers involved, particularly in the vPDT arm. This could have been addressed within the probabilistic modelling, but the ERG does not have confidence in the probabilistic modelling.

No comparison of ranibizumab with bevacizumab has been made in the current manufacturer's submission.

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 £1,786 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 £8,673. 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 £7,116.

Superseded – see erratum

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 £1,178, 0.143 QALYs and £4,037 respectively using Brown et al 1999.[5] The corresponding figures using Czoski-Murray et al are £1,178, 0.065 and £2,481[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 £1,342, and the net gains to 0.189 QALYs and the net health benefits to £5,123 using Brown et al[5] and to 0.119 QALYs and £3,728 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 £1,276. 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 £2,570. 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 £1,175. Given the QALY loss for this scenario the ICER for vPDT compared to ranibizumab is £254k 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.

In particular, the higher rate of non-subfoveal involvement in the Novartis trial may benefit ranibizumab.

7 OVERALL CONCLUSIONS

The current submission focuses on a phase III RCT, sponsored by the manufacturer (Novartis), which compares two ranibizumab 0.5mg arms (disease activity arm and stabilisation arm) with a vPDT arm at three months. In particular, the Novartis phase III trial consisted of a 3-month double-blind phase during which the efficacy and safety of ranibizumab is compared to those of vPDT, and a 9-month non-comparative phase, which provided data on the efficacy and safety of ranibizumab only. Additional evidence for the assessment of the safety and efficacy of ranibizumab is provided by the findings of two small RCTs comparing ranibizumab with bevacizumab and 6 non-randomised studies. Further evidence for the assessment of the efficacy of vPDT is provided by the findings of the VIP trial. No standard meta-analyses or indirect mixed treatment comparisons are presented in the current submission. Data from the Novartis phase III trial and the VIP trial are used in the economic model.

Clinical Effectiveness

Results from the Novartis phase III trial indicate that 0.5mg ranibizumab is clinically more effective than vPDT in improving visual acuity at 3 months. In particular statistically significant differences were observed between ranibizumab and vPDT at 3 months for all main BCVA endpoints (mean average change for months 1 to 3, [redacted] In addition, improvements in BCVA were observed in both ranibizumab arms over 12 months, but no statistical comparisons could be made with vPDT because of the switching of treatments in this group. Ranibizumab also achieved a greater reduction in CRT compared to vPDT at 3 months. [redacted].

Our conclusions are that:

- ranibizumab was clinically more effective than vPDT in treating the visual impairment of people with myopic CNV at three months;
- improvement in visual outcomes were observed up to 12 months in the ranibizumab only group (no comparison with vPDT);
- ranibizumab did not show serious ocular and non-ocular adverse events.

Main concerns relate to the lack of efficacy and safety assessments beyond 12 months and the lack of comparison of ranibizumab to bevacizumab (which is used off-label for the treatment of myopic CNV).

Cost-effectiveness

The manufacturer presented a clear and well-documented model structure. The model shows good validation with the trial data at 1 year for ranibizumab.

There are, however, areas of weakness:

- The Novartis phase III trial, from which effectiveness data for ranibizumab are drawn, and the VIP trial, from which the majority of effectiveness data for vPDT are drawn, are not balanced in terms of the proportion of patients presenting with non-subfoveal involvement.This may result in an inflated effect of the benefit of ranibizumab.
- The ERG has revised a number of model inputs which are summarised in section 5.4 of this report. These revisions tend to reduce the estimated net savings and net QALY gains from ranibizumab when compared with vPDT, but they do not reverse them.
- While it may be a misinterpretation on the part of the ERG, there is no obvious read across between the patient level data supplied by the manufacturer following clarification and the transition probability matrices (TPMs) of the model. This applies with particular force to the ranibizumab arm. Therefore, it is unclear 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 during the clarification process appears to provide little or no evidence that changes in the BCVA of the WSE have any discernible impact upon patients' quality of life. As a consequence, 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 may 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, which limit the duration of this. The ERG sensitivity analyses seem to reduce the estimated net savings and net QALY gains from ranibizumab compared with vPDT without, however, reversing them.
- The method used to calculate the cyclical worsening from natural history studies is unclear for most of the studies. Including all these studies reduces again the estimated net savings and net QALY gains from ranibizumab when compared with vPDT but, typically, does not reverse them.

- Adverse events were only included if they affected more than around 5% of the patients in the relevant arm of the Novartis phase III trial. Subsequently, retinal tears were not included. Retinal tears, if untreated, may lead to retinal detachment and increase the risk of visual loss, especially if patients are not followed very frequently. Retinal detachment occurs more often in myopic eyes than in the general population and could potentially be increased by intravitreal injections.
- 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.

Superseded – see erratum

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.

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9 APPENDICES

Appendix 1: ERG Additional Search for Clinical Effectiveness Studies

Database: Embase <1980 to 2013 Week 24>, Ovid MEDLINE(R) <1946 to June Week 1 2013>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <June 18, 2013>
Ovid Multifile Search URL: https://shibboleth.ovid.com/

1 Myopia, Degenerative/ use mesz
2 degenerative myopia/ use emez
3 myopia/
4 ((degenerat$ or patholog$ or progress$ or high$) adj3 myopi$).tw
5 or/1-4
6 Choroidal Neovascularization/ use mesz
7 subretinal neovascularization/ use emez
8 ((choroid$ adj3 neovasc$) or cnv or mcnv).tw.
9 (sub?retina$ adj3 (choroid$ or neovascular$)).tw.
10 or/6-9
11 5 and 10
12 ranibizumab.tw,hw,rn.
13 bevacizumab.tw,hw,rn.
14 (anti vegf or anti vascular endothelial growth factor).ti,ab,rn
15 exp vasculotropin antibody/ use emez
16 verteporfin.tw,rn
17 verteporfin/ use emez
18 ranibizumab/ use emez
19 bevacizumab/ use emez
20 or/12-19
21 11 and 20
22 exp clinical trial/ use emez
23 randomized controlled trial.pt.
24 controlled clinical trial.pt.
25 randomization/ use emez
26 randomi?ed.ab.
27 placebo.ab
28 drug therapy.fs.
29 randomly.ab.

30 trial.ab.

31 groups.ab.

32 or/22-31

33 exp animals/ not humans/

34 nonhuman/ not human/

35 32 not (33 or 34)

36 21 and 35

37 remove duplicates from 36

Cochrane Library (CENTRAL Issue 5 May 2013)

URL: http://www3.interscience.wiley.com/

Issue 5 of 12, May 2013

#1 MeSH descriptor: [Myopia, Degenerative] explode all trees

#2 MeSH descriptor: [Myopia] explode all trees

#3 ((degenerat* or patholog* or progress*) near/3 myopi*) .

#4 #1 or #2 or #3

#5 MeSH descriptor: [Choroidal Neovascularization] explode all trees

#6 (sub?retina* near/3 (choroid* or neovascular*)) .:ti,ab,kw

#7 ((choroid* near/3 neovasc*) or cnv or mcnv) .:ti,ab,kw

#8 #5 or #6 or #7

#9 #4 and #8

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

Deterministic results

Two sets of deterministic results are presented within the submission, those of the base case of section 7.7.6 and those of appendix 16. The deterministic results of appendix 16 include pairwise comparisons with vPDT, observation and bevacizumab. 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]

Superseded – see erratum

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[18] 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.

[17] 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].

[18] 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.

For the comparison of ranibizumab with observation, only the Appendix 16 results are available.

Table 56 Deterministic results: ranibizumab vs observation

	Section 7.7.6			**Appendix 16**		
	Ranibizumab	**Observation**	**net**	**Ranibizumab**	**Observation**	**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]	[redacted]	

The ranibizumab dosing schedule for the comparison with observation appears to be the same as that used for the comparisons with vPDT, around a total of [redacted] ranibizumab injections. But it appears that the clinical effectiveness estimates for ranibizumab differ from those of the comparisons with vPDT due to the undiscounted life years differing. This may suggest that for the comparison with observation the clinical effectiveness estimates for ranibizumab are drawn from the manufacturer ITC.

For the comparison of ranibizumab with bevacizumab, again only the appendix 16 results are available.

[19] Note that this has also been adjusted to be the with PAS treatment cost.

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]

Superseded – see erratum

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 Lacono 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*

blinded to treatment. Finally, it is not reported if an intention-to-treat approach was used for the analyses. The lack of rigour associated with this study was further ratified by the critical appraisal within the bevacizumab in eye conditions NICE DSU report by Poku et al 2013. The second trial, by Iacono 2012, is an explorative study and was not designed to produce comparative results. Multiple testing was not accounted for even though there are three defined primary variables and further comparisons between and within groups. The analyses are reported as intent-to-treat but elsewhere the manuscript stated that the analyses excluded "patients who did not complete all visits." Therefore the analyses are inconsistent with the standard intent-to-treat approach. Finally, there are inconsistencies in the reporting of the results as well as limited safety data presented."

Appendix 3 Transition probabilities and patient level data: ranibizumab arm

Table 58 Patient numbers

	Ranibizumab - month 0 to month 3							
	HS01	HS02	HS03	HS04	HS05	HS06	HS07	HS08
HS01	0	0	4	0	0	0	0	0
HS02	0	3	15	9	2	0	0	0
HS03	0	0	5	24	5	3	4	0
HS04	0	0	0	5	8	5	3	0
HS05	0	0	0	2	5	5	0	0
HS06	0	0	0	0	1	2	2	0
HS07	0	0	0	0	0	0	0	0
HS08	0	0	0	0	0	0	0	0

Table 59 TPM implied by patient numbers

	Ranibizumab - month 0 to month 3							
	HS01	HS02	HS03	HS04	HS05	HS06	HS07	HS08
HS01	100%	0%	17%	0%	0%	0%	0%	0%
HS02	0%	100%	63%	23%	10%	0%	0%	0%
HS03	0%	0%	21%	60%	24%	20%	44%	0%
HS04	0%	0%	0%	13%	38%	33%	33%	0%
HS05	0%	0%	0%	5%	24%	33%	0%	0%
HS06	0%	0%	0%	0%	5%	13%	22%	0%
HS07	0%	0%	0%	0%	0%	0%	0%	0%
HS08	0%	0%	0%	0%	0%	0%	0%	100%

Table 60 TPM of electronic model

	Ranibizumab - month 0 to month 3							
	HS01	HS02	HS03	HS04	HS05	HS06	HS07	HS08
HS01	100%	0%	18%	0%	0%	0%	0%	0%
HS02	0%	100%	68%	24%	13%	0%	0%	0%
HS03	0%	0%	9%	59%	31%	23%	0%	0%
HS04	0%	0%	5%	12%	25%	31%	44%	0%
HS05	0%	0%	0%	6%	25%	31%	33%	0%
HS06	0%	0%	0%	0%	6%	15%	0%	0%
HS07	0%	0%	0%	0%	0%	0%	22%	0%
HS08	0%	0%	0%	0%	0%	0%	0%	100%

Table 61 Patient numbers

	Ranibizumab - month 3 to month 6							
	HS01	HS02	HS03	HS04	HS05	HS06	HS07	HS08
HS01	3	3	0	0	0	0	0	0
HS02	1	21	8	1	1	0	0	0
HS03	0	4	23	6	0	0	0	0
HS04	0	0	6	12	6	0	0	0
HS05	0	0	0	1	8	1	0	0
HS06	0	1	0	2	0	1	0	0
HS07	0	0	0	0	0	1	2	0
HS08	0	0	0	0	0	0	0	0

Table 62 TPM implied by patient numbers

	Ranibizumab - month 3 to month 6							
	HS01	HS02	HS03	HS04	HS05	HS06	HS07	HS08
HS01	75%	10%	0%	0%	0%	0%	0%	0%
HS02	25%	72%	22%	5%	7%	0%	0%	0%
HS03	0%	14%	62%	27%	0%	0%	0%	0%
HS04	0%	0%	16%	55%	40%	0%	0%	0%
HS05	0%	0%	0%	5%	53%	33%	0%	0%
HS06	0%	3%	0%	9%	0%	33%	0%	0%
HS07	0%	0%	0%	0%	0%	33%	100%	0%
HS08	0%	0%	0%	0%	0%	0%	0%	100%

Table 63 TPM of electronic model

	Ranibizumab - month 3 to month 6							
	HS01	HS02	HS03	HS04	HS05	HS06	HS07	HS08
HS01	75%	11%	0%	0%	0%	0%	0%	0%
HS02	25%	75%	23%	6%	0%	0%	0%	0%
HS03	0%	11%	65%	29%	0%	33%	0%	0%
HS04	0%	0%	13%	47%	46%	0%	0%	0%
HS05	0%	0%	0%	6%	54%	0%	0%	0%
HS06	0%	4%	0%	12%	0%	33%	0%	0%
HS07	0%	0%	0%	0%	0%	33%	100%	0%
HS08	0%	0%	0%	0%	0%	0%	0%	100%

Table 64 Patient numbers

	Ranibizumab - month 6 to month 9							
	HS01	HS02	HS03	HS04	HS05	HS06	HS07	HS08
HS01	4	0	0	0	0	0	0	0
HS02	1	23	4	2	0	0	0	0
HS03	1	8	25	5	0	0	0	0
HS04	0	1	4	14	1	0	0	0
HS05	0	0	0	3	9	2	0	0
HS06	0	0	0	0	0	2	1	0
HS07	0	0	0	0	0	0	2	0
HS08	0	0	0	0	0	0	0	0

Table 65 TPM implied by patient numbers

	Ranibizumab - month 6 to month 9							
	HS01	HS02	HS03	HS04	HS05	HS06	HS07	HS08
HS01	67%	0%	0%	0%	0%	0%	0%	0%
HS02	17%	72%	12%	8%	0%	0%	0%	0%
HS03	17%	25%	76%	21%	0%	0%	0%	0%
HS04	0%	3%	12%	58%	10%	0%	0%	0%
HS05	0%	0%	0%	13%	90%	50%	0%	0%
HS06	0%	0%	0%	0%	0%	50%	33%	0%
HS07	0%	0%	0%	0%	0%	0%	67%	0%
HS08	0%	0%	0%	0%	0%	0%	0%	100%

Table 66 TPM of electronic model

	Ranibizumab - month 6 to month 9							
	HS01	HS02	HS03	HS04	HS05	HS06	HS07	HS08
HS01	50%	0%	0%	0%	0%	0%	0%	0%
HS02	25%	74%	9%	0%	0%	0%	0%	0%
HS03	25%	22%	78%	13%	0%	0%	0%	0%
HS04	0%	4%	13%	73%	20%	0%	0%	0%
HS05	0%	0%	0%	13%	80%	50%	0%	0%
HS06	0%	0%	0%	0%	0%	50%	33%	0%
HS07	0%	0%	0%	0%	0%	0%	67%	0%
HS08	0%	0%	0%	0%	0%	0%	0%	100%

Table 67 Patient numbers

	Ranibizumab - month 9 to month 12							
	HS01	HS02	HS03	HS04	HS05	HS06	HS07	HS08
HS01	4	4	0	0	0	0	0	0
HS02	0	23	12	1	0	0	0	0
HS03	0	3	26	5	1	0	0	0
HS04	0	0	1	13	5	0	0	0
HS05	0	0	0	1	7	1	0	0
HS06	0	0	0	0	1	1	1	0
HS07	0	0	0	0	0	1	1	0
HS08	0	0	0	0	0	0	0	0

Table 68 TPM implied by patient numbers

	Ranibizumab - month 9 to month 12							
	HS01	HS02	HS03	HS04	HS05	HS06	HS07	HS08
HS01	100%	13%	0%	0%	0%	0%	0%	0%
HS02	0%	77%	31%	5%	0%	0%	0%	0%
HS03	0%	10%	67%	25%	7%	0%	0%	0%
HS04	0%	0%	3%	65%	36%	0%	0%	0%
HS05	0%	0%	0%	5%	50%	33%	0%	0%
HS06	0%	0%	0%	0%	7%	33%	50%	0%
HS07	0%	0%	0%	0%	0%	33%	50%	0%
HS08	0%	0%	0%	0%	0%	0%	0%	100%

Table 69 TPM of electronic model

	Ranibizumab - month 9 to month 12							
	HS01	HS02	HS03	HS04	HS05	HS06	HS07	HS08
HS01	100%	6%	0%	0%	0%	0%	0%	0%
HS02	0%	88%	31%	10%	0%	0%	0%	0%
HS03	0%	6%	69%	10%	0%	0%	0%	0%
HS04	0%	0%	0%	80%	100%	0%	0%	0%
HS05	0%	0%	0%	0%	0%	0%	0%	0%
HS06	0%	0%	0%	0%	0%	0%	100%	0%
HS07	0%	0%	0%	0%	0%	100%	0%	0%
HS08	0%	0%	0%	0%	0%	0%	0%	100%