

Ranibizumab for the treatment of macular oedema
caused by retinal vein occlusion (RVO)
STA REPORT

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Table of contents

1	SUMMARY	9
1.1	Scope of the manufacturer submission	9
1.2	Summary of clinical effectiveness evidence submitted by the manufacturer	9
1.3	Summary of the ERG's critique of clinical effectiveness evidence submitted	10
1.4	Summary of cost effectiveness submitted evidence by the manufacturer	11
1.5	Summary of the ERG's critique of cost effectiveness evidence submitted	11
1.6	ERG commentary on the robustness of evidence submitted by the manufacturer.....	12
1.6.1	Areas of uncertainty	12
1.7	Summary of additional work undertaken by the ERG	13
1.8	Key issues	14
2	BACKGROUND	15
2.1	Critique of manufacturer's description of underlying health problem.....	15
2.2	Critique of manufacturer's overview of current service provision	19
3	CRITIQUE OF MANUFACTURER'S DEFINITION OF DECISION PROBLEM	25
3.1	Population	26
3.2	Intervention.....	27
3.3	Comparators.....	27
3.4	Outcomes	30
3.5	Other relevant factors.....	31
4	CLINICAL EFFECTIVENESS	32
4.1	Critique of the methods used by the manufacturer to systematically review clinical effectiveness evidence	32
4.1.1	Description and discussion of appropriateness of manufacturer's search strategy	32
4.1.2	Inclusion/exclusion criteria used in study selection.....	33
4.1.3	Studies included in clinical effectiveness review.....	35
4.2	Summary and critique of submitted clinical effectiveness evidence	36
4.2.1	Quality of included RCTs	36
4.2.2	Overview of included RCTs	36
4.3	Results.....	41
4.3.1	Ranibizumab in the treatment of MO secondary to BRVO	41
4.3.2	Ranibizumab in the treatment of MO secondary to CRVO	47
4.3.3	Long-term effects of ranibizumab in treating MO secondary to RVO	50
4.3.4	Adverse effects.....	54
4.4	Additional analysis.....	58

4.4.1	Meta-analysis of RCTs identified for ranibizumab in the treatment of MO secondary to CRVO	58
4.4.2	Indirect comparisons between ranibizumab and comparators listed in the final scope.	61
4.5	Subgroup analysis	74
4.6	Conclusions.....	78
4.6.1	Summary of results	78
4.6.2	Clinical issues	79
5	ECONOMIC EVALUATION	80
5.1	Introduction.....	80
5.2	Overview of the manufacturer’s review of cost-effectiveness evidence.....	80
5.3	Summary of manufacturer’s economic evaluation	80
5.3.1	Model structure	81
5.3.2	Population	81
5.3.3	Interventions and comparators	82
5.3.4	Model parameters.....	82
5.3.5	Treatment effectiveness	87
5.3.6	Health related quality of life	89
5.3.7	Mortality	91
5.3.8	Resources and costs	92
5.3.9	Perspective, time horizon and discounting.....	93
5.3.10	Cost effectiveness results	93
5.3.10	Sensitivity analyses.....	99
5.3.11	Model validation	103
5.4	Critique of manufacturer’s economic evaluation.....	103
5.4.1	NICE reference case checklist	103
5.4.2	Model structure	106
5.4.3	Population	106
5.4.4	Health related quality of life	107
5.4.5	Interventions and comparators	111
5.4.6	Treatment effectiveness	112
5.4.7	Mortality	118
5.4.8	Time horizon	119
5.4.9	Resources and costs	119
5.4.10	Sensitivity analyses.....	119
5.4.11	Minor issues	120

6	ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG	121
6.1	Immediate versus delayed treatment in BRVO.....	121
6.1.1	Scenario analysis of the better-seeing eye/worse-seeing eye.....	121
6.1.2	Model modifications	122
6.2	Cost minimisation and threshold analysis of bevacizumab	128
7	CONCLUSIONS.....	132
7.1	Implications for research.....	133
8	REFERENCES	134
	Appendix 1. Key characteristics of the BRAVO, CRUISE and ROCC RCTs	142
	Appendix 2. Quality assessments of BRAVO, CRUISE and ROCC	147
	Appendix 3. Adverse effects from BRAVO, CRUISE and HORIZON	153
	Appendix 4. Details of the manufacturer’s approach to the inclusion of dexamethasone	160

Abbreviations

AC	Appraisal Committee
AE(s)	Adverse event(s)
AMD	Age-related macular degeneration
APD	Afferent pupillary defect
BCVA	Best corrected visual acuity
BRAVO	Ranibizumab for the treatment of macular edema following BRANCH Retinal Vein Occlusion: Evaluation of Efficacy and Safety
BRVO	Branch retinal vein occlusion
BSE	Better-seeing eye
BVOS	Branch Vein Occlusion Study
CI	Confidence interval
CrI	Credible interval
CFT	Central foveal thickness
CRD	Centre for Reviews and Dissemination
CRUISE	Central Retinal Vein Occlusion Study: Evaluation of Efficacy and Safety
CRVO	Central retinal vein occlusion
CSR	Clinical study report
CVOS	Central Vein Occlusion Study
EMA	European Medicines Agency
ERG	Evidence Review Group
ETDRS	Early Treatment Diabetic Retinopathy Study
EU	European Union
FDA	Food and Drug Administration
FFA	Fundus fluorescein angiography
GENEVA	Global Evaluation of implantable dexamethasone in retinal vein occlusion with macular edema
GLP	Grid laser photocoagulation
HR	Hazard ratio
HRG	Healthcare Resource Group
HRQoL	Health-related quality-of-life
ICER	Incremental cost-effectiveness ratio
IOP	Intraocular pressure
IRC	Independent Review Committee
ITT	Intention to treat
IV	Intravenous
MO	Macular oedema
MS	Manufacturer's submission

NEI VFQ-25	National Eye Institute Visual Functioning Questionnaire–25
NICE	National Institute for Health and Clinical Excellence
OCT	Optical coherence tomography
PAS	Patient access scheme
PP	per protocol
PRN	<i>Pro re nata</i>
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
RCO	Royal College of Ophthalmologists
RNIB	Royal National Institute of Blind People
RVO	Retinal vein occlusion
RR	Relative risk
SA	Sensitivity analysis
SPC	Summary of Product Characteristics
STA	Single technology appraisal
TTO	Time trade off
VA	Visual acuity
VEGF	Vascular endothelial growth factor
VI	Visual Impairment
vs	Versus
WSE	Worse-seeing eye

1 SUMMARY

1.1 *Scope of the manufacturer submission*

The manufacturer of ranibizumab (Lucentis[®]; Novartis Pharmaceuticals) submitted to NICE clinical and economic evidence in support of the effectiveness of ranibizumab in the treatment of macular oedema (MO) secondary to retinal vein occlusion (RVO). The manufacturer submitted evidence separately for MO secondary to branch RVO (BRVO) and central RVO (CRVO).

The manufacturer's submission diverged from the final scope issued by NICE in the following areas:

- **Population.** The population specified in the scope was people with either ischaemic or non-ischaemic RVO. The manufacturer submitted evidence that appears to be limited to patients with non-ischaemic disease. Approximately 20% of CRVO patients are reported to have ischaemic disease.
- **Comparators.** The manufacturer omitted comparisons against bevacizumab and dexamethasone in MO secondary to BRVO and to CRVO from the clinical effectiveness section. The manufacturer included an exploratory economic analysis of ranibizumab versus dexamethasone in both conditions, but did not include an economic analysis for bevacizumab. The manufacturer cited various reasons as to why it did not carry out these comparisons. The principal reason for omission of a comparison versus bevacizumab was that this agent is unlicensed for ocular use, and the reason given for not comparing against dexamethasone was that there is no evidence comparing ranibizumab and dexamethasone directly and there are no suitable data to facilitate a reliable indirect comparison.
- **Outcomes.** The manufacturer presented data on improvement in visual acuity in only the treated eye but not in the whole person, as was specified in the final scope. The trials identified by the manufacturer did not include data on change in visual acuity in the whole person.

1.2 *Summary of clinical effectiveness evidence submitted by the manufacturer*

The main sources of evidence cited in the manufacturer's submission are the BRAVO and CRUISE RCTs, which evaluate ranibizumab in patients with MO secondary to BRVO and to CRVO, respectively. The manufacturer also identified a smaller RCT (ROCC RCT) that assessed ranibizumab 0.5 mg in people with MO secondary to CRVO.

In both BRAVO and CRUISE, an inclusion criterion was that MO had been diagnosed within 12 months of study initiation. BRAVO and CRUISE were three armed RCTs assessing the effects of two doses of ranibizumab (0.3 mg and 0.5 mg) and sham injection. For the purposes of this single technology appraisal (STA), only ranibizumab 0.5 mg is of interest as this is the licensed dose. In BRAVO, concomitant grid laser photocoagulation (GLP) could be administered from month 3 (all groups). From 6–12 months, all patients in BRAVO and CRUISE entered an observation phase during which they received ranibizumab *pro re nata* (PRN) and, if eligible, concomitant GLP.

In both BRAVO and CRUISE, the mean improvement in BCVA from baseline (ETDRS letters) was statistically significantly higher at 6 months in the ranibizumab 0.5 mg groups compared with the sham injection groups (BRAVO: 18.3 with ranibizumab vs 7.3 with sham injection, $p < 0.0001$; CRUISE: 14.9 with ranibizumab vs 0.8 with sham injection, $p < 0.0001$). In addition, the proportion of patients achieving an improvement of 15 or more letters was also larger with ranibizumab compared with sham injection (BRAVO: 61.1% with ranibizumab vs 28.8% with sham injection, $p < 0.0001$; CRUISE: 47.7% with ranibizumab vs 16.9% with sham injection, $p < 0.0001$). The number of adverse events was low in both BRAVO and CRUISE. Data from a single-arm extension study (HORIZON) of BRAVO and CRUISE, during which all patients who entered the study received ranibizumab PRN, indicate a deterioration in BCVA in people with MO secondary to CRVO, which could suggest that the PRN dosing regimen is insufficient in this population and a more frequent treatment regime would be required to maintain the initial observed benefit.

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

The ERG believes the BRAVO and CRUISE RCTs to be well conducted trials, but has reservations about the generalisability of the findings to the decision problem issued by NICE. One criterion in both trials was the exclusion of people with brisk afferent pupillary defect (APD). APD is an indicator of retinal ischaemia and so people with RVO and ischaemia of the retina are unlikely to have been included in BRAVO and CRUISE. It is unclear how macular ischaemia was assessed. It follows that the population in which ranibizumab has been assessed are those with MO secondary to the respective RVO and no retinal ischaemia.

In CRUISE, as patients were allowed to receive ranibizumab PRN from month 6 onwards, the ERG considers the data at 6 months (end of the treatment phase) to be the most relevant for this STA. However, it was noted by the authors of the ROCC RCT that 6 months' follow-up may be insufficient to assess the long-term effects of ranibizumab.

In BRAVO, the use of concomitant GLP confounds the results from this trial. For a valid comparison of ranibizumab versus GLP, all patients in the “sham” treatment group should have received GLP at the point of randomisation and no patients in the ranibizumab group should have received GLP. Alternatively, for BRAVO to be a valid comparison of ranibizumab versus sham, no patients in either treatment group should have received GLP. However, this scenario might not be feasible as GLP is considered standard care in patients with MO secondary to BRVO. It should also be noted that the effects of GLP can continue for up to 3 years after administration. Thus, the ERG believes that BRAVO does not present a direct comparison of ranibizumab versus either sham injection or GLP alone (listed as standard care in the final decision problem) for people with MO secondary to BRVO.

Although long-term data (24 months’ follow-up) are available for patients from BRAVO and CRUISE, these data are from an extension study in which everyone received ranibizumab PRN (HORIZON). There are no long-term data on how ranibizumab compares with other treatments listed in the decision problem.

One key limitation to the evidence presented is a lack of comparisons in either clinical condition for ranibizumab versus dexamethasone intravitreal implant or bevacizumab, both of which were listed as comparators of interest in the final scope.

1.4 Summary of cost effectiveness submitted evidence by the manufacturer

The manufacturer presents the case for the use of ranibizumab in MO secondary to BRVO and CRVO compared with the use of the recently approved dexamethasone intravitreal implant or current standard of care (GLP in MO secondary to BRVO and best supportive care in MO secondary to CRVO). The economic evaluation is conducted from a best-seeing eye (BSE) perspective in the base case. For ranibizumab versus standard care, the base case incremental cost-effectiveness ratios (ICERs) generated by the manufacturer were £8,643 and £20,494 for MO secondary to CRVO and BRVO, respectively. The manufacturer incorporates dexamethasone intravitreal implant into the economic analysis in an exploratory way. For the analysis of ranibizumab versus dexamethasone intravitreal implant, the base case ICERs obtained from the manufacturer’s analysis are £7,174 and £5,486 for MO secondary to CRVO and BRVO, respectively.

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

The ERG considers the manufacturer’s use of a BSE model to be inappropriate in MO secondary to RVO because RVO is a predominantly unilateral condition, and thus most patients will receive treatment in only their worse-seeing eye (WSE). The ERG extensively investigated the assumptions

and sources used in relation to the eye affected and utility gained from treatment. The ICERs generated from these investigations are always higher than the manufacturer's base case ICER, and the ERG selected the most reasonable representation of the expected gain of treatment in the RVO population.

Considering the assessment of ranibizumab versus best supportive care in MO secondary to CRVO, application of the ERG's adjustment for the expectation that treatment will predominantly be administered to the WSE increased the ICER to £49,323. Further modifications to incorporate adjustments for age, where appropriate, and increased risk of mortality associated with RVO and visual impairment in the WSE reduced the ICER to £43,760. For the analysis of the dexamethasone intravitreal implant, after adjustment of the perspective to consider the WSE, the ERG generated ICERs of £42,147 and £34,598 in MO secondary to CRVO and BRVO, respectively. Adjustments for age, where appropriate, and increased risk of mortality associated with RVO and visual impairment in the WSE yielded ICERs of £37,247 and £31,122 for MO secondary to BRVO and CRVO, respectively. In addition, the ERG notes that the manufacturer's economic assessment of ranibizumab versus dexamethasone is potentially biased in favour of ranibizumab.

The ERG identified other limitations in the approach taken by the manufacturer, resulting in further recommended modifications. For ranibizumab compared with GLP in MO secondary to BRVO, the manufacturer bases their analysis entirely on the BRAVO trial, which, as the ERG notes, is unsuitable to inform the comparison of ranibizumab versus GLP. The ERG proposes using the BRAVO trial to inform a comparison between immediate and delayed (by 6 months) therapy with ranibizumab, alongside rescue GLP. Application of this analysis to the manufacturer's model results in an ICER of £6,500 for immediate versus delayed treatment. However, once the modifications recommended by the ERG (WSE model perspective: adjustments for age, and increased risk of mortality associated with RVO and visual impairment in the WSE) are incorporated into this analysis, the ICER increases to £31,410.

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

1.6.1 Areas of uncertainty

The lack of analyses comparing the clinical effectiveness of ranibizumab versus bevacizumab and dexamethasone generates uncertainty around the comparative effectiveness of ranibizumab. Although dexamethasone is only recently approved for the treatment of MO secondary to RVO, the comparative effectiveness of the two treatments is of interest. Uncertainty on the effects of ranibizumab is

compounded by the use of the BSE analysis rather than the WSE. Future research could focus on identification of utilities associated with visual impairment in the WSE.

In BRAVO, the concomitant use of GLP in the sham injection and ranibizumab 0.5 mg groups means that ranibizumab is not compared directly with either sham injection or GLP. In this case, the ERG is of the opinion that data at 3 months are the most relevant to the decision problem presented. Although most of the benefit with ranibizumab is seen in the first 3 months of treatment, 3 months' follow-up is insufficient to determine the long-term effects of ranibizumab compared with GLP. Three months' follow-up is also inadequate to determine whether continuous treatment with ranibizumab would be required over a sustained period of time. The ERG is aware of an ongoing trial (RABAMES) that is assessing the effects of ranibizumab alone, GLP alone, and ranibizumab plus GLP, which could go some way to elucidating this issue.

Considering the duration of treatment with ranibizumab, the summary of product characteristics indicates that treatment with ranibizumab can be suspended when visual acuity has been stable for 3 months. However, the authors of the ROCC RCT noted that the effects of ranibizumab may not be sustained when ranibizumab treatment is ceased at 3 months, and continuous treatment may be required long-term to maintain benefit. Longer-term studies comparing ranibizumab versus other active treatments would help to clarify this issue.

1.7 Summary of additional work undertaken by the ERG

The ERG carried out exploratory indirect comparisons of ranibizumab versus:

- dexamethasone in MO secondary to BRVO and to CRVO;
- bevacizumab in MO secondary to BRVO;
- GLP in MO secondary to BRVO.

The ERG's analyses suggested a trend favouring ranibizumab over dexamethasone in MO secondary to both BRVO and CRVO. Based on exploratory analyses of the proportion of people improving by 15 or more ETDRS letters, compared with dexamethasone intravitreal implant, the ERG found a relative risk (RR) of 0.53 (95% Confidence Interval [CI]: 0.26 to 1.07) in patients with MO secondary to CRVO for achieving this outcome at 6 months, where $RR < 1.0$ favours ranibizumab. In patients with MO secondary to BRVO, the RR of achieving an improvement of 15 or more letters at 3 months was 0.56 (95% CI: 0.33 to 0.96), again, favouring ranibizumab over dexamethasone intravitreal implant. However, the results should be interpreted with caution as the likely bias identified in the trials used is in favour of ranibizumab and so the results may overestimate the efficacy of ranibizumab.

The ERG found that ranibizumab and bevacizumab may have similar efficacy in MO secondary to BRVO, as indicated by the results of an exploratory mixed treatment comparison, where the mean difference in change in ETDRS letters (from baseline) at 3 months was -2.9 letters (95% credible interval [CrI]: -10.1 to 4.3). The recently published CATT trial directly compares ranibizumab and bevacizumab in patients with neovascular age-related macular degeneration. This study considers an improvement of <5 letters to be clinically non-significant and concluded that “At 1 year, bevacizumab and ranibizumab had equivalent effects on visual acuity when administered according to the same schedule”.

Regarding the comparison of ranibizumab versus GLP, the exploratory mixed treatment comparison favours ranibizumab, with a mean difference at 3 months of -8.0 letters (95% CrI: -17.0 to 1.2). However, it should be noted that the benefit of GLP is not in the short-term but in the long-term and can occur for up to 3 years.

1.8 Key issues

In summary, the ERG believes the key issues to be as follow:

- Absence of evidence of efficacy in patients with retinal ischaemia or macular ischaemia: evidence of efficacy in macular ischaemia is relevant to patients with MO secondary to BRVO;
- Assessment of visual acuity in only the treated eye and not the whole person;
- Use of BSE, rather WSE, in the base case economic analysis;
- Lack of direct comparison with GLP in those with MO secondary to BRVO in BRAVO;
- Short follow-up (6 months) for comparison with standard care in CRVO (best supportive care);
- Lack of direct or indirect comparisons of ranibizumab with dexamethasone, and bevacizumab in both BRVO and CRVO;
- Uncertainty surrounding required duration of ranibizumab treatment.

2 BACKGROUND

2.1 Critique of manufacturer's description of underlying health problem

In the Context section of the manufacturer's submission (MS; section 2, begins on pg 30), the manufacturer describes various aspects of the clinical problem, including aetiology, and underlying course of macular oedema (MO) secondary to retinal vein occlusion (RVO). Summaries of the aetiology (Box 1), the incidence and prevalence of ischaemic and non-ischaemic retinal vein occlusion (Box 2), prognosis (Box 3) and effects of RVO on other areas of health (Box 4) are provided in Boxes 1 to 4. All information in the boxes is taken directly from the MS unless otherwise stated.

Box 1. Aetiology of MO secondary to RVO

Retinal vein occlusion (RVO) is a major cause of visual impairment in the UK, secondary only to diabetic retinopathy.^(1;2) Macular oedema (MO), the accumulation of fluid in the macula of the eye, is a common complication of RVO and is a major contributor to the loss of vision. Vision loss is associated with a high burden of disease, both in terms of reduced health-related quality of life (HRQL) and substantial economic costs.⁽³⁻⁷⁾

RVO particularly affects older people, as incidence and prevalence increases with age. In a study of 4068 people, it has been found that incident RVO was associated with baseline age (odds ratio [OR] per 10 years; 1.70; 95% confidence interval [CI]: 1.36 to 2.12).⁽⁸⁾ Australian data indicates that the prevalence is 0.7% for those younger than 60 years, 1.2% for those 60 to 69 years, 2.1% for those 70 to 79 years and 4.6% for people 80 years or older.⁽⁹⁾ Other risk factors for RVO include hypertension, hyperlipidaemia, glaucoma and diabetes.

RVO occurs when there is a blockage in the venous system of the retina. The primary cause is often thrombus (blood clot) formation, but other causes can include external compression or vasculitis.⁽¹⁾ Occlusion can occur in the central retinal vein, leading to central RVO (CRVO) or in one of the branch veins, leading to branch RVO (BRVO). CRVO is approximately six times less prevalent than BRVO,⁽¹⁰⁾ but it is a more serious condition.

CRVO and BRVO can occur in both eyes at the same time. A systematic review of studies of the natural history of BRVO found that 5%-6% of patients at baseline had bilateral BRVO, with 10% developing fellow-eye involvement over time.⁽¹⁰⁾ Studies in CRVO report a large range in the percentage of CRVO patients at baseline who have bilateral RVO (0.4% from CVOS study including 711 eyes to 43% in Pollack *et al.*, which included only 7 eyes). The majority of studies reported that under 10% of CRVO patients showed bilateral RVO at baseline.⁽¹¹⁾ One study reported that 5% of CRVO cases develop RVO in the fellow eye over a 1 year period.⁽¹¹⁾ There was no data identified

describing the incidence of fellow eye macular oedema caused by RVO.

Box 2. Ischaemic and non-ischaemic retinal vein occlusion

Both types of RVO [BRVO and CRVO] can either be ischaemic, where there is reduced blood supply to the retina (also known as non-perfused), or non-ischaemic, where blood supply remains relatively normal. There may be differing definitions of ischaemia.^(1;12) The definition for ischaemic RVO used by the Central Vein Occlusion Study (CVOS) was the presence of more than 10 fluorescein angiography disc areas of capillary non-perfusion,⁽¹³⁾ whereas for the Branch Vein Occlusion Study (BVOS) it was 5 disc areas.⁽¹⁴⁾ Patients with severe ischaemia may be defined as those who present with brisk afferent pupillary defect (APD).^(15;16) The presence of APD has been found to be a highly sensitive and reliable indicator of ischaemia.⁽¹⁷⁾

Approximately 20% of CRVO patients are reported to have ischaemic disease,⁽¹¹⁾ although as previously stated there is discrepancy over the definitions of ischaemia used in the literature.⁽¹⁾ The proportion of BRVO patients with ischaemia is not well established. Furthermore, ischaemia can occur in the macula or at peripheral sites of the retina; it is only that occurring in the macula that is relevant to the decision problem in this submission. Patients with ischaemic RVO, where retinal capillaries have closed, are at greatest risk of experiencing neovascularisation (growth of abnormal blood vessels), which can lead to glaucoma or vitreous haemorrhage. Ischaemic RVO has different treatment paradigms to the non-ischaemic conditions.

Box 3. Prognosis

Although some patients can experience an improvement in MO and thus VA, in general the condition persists and vision declines over time. The aim of treatment, therefore, is to reduce MO and improve or prevent further deterioration in VA.

A systematic review of the literature describing the natural history of untreated CRVO concluded that VA generally decreases over time.⁽¹¹⁾ In the small proportion of studies that reported a spontaneous improvement in VA for patients over a defined time period (ranging from 3 to 40 months), their final VA was never greater than 20/40 (approximately equivalent to 70 ETDRS letters).⁽¹¹⁾ Further evidence suggests that for those CRVO patients with an initial VA of 20/50 to 20/200 (approximately equivalent to 65 - 35 ETDRS letters), only 20% of eyes are likely to improve spontaneously.⁽¹⁾ A similar review of the course of BRVO found that of the eyes that had MO at presentation, 18 to 41% may show some degree of resolution, but that on average VA did not improve above 20/40 (approximately equivalent to 73 ETDRS letters).⁽¹⁰⁾ Furthermore, approximately 20% of untreated BRVO eyes with MO experience a significant deterioration of vision over time.^(14;18)

Thus, although both CRVO and BRVO can improve spontaneously, in the majority of cases it does not resolve and may progress to a chronic state in which the prognosis and response to treatment is poor.⁽¹⁹⁻²¹⁾ Chronic MO is associated with persistent hypoxia, which may lead to permanent structural damage in the macula and thus irreversible visual impairment.⁽²⁾ Additionally, haemorrhage into the

vitreous is more likely to occur when MO is persistent; this contributes to a worsening of VA and poor prognosis.⁽²⁾ It is therefore important to treat MO due to RVO at an early stage.

The Evidence Review Group (ERG) considers the manufacturer's overview of the underlying health problem to be largely accurate, but would like to expand on some of the assertions made by the manufacturer.

In their outline of the aetiology of RVO (Box 1), the manufacturer comments that RVO is a major cause of visual impairment in the UK, being second only to diabetic retinopathy. However, as outlined in the RCO guidelines,⁽¹⁾ RVO is not the second most common cause of visual impairment in general but the second most common cause of visual impairment due to a retinal vascular disease.

In their description of prognosis of RVO (Box 3; MS; pg 31), the manufacturer states that "Although some patients can experience an improvement in MO and thus VA, in general the condition persists and vision declines over time". The manufacturer goes on to report data from a review of the prevalence of BRVO that "...found that of the eyes that had MO at presentation, 18 to 41% may show some degree of resolution...".⁽¹⁰⁾ It is important to highlight that the review cited in support of this statement reported that 18% of eyes presenting with MO secondary to BRVO had resolution of their MO within 4.5 months post occlusion, rising to 41% by 7.5 months (data from one study of 20 eyes). Furthermore, although the review stated that few identified studies reported improvement beyond 20/40, the review noted that visual acuity in people with BRVO generally improved, with mean improvement ranging from 1 letter at 6 weeks to 28 letters up to 24 months.

Considering the natural history of CRVO (outlined in Box 1), the ERG considers it important to highlight a second report on the natural history of visual outcome in this condition.⁽²²⁾ The authors recorded data on 667 consecutive patients (697 eyes; 30 patients had bilateral CRVO). In patients with an initial visual acuity of 20/60 or better, all of whom had non-ischaemic CRVO, the authors reported that only 17% of patients had worsening in visual acuity at 3 months and only 20% showed deterioration during the 2–5 year follow-up period. These findings are not in complete accordance with the overall finding of the systematic review cited by the manufacturer that visual acuity in patients with untreated CRVO generally decreases over time, and that, in those studies reporting an improvement in visual acuity, improvement was never greater than 20/40.⁽¹¹⁾ Hayreh *et al.*⁽²²⁾ also reported that, in eyes with non-ischaemic CRVO and visual acuity of 20/70 or worse, 32% of patients had improvement in visual acuity at 3 months and 47% had improvement in visual acuity during the 2–5 year follow-up period. In those with MO secondary to CRVO, Hayreh *et al.*⁽²²⁾ reported that the median time to resolution of MO in those with non-ischaemic and ischaemic CRVO was 23 months and 29 months, respectively.

The importance of differentiating between ischaemic and non-ischaemic CRVO is highlighted by Hayreh *et al.*⁽²²⁾ and the interim guidelines produced by the Royal College of Ophthalmologists (RCO).⁽¹⁾ Both reports indicate that the prognosis, in terms of visual acuity, is good in non-ischaemic CRVO and poor in ischaemic CRVO. Hayreh *et al.*⁽²²⁾ note, as does the manufacturer, that the disparity in the criteria used to define ischaemia in CRVO means that, in previous studies on the natural history of CRVO, groups classified as non-ischaemic probably included patients with ischaemic CRVO, and vice versa, and so the results are unreliable. In addition, it was noted that studies assessing CRVO have not always differentiated between ischaemic and non-ischaemic CRVO.

The ERG notes that the cited definitions for ischaemia from BVOS and CVOS (Box 2) are for ischaemia in the peripheral retina. It is important to note that RVO may also lead to macular ischaemia, and the prognosis may differ if the macula is ischaemic than if it is not. As the manufacturer notes, for the decision problem addressed here macular ischaemia is more relevant than peripheral ischaemia.

In their rationale for early treatment of MO secondary to RVO, the manufacturer states “Chronic MO is associated with persistent hypoxia, which may lead to permanent structural damage in the macula and thus irreversible visual impairment⁽²⁾. Additionally, haemorrhage into the vitreous is more likely to occur when MO is persistent; this contributes to a worsening of VA and poor prognosis.⁽²⁾ It is therefore important to treat MO due to RVO at an early stage.” The ERG notes that the reference cited in support of these statements focuses on the natural history of BRVO alone. The author of this study stated that “50–60% of eyes with BRVO have a final VA of 20/40 or better even without any treatment”. With regards to the early treatment of MO, the author of the paper states that visual impairment resulting from persistent hypoxia is almost always lasting. However, the author does not specify a timeframe in which visual impairment becomes “irreversible”. The ERG considers that, at this time, there is uncertainty concerning the period of time for which an MO secondary to RVO can be observed without treatment, that is, for how long the condition may be “reversed” by treatment. In addition, the author does not directly report that eyes with chronic MO are at a greater risk of vitreous haemorrhage. Expert opinion (NL) is that there is no rationale for increased risk of vitreous haemorrhage due to chronic MO.

Box 4. Effects of RVO on other areas of health

Quality of life

Loss of VA is associated with a considerable reduction in HRQL, due to the increased difficulty experienced when performing everyday tasks such as driving and the impact it may have on the patient’s ability to work.^(3;6) It has specifically been reported that both CRVO and BRVO are associated with a decrease in vision-related QoL scores (as measured by the VFQ-25) and this

reduction in QoL was related to the degree of VA.^(3;4)

Although QoL is usually reported as a function of the better-seeing eye, this does not necessarily mean that there will be no QoL benefits in treating the worse-seeing eye; studies in both BRVO and CRVO have found that QoL scores were associated with the level of VA in the affected eye, even if the other eye had good vision.^(4;15;16) There is also evidence from ranibizumab-treatment of wet AMD that treatment of the worse-seeing eye still improves patient-reported vision-related functioning.⁽²³⁾ A further argument for treating the worse-seeing eye is to maintain VA in that eye in case of future loss in the better-seeing eye, due to RVO or other eye conditions.

Mortality

It has been noted in some studies that for patients younger than 65–70 years, RVO is associated with a higher mortality rate than that seen in the general population.^(24;25) This is likely to be multifactorial in cause. For example, a large (N=549) UK hospital-based study has reported that over a nine year period patients with RVO experienced a higher rate of death from myocardial infarction than those without RVO.⁽²⁶⁾ This finding is corroborated by a smaller UK study (N=89), which found that patients with RVO had a higher risk of cardiovascular disease than the norm.⁽²⁷⁾ However, other data exists that did not find any association between RVO and cardiovascular mortality.⁽²⁴⁾

In the overview of the impact of RVO on other areas of health, the manufacturer indicates that “data exists that did not find any association between RVO and cardiovascular mortality⁽²⁴⁾”. The ERG notes that the reference cited in support of this statement found that having RVO doubled the risk of cardiovascular mortality in people <70 years old (age range 43 to 69 years; HR 2.5; 95% CI: 1.2 to 5.2).⁽²⁴⁾

2.2 Critique of manufacturer’s overview of current service provision

The manufacturer states that, at the time of writing their report, no NICE guidance was available for the treatment of MO secondary to RVO. As the manufacturer notes, at that time, dexamethasone intravitreal implant (Ozurdex[®]) for the treatment of MO secondary to RVO was undergoing assessment as part of the National Institute for Health and Clinical Excellence’s (NICE) single technology appraisal (STA) process. In June 2011, the committee issued a Final Appraisal Determination⁽²⁸⁾ recommending dexamethasone intravitreal implant as an option for the treatment of MO following CRVO, and as an option for the treatment of MO following BRVO when (i) treatment with laser photocoagulation has not been beneficial, or (ii) treatment with laser photocoagulation is not considered suitable because of the extent of macular haemorrhage: the final report has yet to be published. The ERG did not identify any additional NICE guidance on the treatment of MO secondary to RVO.

The manufacturer provides an overview of interim guidelines from the RCO, which outline the treatment pathways for MO secondary to branch and to central RVO (Box 5).⁽¹⁾

The manufacturer describes the proposed place of ranibizumab in the treatment pathway based on the guidelines issued by the RCO (Box 6), and outlines potential additional requirements associated with implementation of ranibizumab in terms of resources and changes to infrastructure (Box 7). Due to a paucity of published data on incidence and prevalence of MO secondary to RVO, the manufacturer was unable to present an estimate of the number of patients in the UK who would be eligible for treatment with ranibizumab (Box 8).

Box 5. Summary of RCO guidelines⁽¹⁾ on the treatment of RVO

BRVO

- The RCO guidelines recommend that for patients with MO secondary to non-ischaemic BRVO seen within 3 months of BRVO onset, pharmacotherapy with dexamethasone intravitreal implant (licensed) or ranibizumab (off label at the time of guidance but has robust clinical evidence of efficacy,) should be considered.⁽¹⁾ These recommendations are based on Grade A evidence for both therapies.
- Laser photocoagulation may also be considered in patients seen 3 months after the initial BRVO event and following absorption of the majority of the haemorrhage.⁽¹⁾ This recommendation is based on Grade A evidence.
- The RCO note that there is some evidence to suggest that BRVO patients with severe visual loss (<6/60 vision) and those in whom symptoms have been present for more than 12 months are unlikely to benefit from laser photocoagulation.⁽¹⁾
- For ischaemic BRVO, the RCO guidelines advise that monitoring for neovascularisation at 3-monthly intervals for up to 12 months should be performed as part of best supportive care.⁽¹⁾

CRVO

The RCO guidelines assess the evidence of various treatments specifically relating to MO secondary to CRVO. However, they do not provide recommendations on this exact indication.⁽¹⁾

- For all non-ischaemic CRVO, the RCO conclude that there is Grade A evidence (at least one good quality RCT directly applicable to the target population) to support the use of dexamethasone intravitreal implant (licensed) or ranibizumab (off label at the time of guidance but has robust clinical evidence of efficacy).
- The RCO guidelines note that randomised controlled trials have failed to indicate VA benefit (despite a reduction in MO severity with treatment) with grid laser photocoagulation in MO secondary to CRVO, although a trend in favour of treatment has been observed in younger patients.⁽¹⁾ Laser photocoagulation is therefore not recommended for the management of CRVO.
- Follow-up after treatment for non-ischaemic CRVO will normally be required for up to 2 years.

The development of disc collaterals or the resolution of the macular oedema should lead to discharge from clinical supervision.⁽¹⁾

- For ischaemic CRVO, the RCO advise only regular monitoring of the condition, (best supportive care) preferably at monthly intervals.⁽¹⁾ This regular monitoring is part of best supportive care that is provided for non-ischaemic CRVO, particularly as up to 30% of non-ischaemic CRVO cases can develop into the ischaemic condition.⁽¹⁾

The ERG considers the manufacturer's overview of the underlying health problem to largely reflect the guidance issued by the RCO, but would like to expand on some of the statements made by the manufacturer.

Considering the treatment of BRVO, the manufacturer states that "The RCO note that there is some evidence to suggest that BRVO patients with severe visual loss (<6/60 vision) and those in whom symptoms have been present for more than 12 months are unlikely to benefit from laser photocoagulation⁽¹⁾". The ERG thinks it important to highlight that the RCO guidelines categorise the evidence in support of this statement as Grade D evidence, which is defined as "Evidence from non-analytic studies, e.g. case reports, case series or expert opinion." Furthermore, the RCO guidelines do not report discrete guidance for this subgroup of patients in the treatment algorithm for the management of MO secondary to BRVO.

In their overview of the recommendations from the RCO for treatments available for CRVO, the manufacturer states "For all non-ischaemic CRVO, the RCO conclude that there is Grade A evidence (at least one good quality RCT directly applicable to the target population) to support the use of dexamethasone intravitreal implant (licensed) or ranibizumab (off label at the time of guidance but has robust clinical evidence of efficacy)". The ERG notes that, although the guidelines recommend consideration of dexamethasone intravitreal implant or ranibizumab for non-ischaemic CRVO, the guidelines indicate that this is for people with "visual acuity of 6/12 or worse and OCT \geq 250 microns (Stratus, or equivalent)".⁽¹⁾

Regarding length of required follow-up in CRVO, the manufacturer states that the guideline indicates that follow-up after treatment for non-ischaemic CRVO will normally be required for up to 2 years. The ERG would like to highlight that, in the section on treatment of MO secondary to CRVO, the guidelines state "Follow-up after the initial 6 months of treatment will depend upon initiation of anti-VEGF agent or steroid treatment for macular oedema but will normally be required for up to 2 years in uncomplicated cases". In the initial 6 months of treatment, frequency of follow-up will be variable and determined by treatment options, baseline visual acuity, and results from optical coherence tomography (OCT) and fundus fluorescein angiography (FFA). For patients with ischaemic CRVO, the RCO guidelines recommend monthly follow-up whenever possible, but go on to state that two monthly monitoring may be acceptable.

Box 6. Manufacturer's positioning of ranibizumab in the treatment pathway for MO secondary to RVO

Inclusion of ranibizumab in the clinical care pathway for MO secondary to RVO has therefore already been proposed by the RCO, and in this context ranibizumab offers an alternative treatment option, with a distinct mechanism of action to dexamethasone intravitreal implant and laser photocoagulation, for the immediate management of this condition. It is of note that in its submission to NICE the manufacturer of dexamethasone intravitreal implant assumed that dexamethasone intravitreal implant would be used only in those in whom laser therapy was inappropriate (due to macular haemorrhage) or in those in whom it had failed. Therefore ranibizumab may be the only alternative treatment option to laser therapy for a majority of patients affected by MO following BRVO.

Box 7. Manufacturer's overview of current and anticipated additional service provision

Anticipated resource use associated with ranibizumab treatment

Monthly monitoring of disease activity

- Hospital outpatient visits [consultant ophthalmologist or non-consultant grade ophthalmologist]
- BCVA assessment will be undertaken as standard during the appointment [no additional resource as conducted during outpatient appointment]
- OCT [OCT session with optometrist]

Injection visit

- Hospital outpatient visit, in a clean room [consultant ophthalmologist or non-consultant grade ophthalmologist]
- BCVA assessment will be undertaken as standard during the appointment [no additional resource as conducted during outpatient appointment]
- OCT [OCT session with optometrist]

Additional resource use for treatment administration

- Anti-microbial drops and topical anaesthesia

Additional infrastructure

Ranibizumab has been routinely used in the NHS since 2008 for the treatment of wet AMD. Appropriate facilities for the administration of intravitreal injections are therefore already well established.

Regular monitoring is part of the recommended best supportive care for any patient with MO secondary to RVO (monthly intervals for CRVO, 3 monthly intervals for BRVO⁽¹⁾). Thus ranibizumab is not expected to impose substantial further requirements on the NHS infrastructure.

The ERG notes that the manufacturer's placement of ranibizumab in the treatment pathway is potentially appropriate for MO secondary to either non-ischaemic BRVO or CRVO. However, the ERG notes, as discussed in subsequent sections, there is uncertainty around the long-term effects of

ranibizumab (section 4.3.3) in the treatment of ocular conditions, and around how ranibizumab compares with grid laser photocoagulation (GLP) in MO secondary to BRVO (section 4.3.1).

In their overview of anticipated resource use, the manufacturer lists antibiotics and anaesthetic drops as the additional resources required. Based on expert opinion (NL), the ERG considers that the costs incurred from cleaning the eye prior to injection (with an agent such as betadine) should also be considered. In addition, specialist instruments will be required to perform the injection, including a speculum to hold the eye open, and callipers (or similar) to determine where the injection will be placed. There may also be additional incidental costs, such as drapes, which are used in many units.

The ERG considers it unlikely that, as stated by the manufacturer, the implementation of ranibizumab would not be expected to impose further requirements on the NHS infrastructure. Based on expert opinion (NL), the ERG would suggest that there will be additional requirements in terms of increased pressure on clinical settings and resources to carry out the injections and subsequent follow-up. Furthermore, the ERG has been informed that, at this time, patients with non-ischaemic CRVO may be followed initially after onset but the majority are discharged, if stable, after 1 year of follow-up, or earlier. In addition, expert opinion (NL) is that patients with BRVO and no peripheral ischaemia who improve spontaneously and those that respond to GLP are not currently monitored. Those with BRVO and peripheral ischaemia are followed at variable intervals to monitor the development of neovascularisation.

Box 8. Estimated number of patients potentially eligible for treatment with ranibizumab

There are no data specific to England and Wales on the incidence and prevalence of RVO.^(10;11) There were no data identified describing the incidence of visual impairment due to MO secondary to RVO; the data relating to MO in patients with RVO was also limited. Furthermore, the majority of published epidemiological evidence is derived from population-based studies using scheduled appointments or screening to identify cases (rather than through symptomatic presentation). In UK clinical practice, a proportion of cases are expected to remain undiagnosed due to the absence of symptoms. Thus, it is difficult to determine with any certainty the eligible population in England and Wales.

Novartis is currently working to refine estimates of the numbers of patients with visual impairment due to MO secondary to RVO in the UK, through primary research.

The manufacturer did not identify evidence on the incidence and prevalence of MO secondary to BRVO and CRVO. The ERG agrees with the manufacturer's comment that there are no conclusive data specific to England and Wales on the potential number of patients who might be eligible for treatment with ranibizumab (Box 8). The systematic reviews assessing the natural history of BRVO⁽¹⁰⁾ and CRVO⁽¹¹⁾ did not report how many patients, on average, presented with MO secondary to BRVO and CRVO, respectively. However, in BRVO, Rogers *et al.*⁽¹⁰⁾ suggest that, over a 1-year period, 5%

to 15% of eyes develop MO. In addition, as discussed in earlier in this section, the review reports that 18% of eyes presenting with MO secondary to BRVO had resolution of their MO within 4.5 months post occlusion, rising to 41% by 7.5 months (data from one study of 20 eyes). McIntosh *et al.*⁽¹¹⁾ state that the studies identified were too small to provide meaningful data on the risk of development of MO in CRVO. The manufacturer noted that an assumption based estimate of incident cases of visual impairment due to MO secondary to BRVO and CRVO, respectively, can be derived but is uncertain.

3 CRITIQUE OF MANUFACTURER’S DEFINITION OF DECISION PROBLEM

In the manufacturer’s submission (MS; pg 41), the manufacturer presents the decision problem issued by the National Institute for Health and Clinical Excellence (NICE),⁽²⁹⁾ and the manufacturer’s rationale for any deviation from the decision problem (Table 1).

Table 1. Summary of decision problem as outlined in the manufacturer’s submission

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
<i>Population</i>	People with macular oedema caused by retinal vein occlusion (RVO)	People with visual impairment due to macular oedema secondary to retinal vein occlusion (RVO)	This is the expected indication.
<i>Intervention</i>	Ranibizumab	Ranibizumab	
<i>Comparator(s)</i>	CRVO: i. Best supportive care (ischaemic only) ii. Bevacizumab iii. Dexamethasone implant BRVO: i. Best supportive care (ischaemic only) ii. Bevacizumab iii. Dexamethasone implant iv. Grid pattern photocoagulation	CRVO: i. Best supportive care ii. Dexamethasone implant BRVO: i. Dexamethasone implant ii. Grid pattern photocoagulation	Very few patients fulfilled the definition of ischaemia in the two key phase III RCTs for ranibizumab (0 in BRAVO and 2 in CRUISE), likely because patients with brisk afferent pupillary defect, which equates to ischaemia, were excluded from the trials. Therefore the subgroup of ischaemic RVO only cannot be considered separately. Bevacizumab is not used routinely in clinical practice in the NHS. In the absence of a regulatory assessment of, in particular safety and quality, and insufficient evidence for efficacy, bevacizumab cannot be considered best practice. Thus, unlicensed bevacizumab is not an appropriate comparator according to NICE guidance
<i>Outcomes</i>	The outcome measures to be considered include: <ul style="list-style-type: none"> • Visual acuity (the affected eye) • Visual acuity (the whole person) • Adverse effects of treatment • Health-related quality of life 	The outcome measures to be considered include: <ul style="list-style-type: none"> • Visual acuity (the affected eye) • Adverse effects of treatment • Health-related quality of life 	Bilateral visual acuity outcomes were not recorded in the phase III trials.
<i>Economic analysis</i>	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.	A cost utility analysis will be presented, with results expressed in terms of incremental cost per quality-adjusted life year. The time horizon for	

	The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	estimating clinical and cost effectiveness will be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared The cost perspective is that of NHS and Personal Social Services.	
<i>Subgroups to be considered</i>	If the evidence allows, consideration will be given to subgroups according to: <ul style="list-style-type: none"> • type of RVO (BRVO and CRVO) • the presence or absence of ischaemia • baseline visual acuity • baseline structural damage to the central fovea • perfusion at the back of the eye • duration of macular oedema (time since diagnosis) 	Consideration will be given to subgroups according to: <ul style="list-style-type: none"> • type of RVO (BRVO and CRVO) • baseline visual acuity • duration of macular oedema (time since diagnosis) 	From the key phase III RCTs, no data were available for the subgroups ischaemic vs non ischaemic patients, perfusion at the back of the eye and damage to the central fovea. The common definition of ischaemia used in RVO is based on perfusion: a case of greater than 10 fluorescein angiography disc areas of capillary non-perfusion is classed as ischaemia. ⁽¹³⁾ Although this characteristic was measured at baseline in BRAVO and CRUISE, very few patients actually fulfilled this definition of ischaemia (0 in BRAVO and 2 in CRUISE). This is likely due to the fact that patients with brisk afferent pupillary defect, which equates to severe ischaemia, were excluded from the trials.
<i>Special considerations, including issues related to equity or equality</i>	Guidance will only be issued in accordance with the marketing authorisation	Guidance will only be issued in accordance with the marketing authorisation	

3.1 Population

The two key randomised controlled trials (RCTs) included in the MS as evidence on the clinical effectiveness of ranibizumab in the treatment of macular oedema (MO) secondary to retinal vein occlusion (RVO) included patients with MO secondary to branch RVO (BRVO; BRAVO⁽¹⁵⁾) or central RVO (CRVO; CRUISE).⁽¹⁶⁾ One exclusion criterion in both RCTs was presence of a brisk afferent pupillary defect (APD). Guidelines issued by the Royal College of Ophthalmologists (RCO) indicate that presence of relative APD is an indicator of retinal ischaemia.⁽¹⁾ In addition, in the MS, the manufacturer reports that the number of patients with >10 disc areas of capillary non-perfusion was also recorded. The MS reports that, of those in the sham injection and ranibizumab 0.5 mg groups, 0 patients in BRAVO and only 2 patients in CRUISE met this categorisation. Presence of >10

disc areas of capillary non-perfusion is listed as one indicator of ischaemia in CRVO in the RCO guidelines⁽¹⁾ and was used as a definition of ischaemia in the Central Vein Occlusion Study (CVOS),⁽¹³⁾ a key trial assessing the natural history of CRVO. A recent study on the natural history of visual outcome in CRVO indicates that presence of relative APD is a key differentiator of ischaemic from non-ischaemic CRVO.⁽²²⁾

On the basis of the information listed above, the ERG notes that the population in BRAVO and CRUISE is limited to people with MO secondary to non-ischaemic BRVO and CRVO, respectively, which are distinct subgroups of the population defined in the scope issued by NICE⁽²⁹⁾ and the eligible UK population.

3.2 Intervention

The ERG notes that the MS provides a good overview of ranibizumab. Ranibizumab has regulatory approval in the USA⁽³⁰⁾ and in the European Union (EU) for the treatment of wet age-related macular degeneration (AMD).⁽³¹⁾ Ranibizumab is also licensed in the USA for the treatment of MO following RVO,⁽³⁰⁾ and has regulatory approval in the EU for treatment of visual impairment as a result of diabetic macular oedema.⁽³¹⁾

Ranibizumab is a humanised recombinant monoclonal antibody fragment that selectively binds to human Vascular Endothelial Growth Factor A (VEGF-A) and prevents it from binding to its receptors. VEGF-A is an important mediator of vascular leakage in MO secondary to RVO. The recommended dose for ranibizumab is 0.5 mg, which is given as an intravitreal injection.⁽³¹⁾ For treatment of MO secondary to RVO and diabetic MO, the recommended treatment regimen is monthly intravitreal injections continued until maximum visual acuity is achieved, which is taken to be when the patient's visual acuity is stable for three consecutive monthly assessments while on ranibizumab treatment. If no improvement in visual acuity over the course of the first three injections is observed, cessation of treatment is recommended. Patients who achieve visual stability should be monitored monthly for visual acuity, and treatment with ranibizumab resumed when monitoring indicates loss of visual acuity due to MO secondary to RVO. Monthly injections should then be administered until stable visual acuity is reached again for three consecutive monthly assessments (implying a minimum of two injections). The interval between two doses should not be shorter than 1 month.

3.3 Comparators

The decision problem issued by NICE in the final scope⁽²⁹⁾ for this single technology appraisal (STA) indicates that comparators of interest common to both MO secondary to CRVO and to BRVO are best supportive care (only for MO secondary to ischaemic RVO), dexamethasone intravitreal implant and

bevacizumab. In addition, grid laser photocoagulation (GLP) is listed as a comparator of interest in MO secondary to BRVO.

In the MS, the manufacturer specifies that best supportive care is the standard of care, and therefore the main comparator, for the following subgroups:

- Patients with visual impairment due to MO secondary to both ischaemic and non-ischaemic CRVO;
- Patients with MO secondary to BRVO who have severe visual loss (less than 6/60 vision) or whose symptoms have been present for over a year;
- Patients with visual impairment due to MO secondary to ischaemic BRVO.

Based on discussion with a clinical expert (NL) and the treatment pathways outlined in the RCO guidelines,⁽¹⁾ the ERG does not agree with the manufacturer's assessment that best supportive care is the most appropriate comparator for:

- Patients with MO secondary to BRVO who have severe visual loss (less than 6/60 vision) or whose symptoms have been present for over a year;
- Patients with visual impairment due to MO secondary to ischaemic BRVO.

As outlined above, the manufacturer indicates that best supportive care is the recommended treatment for patients with MO secondary to BRVO who have severe visual impairment or whose symptoms have been present for over a year. However, based on expert opinion (NL), the ERG considers that GLP, and not best supportive care, is the recommended treatment for this population. The ERG notes that the baseline characteristics of the patients included in BRAVO and CRUISE (MS; Table B7, pg 71 for BRAVO and Table B8, pg 73 for CRUISE) indicate this variation would not affect interpretation of the results from BRAVO or CRUISE as: only a small proportion of patients had duration of MO secondary to RVO for longer than 12 months (4 patients in BRAVO and 4 patients in CRUISE); and the median visual acuities in the sham injection group and ranibizumab 0.5 mg group in BRAVO and CRUISE seem to be considerably better than 6/60 (equivalent to 20/200) vision: median approximate Snellen equivalent of 20/80 (equivalent to 6/24) in each arm in BRAVO and 20/100 (equivalent to 6/30) in each arm in CRUISE.

For patients with visual impairment due to MO secondary to ischaemic BRVO, the RCO guidelines indicate that best supportive care is most appropriate for those with macular ischaemia.⁽¹⁾ The statement in the RCO guidelines does not incorporate those with retinal ischaemia. The ERG notes that not all patients with ischaemic BRVO will have macular ischaemia: ischaemic BRVO denotes the presence of areas of ischaemic retina, which are not necessarily located at the macula and do not necessarily affect the perifoveal capillaries. It is important to note that patients with macular ischaemia and MO secondary to BRVO are usually not considered to be suitable patients for GLP.

In the MS, the manufacturer outlines arguments against carrying out comparisons (either direct or indirect) of ranibizumab versus bevacizumab or dexamethasone intravitreal implant in MO secondary to non-ischaemic BRVO and non-ischaemic CRVO. In the case of MO secondary to BRVO, the manufacturer also indicates that the current standard of care for non-ischaemic MO due to BRVO is GLP (MS; pg 36), and thus this should be the main comparator for ranibizumab in non-ischaemic BRVO. The manufacturer obtained opinions from three clinical experts on the appropriateness of carrying out comparisons of ranibizumab versus the two agents. All experts fed back that the populations in the trials of bevacizumab and dexamethasone intravitreal implant were sufficiently different to preclude comparison. The ERG notes that indirect comparisons of ranibizumab versus dexamethasone intravitreal implant and versus bevacizumab could have been attempted, with the results interpreted in light of any likely bias incurred by differences in trial design or patient populations. The ERG has performed exploratory analyses based on the evidence provided in the MS (section 4.4.2). With regards to the comparison of ranibizumab versus GLP in MO secondary to BRVO, for reasons discussed in more detail in section 4.3.1, the ERG considers that the design of the BRAVO trial does not facilitate a direct comparison of ranibizumab with GLP, and that an indirect comparison of ranibizumab using other studies of GLP could have been attempted.

Dexamethasone intravitreal implant, as noted by the manufacturer, was included in the RCO guidelines⁽¹⁾ as a pharmacological treatment that could be considered for the treatment of visual impairment due to MO secondary to RVO. The manufacturer commented that dexamethasone intravitreal implant is a recently approved agent and as such is not currently used routinely in NHS clinical practice, but it may be considered to represent the best alternative care to the current standard of care. The manufacturer identified no evidence comparing ranibizumab versus dexamethasone intravitreal implant directly, and concluded that substantial differences among identified trials for ranibizumab and dexamethasone intravitreal implant, in terms of population baseline characteristics, design and reporting, precluded the possibility of carrying out a reliable indirect comparison of these agents. However, the manufacturer incorporated the available data into the economic model, but acknowledged that there are severe limitations to the approach, and the results should be considered exploratory and interpreted with caution.

Considering bevacizumab, in the MS, the manufacturer presents several arguments in support of the rationale for not comparing bevacizumab versus ranibizumab:

- Bevacizumab is not licensed to treat ocular conditions;
- As an unlicensed treatment, bevacizumab cannot be considered best practice;
- Bevacizumab is not used routinely in clinical practice in the NHS to treat MO secondary to RVO;

- There are limited data for bevacizumab in this indication; the RCO guidelines note that evidence for bevacizumab is limited to non-analytic studies, such as case reports, case series or expert opinion;⁽¹⁾
- Lack of reliable efficacy data for bevacizumab in the treatment of MO secondary to RVO renders an indirect comparison of ranibizumab and unlicensed bevacizumab unviable;
- Safety and quality of bevacizumab should be assessed by the regulatory authorities before it is assessed in an appraisal: the manufacturer highlights potential systemic and ocular safety signals for bevacizumab⁽³²⁻³⁴⁾ that it notes render it inappropriate to include bevacizumab as a comparator.

In light of these points, the manufacturer states that unlicensed bevacizumab is not an appropriate comparator according to NICE guidance. The NICE ‘Guide to the Methods of Technology Appraisal’⁽³⁵⁾ states: “The Appraisal Committee does not normally make recommendations regarding the use of a drug outside the terms of its marketing authorisation, as published in the manufacturer’s summary of product characteristics. It can, however, consider unlicensed comparator technologies if these are used regularly in the NHS.”

The ERG recognises that bevacizumab is unlicensed for the treatment of ocular conditions, but considers that a comparison with ranibizumab is appropriate for this indication, and could have been attempted. Although the manufacturer asserts that clinical experts have fed back at previous NICE scoping meetings that unlicensed bevacizumab is not routinely used in clinical practice, the ERG considers that bevacizumab is used throughout the NHS to treat ocular conditions. This view is corroborated by the RCO guidelines,⁽¹⁾ which state that bevacizumab is used extensively in clinical practice, and by findings from the NICE Appraisal Committee for dexamethasone intravitreal implant for the treatment of MO secondary to RVO.⁽³⁶⁾ In addition, studies have been published assessing the effects of bevacizumab in people with MO secondary to RVO (Moradian 2011⁽³⁷⁾, Russo 2009⁽³⁸⁾). The ERG discusses the feasibility of comparing ranibizumab versus bevacizumab in section 4.4.2.

3.4 Outcomes

The manufacturer has addressed most of the outcomes listed in the final scope issued by NICE.⁽²⁹⁾ The primary outcome reported in the BRAVO and CRUISE randomised controlled trials (RCTs) is change in best corrected visual acuity (BCVA) from baseline in the treated eye. The decision problem issued by NICE⁽²⁹⁾ also requested assessment of visual acuity of the whole person. The manufacturer highlights that whole person BCVA data are not available from BRAVO and CRUISE.

Additional measures of visual acuity assessed in the study eye were:

- Mean change from baseline BCVA letter score over time to month 6;
- Percentage of patients who gained ≥ 15 letters from baseline BCVA at month 6;
- Percentage of patients who lost < 15 letters from baseline BCVA at month 6.

The MS also presents data on the outcome [REDACTED]

Other outcomes assessed included:

- Incidence and severity of ocular and non-ocular adverse events (AEs) and serious AEs.

Data presented in the clinical section of the MS for the outcomes measured are based on the last observation carried forward. The ERG notes that imputation of missing data using the last observation carried forward method is likely to provide an inappropriate level of precision around the effect estimate (which in itself may be wrong) with no way of validating it. However, the ERG also notes that, because of the high rate of follow-up at month 6, any bias will be minimal in BRAVO and CRUISE. The manufacturer states (MS; pg 88) that, “unless otherwise noted, the intent-to-treat approach was used for efficacy analyses and included all patients as randomised. Missing values for efficacy outcomes were imputed using the last observation carried-forward method.”

3.5 Other relevant factors

The manufacturer has submitted a patient access scheme (PAS) for the use of ranibizumab in patients with MO secondary to RVO. As the PAS means that “[REDACTED] [REDACTED] the ERG does not believe there would be any additional costs incurred with its implementation.

4 CLINICAL EFFECTIVENESS

4.1 Critique of the methods used by the manufacturer to systematically review clinical effectiveness evidence

4.1.1 Description and discussion of appropriateness of manufacturer's search strategy

The manufacturer's submission (MS) describes the search terms and strategies for the manufacturer's review of the literature up to 18 November 2010. The manufacturer searched multiple databases, including EMBASE, MEDLINE, MEDLINE In-Process and CENTRAL to identify relevant studies assessing the clinical effectiveness, cost effectiveness, and adverse effects of ranibizumab in patients with macular oedema (MO) secondary to branch or central retinal vein occlusion (RVO). The manufacturer also carried out extensive searches of online trial registries and proceedings from several key conferences (including Association of Research in Vision and Ophthalmology [ARVO] and European Association for Vision and Eye Research [EVER]). The ERG considers the search strategy used by the manufacturer to be comprehensive. As the manufacturer highlights, the search strategy did not include search terms that limited the search results to only randomised controlled trials (RCTs); searches were limited to human studies. However, the MS states that only RCTs were included in the assessment on the clinical effectiveness of ranibizumab. The manufacturer used multiple search terms for conditions and treatments, including terms for interventions listed as comparators of interest in the final scope issued by the National Institute for Health and Clinical Excellence (NICE).⁽²⁹⁾ Although search terms for best supportive care were not specifically included in the search strategy, the ERG is confident that studies in which best supportive care was a comparator would have been identified for appraisal. It is not clear whether reference lists of identified RCTs were evaluated for suitable studies. The manufacturer also carried out a separate search for the identification of non-RCT data for bevacizumab. As part of the clarification process, the ERG requested the search strategy used to identify non-RCT data on bevacizumab. The manufacturer supplied the search strategy as academic in confidence. The ERG notes that the manufacturer's search strategy was comprehensive and considers that all studies could have been identified. [REDACTED]

[REDACTED]

[REDACTED]

The ERG validated the manufacturer's search in EMBASE, MEDLINE and Medline In-Process, and the Cochrane library (08/06/2011), and generated a comparable number of studies to that generated by the manufacturer's search.

The manufacturer restricted their search to English language studies. To assess the potential impact of omission of non-English language studies, the ERG assessed RCTs identified in the Cochrane library (which includes studies in all languages) against the criteria listed in the MS. Fifteen non-English language RCTs were identified, none of which the ERG thought relevant to the decision problem. As only a limited number of non-English language studies were identified, to investigate further, the ERG searched EMBASE and MEDLINE and MEDLINE In-Process using the manufacturer's search strategy for clinical effectiveness with and without the restriction to English language studies: the ERG did not deduplicate search results. In the search carried out by the ERG on 08/06/2011, limiting to English language studies reduced the number of potentially relevant studies by 434 studies in MEDLINE and 866 studies in EMBASE.

The ERG would like to highlight that the search terms for studies assessing the measurement and evaluation of health effects restricts the search to studies of MO secondary to RVO. The ERG notes that the effect of vision loss on health-related quality-of-life would be the same regardless of the cause, and so considers that it could have been appropriate to carry out a broader search to include terms for related conditions when reviewing the literature for studies assessing health effects.

Overall, the ERG considers the manufacturer's search strategy to be comprehensive but would like to highlight that limiting the search for studies assessing the measurement and valuation of health effects to MO secondary to RVO could have resulted in the exclusion of studies reporting utility values in the worse-seeing eye (WSE) in other ocular conditions. For example, one study not referenced in the MS that the ERG considers would inform the analysis of health effects is that by Brazier *et al.*⁽⁴⁰⁾ In addition, although the ERG notes that the key RCTs assessing the effects of ranibizumab in treating MO secondary to RVO have been identified, the ERG would like to note that non-English language studies that address the decision problem could be available.

4.1.2 Inclusion/exclusion criteria used in study selection

Inclusion/exclusion criteria applied by the manufacturer for their systematic review are summarised in Table 2.

Table 2. Summary of inclusion and exclusion criteria of systematic review of literature

	Inclusion	Exclusion
Population	<ul style="list-style-type: none"> • People aged 18 or over with visual impairment due to macular oedema secondary to retinal vein occlusion • Diagnosis of vein occlusion established by fluorescein angiography, optical coherence tomography (OCT) or a clinical assessment • Trials in which people had concomitant ocular disease (e.g., cataract or diabetic retinopathy) were included 	Mixed patient populations for which the results for RVO patients were not reported separately
Intervention	<ul style="list-style-type: none"> • Ranibizumab (used within its licensed dosage indication) either alone or in conjunction with laser photocoagulation therapy • Comparisons of ranibizumab versus: bevacizumab (Avastin); dexamethasone (Ozurdex intravitreal implant); laser photocoagulation; placebo or sham injections; mixed treatments; and observation/watchful waiting 	Studies not involving ranibizumab used within its licensed dosage indication
Outcomes	<ul style="list-style-type: none"> • Primary outcome for the review: “proportion of patients with an improvement in best corrected visual acuity, as measured by an improvement from baseline to six months of 10 or more letters read on an Early Treatment Diabetic Retinopathy Study Chart at four metres, equivalent to 0.2 logMAR”. <p>Any additional follow-up times will be reported.</p> <ul style="list-style-type: none"> • MS stated that “Studies reporting certain secondary outcomes, including QALYs, blindness avoided, structural damage to the central fovea, ischaemia and adverse events, were also eligible for inclusion” 	
Study design	<ul style="list-style-type: none"> • RCTs (including cross-over RCTs if data were presented at cross-over) • Abstracts or conference presentations • Unpublished studies 	<ul style="list-style-type: none"> • Non-RCT study designs • Articles reporting results of RCTs published elsewhere (e.g., reviews, meta-analyses/pooled analyses, editorials, notes, comments and letters)
Language restrictions	<ul style="list-style-type: none"> • English 	<ul style="list-style-type: none"> • All non-English language articles

The manufacturer presented flow diagrams of the numbers of studies included and excluded at each stage of the appraisal process.

The ERG finds it counterintuitive that the manufacturer’s RCTs (BRAVO and CRUISE) use improvement in visual acuity of ≥ 15 letters on the Early Treatment Diabetic Retinopathy Study

(ETDRS) scale as a secondary outcome, and yet the manufacturer used improvement in visual acuity of ≥ 10 letters on the ETDRS scale as the primary outcome for their literature search. In their response to the clarification questions, the manufacturer states that improvement in best corrected visual acuity (BCVA) of ≥ 15 letters is the “gold standard” outcome measure, which implies it would be the most widely used in other trials. The ERG is concerned that using improvement in visual acuity of ≥ 10 letters in their literature search may have excluded other trials of interest, and would have led to exclusion of BRAVO and CRUISE had the manufacturer not performed a *post-hoc* analysis. In their response to the clarification question, the manufacturer noted that the mean change in BCVA from baseline was also a primary outcome for their review, and that this statement had been omitted from the MS in error. Inclusion of mean change in BCVA from baseline as an outcome would not guarantee inclusion of those trials reporting only improvement in visual acuity of ≥ 15 letters.

The ERG would like to highlight that the manufacturer excluded reviews, meta-analyses, and pooled analysis during the appraisal process. The Centre for Reviews and Dissemination (CRD) highlights using reference lists of these types of publication as a source of potential additional studies.⁽⁴¹⁾ However, the ERG considers that no relevant studies have been omitted from the Clinical Effectiveness section.

4.1.3 Studies included in clinical effectiveness review

In the MS, the flow diagram outlining the appraisal process indicates that 14 articles were identified and included in the manufacturer’s systematic review. Of these, one is an RCT assessing the effects of ranibizumab in treating MO secondary to branch RVO (BRVO; BRAVO⁽¹⁵⁾) and two are RCTs assessing the effects of ranibizumab in treating MO secondary to central RVO (CRVO; CRUISE⁽¹⁶⁾ and ROCC⁽⁴²⁾). Of the remaining 11 articles, 9 are conference abstracts relating to the BRAVO (5 abstracts⁽⁴³⁻⁴⁷⁾), CRUISE (2 abstracts^(48;49)) and ROCC (2 abstracts^(50;51)) RCTs. The remaining two articles are clinical trial records for CRUISE and ROCC.

The manufacturer notes that the ROCC RCT⁽⁴²⁾ was a small RCT with follow-up data for only 6 months. The manufacturer commented (MS; pg 55) that “as a larger number of patients with MO secondary to CRVO have been studied in the CRUISE study for a longer period of time, the ROCC study was not deemed to be a pivotal trial for ranibizumab in this patient population.” For these reasons, the manufacturer presents methodology and results of ROCC in the appendices of their submission (MS; Section 10.1, Appendix 14, pg 351), rather than in the main body of the text. Although the ERG agrees with the point raised by the manufacturer that the ROCC RCT is small in comparison with CRUISE and the results from ROCC do not have a large influence on the meta-analysis, the ERG considers it important to highlight the results from the ROCC RCT because of differences in baseline characteristics and trial design. ROCC included a small number of patients

with MO secondary to CRVO with a degree of ischaemia (non-perfusion in an area >5 disc areas), and initially treated patients with monthly intraocular ranibizumab for 3 months, after which treatment was at the discretion of the treating physician if MO with cysts in the central macular persisted. These points will be discussed in more detail in the section 4.4.2.

The manufacturer also identified one long-term extension study⁽⁵²⁾ that presented data at 12 months follow-up after completion of BRAVO and CRUISE, and one non-RCT study that has been highlighted as supporting the long-term efficacy of ranibizumab in the treatment of MO secondary to BRVO.^(53;54)

4.2 Summary and critique of submitted clinical effectiveness evidence

4.2.1 Quality of included RCTs

The manufacturer assessed the quality of the three identified RCTs and rated BRAVO⁽¹⁵⁾ and CRUISE⁽¹⁶⁾ as high-quality. The manufacturer notes some methodological issues with ROCC⁽⁴²⁾ (MS; Table 10, pg 356). The ERG has validated the three RCTs and predominantly agrees with the manufacturer's assessments (see Appendix for quality assessments).

4.2.2 Overview of included RCTs

The trial designs of BRAVO⁽¹⁵⁾ and CRUISE⁽¹⁶⁾ are similar, with the key differences being the underlying condition being assessed and the addition of rescue grid laser photocoagulation (GLP) in BRAVO. The key characteristics of BRAVO and CRUISE are presented in Appendix 1.

Trial conduct

BRAVO⁽¹⁵⁾ and CRUISE⁽¹⁶⁾ are 3-armed RCTs carried out at multiple centres in the USA (93 sites for BRAVO and 95 sites for CRUISE). Initially, patients were screened for 28 days (days -28 to -1), after which those eligible for treatment entered a 6-month treatment phase followed by a 6-month observation phase; during the observation phase both groups could receive ranibizumab *pro re nata* (PRN). Data in the MS indicate that >80% of patients from the sham injection group in both BRAVO and CRUISE (MS; Table B16, pg 91) received ranibizumab 0.5 mg PRN during the observation phase. Data at 12 months' follow-up for BRAVO and CRUISE are reported in a subsequent publication.⁽⁴⁴⁾

Patients were randomised 1:1:1 to sham injection, monthly intraocular ranibizumab 0.3 mg or monthly intraocular ranibizumab 0.5 mg. Data for the ranibizumab 0.3 mg arm are not reported in the MS, as the manufacturer highlights, ranibizumab 0.5 mg is the dose that is currently used in other ocular indications and is the dose for which European Medicines Agency (EMA) approval is

anticipated for treatment of MO secondary to RVO. Randomisation was carried out using a dynamic randomisation method, using an interactive voice response system (IVRS) to prevent bias in treatment assignment. Randomisation was stratified by study centre and by baseline BCVA, of which there were three baseline categories (≤ 34 letters, 35–54 letters, and ≥ 55 letters).

In BRAVO, from the month 3 visit in the treatment phase and again from the month 9 visit during the observation phase, patients in both the sham injection group and the ranibizumab 0.5 mg group became eligible for concomitant GLP treatment based on prespecified criteria. The ERG's views on the implications of use of concomitant GLP in BRAVO are discussed in section 4.3.1.

Population in BRAVO and CRUISE

Baseline characteristics for patients are presented in the MS (MS; Table B7, pg 71 for BRAVO and Table B8, pg 73 for CRUISE).

The ERG notes that baseline characteristics are reasonably balanced for the ranibizumab 0.5 mg and sham injection groups in both BRAVO and CRUISE. However, in BRAVO, the ERG would like to highlight the observed slight differences in baseline CFT (488.0 micrometres in the sham injection group vs 551.7 micrometres in the ranibizumab 0.5 mg group) and in the proportion of patients with MO of duration of >9 – ≤ 12 months from diagnosis to screening (16/132 [12.1%] in the sham group vs 7/131 [5.3%] in the ranibizumab 0.5 mg group). In CRUISE, the ERG notes minor differences in the proportion of patients with MO of duration of >3 – ≤ 6 months from diagnosis to screening (27/130 [20.8%] in the sham injection group vs 17/130 [13.1%] in the ranibizumab 0.5 mg group) and for >6 – ≤ 9 months from diagnosis to screening (4/130 [3.1%] in the sham injection group vs 10/130 [7.7%] in the ranibizumab 0.5 mg group).

Both BRAVO and CRUISE excluded people with brisk afferent pupillary defect (APD), which, as the manufacturer highlights (MS; pg 171), is indicative of retinal ischaemia.⁽¹⁾ Other definitions of ischaemia that have been implemented in trials are those used in BVOS,⁽¹⁴⁾ which assessed the effects of GLP in MO secondary to BRVO, and CVOS,⁽¹³⁾ which assessed GLP for MO with reduced visual acuity secondary to CRVO. In BVOS,⁽¹⁴⁾ ischaemic disease was defined as “branch vein occlusion involving a retinal area at least 5 disk areas”, whereas CVOS⁽¹³⁾ defined ischaemic disease as the presence of “at least than 10 fluorescein angiography disc areas of capillary non-perfusion”. The ERG notes that neither BRAVO nor CRUISE included a definition for ischaemia. Although APD is an indicator of retinal ischaemia, it is not indicative of macular ischaemia. As discussed in section 2.1, ischaemia occurring in the macula is the most relevant to the decision problem addressed by this single technology appraisal (STA), particularly in the case of BRVO. In the MS (MS; pg 42), the manufacturer states that they applied the criteria used in CVOS, and state that this is the common

- and prior anti-VEGF treatment in study or fellow eye within 3 months before day 0 or systemic anti-VEGF or pro-VEGF treatment within 6 months before day 0.

was well-balanced between the sham injection and the ranibizumab 0.5 mg groups in both BRAVO and CRUISE (data presented in Table 3).

Table 3. *****

*****	*****	*****	*****	*****	*****
*****	*****	*****	*****	*****	*****
*****	*****	*****	*****	*****	*****
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*****	*****	*****	*****	*****	*****
*****	*****	*****	*****	*****	*****
*****	*****	*****	*****	*****	*****
*****	*****	*****	*****	*****	*****

Treatment schedule

In both BRAVO⁽¹⁵⁾ and CRUISE,⁽¹⁶⁾ patients in the sham and ranibizumab injection groups received monthly intraocular injections for the 6 months of the treatment phase. The mean number of injections administered in both RCTs indicates a high rate of adherence to the protocol (BRAVO: 5.6 in the sham injection group vs 5.7 in the ranibizumab 0.5 mg group; CRUISE: 5.5 in the sham injection group vs 5.6 in the ranibizumab 0.5 mg group).

In the MS (MS; pg 13), the manufacturer indicates that stopping treatment with ranibizumab 0.5 mg is recommended when a patient’s visual acuity is stable for at least 3 consecutive months, and that treatment be resumed should monitoring indicate a loss of visual acuity due to MO secondary to RVO. The manufacturer reports (MS; pg 168) that a proportion of patients receiving ranibizumab 0.5 mg achieved clinical stability with good BCVA before the 6 month time point of the treatment phase (51% in BRAVO ranibizumab 0.5 mg group and 45% in CRUISE ranibizumab 0.5 mg arm). The manufacturer comments that the RCTs may therefore overestimate the amount of treatment necessary to achieve a stable (over 3 months) clinical outcome. However, this assumption does not seem to be supported by the mean number of injections of ranibizumab PRN given during the 6–12 month observational periods in BRAVO⁽¹⁵⁾ and CRUISE,⁽¹⁶⁾ and during the 12 month HORIZON⁽⁵²⁾ study. As the observation period and HORIZON are both open-label extension studies during which eligible patients received ranibizumab PRN, it would be anticipated that those who had previously received 6 months of continuous ranibizumab 0.5 mg would require substantially fewer injections than those entering the observation phase having previously received sham injections. However, the

data reported in Table 4 suggest that groups within each trial (that is, BRAVO and CRUISE) received broadly similar numbers of injections. The ERG notes that the BCVA at 24 months, particularly in patients with MO secondary to CRVO, suggest that the PRN regimens may be insufficient to maintain the benefit initially observed in the treatment phase. This is discussed in more detail in section 4.3.3. The ERG notes that the protocol of the ROCC RCT⁽⁴²⁾ followed the recommended administration regimen. Patients were randomised to receive ranibizumab 0.5 mg/0.05 mL or sham injection for the first 3 months, after which, treatment was administered at the discretion of the treating physician if MO with cysts in the central macular area persisted. The authors of the ROCC RCT noted a “dramatic loss of gained letters if ranibizumab was not repeated at month 4”; absolute numbers for loss not reported (data presented graphically in the full publication). The authors commented that there was a potential concern that repeated monthly injections may be needed to maintain anatomic and visual improvements.

Table 4. Mean number of injections during treatment and observation phases of BRAVO and CRUISE

	BRAVO		CRUISE	
	Sham/0.5 mg	Rani	Sham/0.5 mg	Rani
Mean number of injections during treatment phase (0–6 months)	5.6	5.7	5.5	5.6
Mean number of injections of ranibizumab PRN during observation phase (6–12 months)	3.6	2.7	3.7	3.3
Mean number of injections of ranibizumab PRN during first 12 months of HORIZON (12–24 months)	2.3	2.4	3.3	3.9
Abbreviations used in table: PRN, <i>pro re nata</i> ; Rani, ranibizumab.				

Outcomes assessed

The primary outcome of both BRAVO and CRUISE was evaluation of the change in BCVA over a 6 month period. The ERG notes that this outcome is assessed in only the study eye and not the whole person, which was requested in the final scope. The ERG notes that limiting the analysis to assessment of the study eye could potentially not give a true indication of the effects of treatment on overall BCVA. If the other eye is unaffected by MO secondary to RVO and has a high BCVA, it could be argued that treating the affected eye will be of minimal clinical benefit as the improvement in whole person BCVA could be small. Studies have reported low rates of development of RVO in the fellow-eye; a systematic review reported that 5%–10% of cases of BRVO may develop an RVO in the fellow eye (time frame over which RVO developed is unclear),⁽¹⁰⁾ whereas 5% of cases (at 1 year) in CRVO may develop fellow-eye RVO.⁽¹¹⁾

Secondary outcomes presented in the MS are (all outcomes relate to the study eye):

- Mean change from baseline BCVA letter score over time to month 6;
 - BCVA was measured based on the ETDRS visual acuity charts and assessed at a starting test distance of 4 metres;
- Mean change from baseline BCVA up to month 12;
- Percentage of patients who gained ≥ 15 letters from baseline BCVA at month 6 and month 12;
- Percentage of patients who lost < 15 letters from baseline BCVA at month 6 and month 12;
- Percentage of patients with central foveal thickness (CFT) ≤ 250 micrometres at month 6 and month 12;
- Mean change from baseline CFT over time up to month 12;
- Incidence and severity of ocular and non-ocular adverse events (AEs) and serious AEs.

Vision-related quality-of-life outcomes were reported as secondary outcomes:

- Mean change from baseline in the NEI VFQ-25 near activities subscale over time up to 6 months and at 12 months;
- Mean change from baseline in the NEI VFQ-25 distance activities subscale over time up to 6 months and at 12 months.

The MS also presents data on the outcome of [REDACTED]

[REDACTED] The ERG notes that this outcome is not listed as a prespecified outcome in either the primary publications of BRAVO and CRUISE or the clinical study reports (CSRs). As part of the clarification process, the ERG confirmed with the manufacturer that these analyses were *post-hoc* analyses.

4.3 Results

As discussed in section 2.1, the recommended management pathways for BRVO and CRVO differ. For this reason, the ERG has considered the results separately for MO secondary to BRVO and to CRVO.

4.3.1 Ranibizumab in the treatment of MO secondary to BRVO

Rate of follow-up in BRAVO was high, with 94% (248/263) of patients in the sham injection group and ranibizumab 0.5mg groups completing the study at month 6, and 90% (237/263) completing the study at month 12 (taken from the BRAVO CONSORT diagram; MS; Figure B4, pg 84).

In the MS, the manufacturer presents data from BRAVO for several visual acuity outcomes at 6 and 12 months (Table B17 [6 months], pg 99, and Table B19 [12 months], pg 112), some of which were exploratory outcomes. Here, the ERG presents data (Table 5) on the prespecified primary outcome of mean change in BCVA from baseline at month 6; data at month 12, which is a secondary outcome, are also presented. As the proportion of patients gaining improvement in vision drives the economic model, the ERG also extracted data on the prespecified secondary outcome of proportion of patients with an improvement of ≥ 15 letters in BCVA and the *post-hoc* analysis of [REDACTED]

[REDACTED] The manufacturer also carried out a *post-hoc* analysis of percentage of patients with an improvement of ≥ 15 letters in BCVA for day 7, month 1, month 2 and month 3; these data are also presented in Table 5 of the ERG report. As part of the clarification process, the ERG requested the absolute number of patients achieving this outcome at the individual timeframes (presented in Table 6).

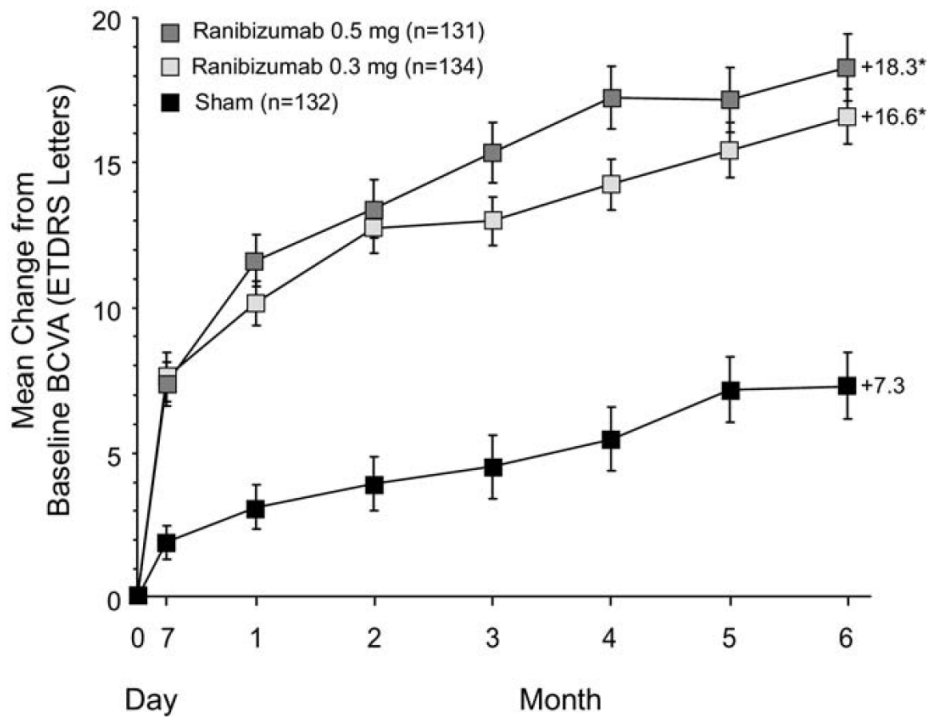
The data indicate that the effect of ranibizumab 0.5 mg is seen early on in treatment. As the manufacturer notes, the earliest statistically significant group difference ($p < 0.0001$ vs sham) was detected at day 7 after treatment. For the primary outcome of mean change in BCVA and the key visual outcome of proportion of patients with an improvement in visual acuity of ≥ 15 letters, as the data presented in Table 5 and Figure 1 indicate, the majority of improvement with ranibizumab was observed by month 3.

Table 5. Summary of efficacy data for ranibizumab 0.5 mg in the treatment of MO secondary to BRVO (BRAVO)^(15;44)

Timeframe	Sham (n = 132)	Rani 0.5mg (n = 131)	Significance
Mean (SD) change from baseline in BCVA score (ETDRS letters)			
Month 6	7.3 (13.0) 95% CI: 5.1 to 9.5	18.3 (13.2) 95% CI: 16.0 to 20.6	p <0.0001
Month 12	12.1 (14.4) 95% CI: 9.6 to 14.6	18.3 (14.6) 95% CI: 15.8 to 20.9	–
Patients who gained ≥ 15 ETDRS letters			
Percentage at day 7	3.8%	14.5%	p <0.005 (<i>post-hoc</i> analysis)
Percentage at month 1	8.3%	32.8%	p <0.005 (<i>post-hoc</i> analysis)
Percentage at month 2	16.7%	39.7%	p <0.005 (<i>post-hoc</i> analysis)
Percentage at month 3	17.4%	50.4%	p <0.005 (<i>post-hoc</i> analysis)
Proportion at month 6, n (%)	[REDACTED] (28.8%)	[REDACTED] (61.1%)	p <0.00001 ^a
Proportion at month 12, n (%)	[REDACTED] (43.9%)	[REDACTED] (60.3%)	–

Proportion of patients who gained ≥10 ETRDS letters			
Month 6, n (%)			
Mean change from baseline NEI VFQ-25 Composite Score			
Month 6 ^c	5.4 95% CI: 3.6 to 7.3	10.4 95% CI: 8.3 to 12.4	p <0.005 for ranibizumab vs sham ^b
a			
Abbreviations used in table: BCVA, best corrected visual acuity; CI, confidence interval; ETRDS, Early Treatment Diabetic Retinopathy Study; NEI VFQ-25, National Eye Institute Visual Functioning Questionnaire-25; Rani, ranibizumab;			

Figure 1. Mean change from study eye baseline BCVA over time to month 6 in patients with MO secondary to BRVO (*denotes p <0.0001 versus sham; figure reproduced from MS; pg 103)



Data for the first 3 months of BRAVO (Table 6) support the findings reported in the MS that most of the benefit with ranibizumab is observed by month 3, with 50.4% of patients [REDACTED] randomised to ranibizumab 0.5 mg reaching the prespecified outcome of improvement of 15 or more letters from baseline score at this time point, compared with 61.1% ([REDACTED]/131) at month 6. Data for the sham group suggest that there is some improvement without treatment at month 3, with 17.4% of patients ([REDACTED]/132) randomised to sham injection reaching the prespecified outcome of improvement of 15 or more letters from baseline score at month 3, rising to 28.8% ([REDACTED]/132) at month 6. These data are in accordance with the rates reported by Rogers *et al.*⁽¹⁰⁾ of 18% of eyes with MO secondary to BRVO showing resolution of MO within 4.5 months post occlusion, rising to 41% by 7.5 months.

As part of the clarification process, the ERG requested data on how many people spontaneously resolved in the sham injection arm in the BRAVO RCT before 3 months (that is, before use of rescue GLP). In the clarification question, the ERG specified a visual acuity of $\geq 20/40$ and CFT of < 250 microns, based on the inclusion criteria listed in BRAVO. The manufacturer commented that spontaneous resolution was not defined in BRAVO and CRUISE, and that there is no widely accepted definition of spontaneous resolution in clinical practice. The manufacturer went on to highlight that the visual acuity and CFT criteria noted by the ERG indicate partial improvement in MO rather than resolution, and that further improvements could be possible. The manufacturer indicated that the number of patients in the sham group meeting a criteria of visual acuity $\geq 20/40$ and CFT < 250 microns at month 3 [REDACTED]

Superseded – see erratum

Table 6. Visual acuity outcomes in the sham and ranibizumab groups at up to 3 months in patients with MO secondary to BRVO (BRAVO)

	Sham (n = 132)			Rani 0.5 mg (n = 131)		
	Month 1	Month 2	Month 3	Month 1	Month 2	Month 3
Mean change (SD) in BCVA from baseline, ETDRS letters	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Number of patients achieving an improvement of ≥ 15 letters, n (%)	(8.3)	(16.7)	(17.4)	(32.8)	(39.7)	(50.4)
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

Abbreviations used in table: BCVA, best corrected visual acuity; BRVO, branch retinal vein occlusion; ETDRS, Early Treatment Diabetic Retinopathy Study; MO, macular oedema; Rani, ranibizumab.

Potential effects of concomitant grid laser photocoagulation

In BRAVO, as noted in the section outlining trial conduct (section 4.2.2), from the month 3 visit in the treatment phase and again from the month 9 visit during the observation phase, patients in both the sham injection group and the ranibizumab 0.5 mg group became eligible for concomitant GLP if their haemorrhage had cleared sufficiently to allow safe application of GLP and they had:

- Snellen equivalent BCVA $\leq 20/40$ or mean central subfield thickness ≥ 250 micrometres;
- and patient had a gain of < 5 letters in BCVA or a decrease of < 50 micrometres in mean central subfield thickness compared with the visit 3 months before the current visit.

If rescue GLP was not given at month 3, the same criteria were applied at month 4, and again at month 5, if rescue GLP was not given at month 4. This sequence was repeated from month 9.

The ERG considers that, based on expert opinion (NL), the criteria specified above are not widely used in clinical practice in the UK to determine eligibility for GLP in patients with MO secondary to BRVO.

At month 6, 57.6% (■/132) of patients in the sham injection group and 21.4% (■/131) of patients in the ranibizumab 0.5 mg group had received GLP once from month 3 to month 6 of the treatment phase.

To investigate the effects of adding GLP, the manufacturer carried out a *post-hoc* analysis stratified by rescue GLP (MS; Appendix 19, pg 378) and concluded that concomitant use of GLP in the ranibizumab arm did not inflate the efficacy results for ranibizumab.⁽⁵⁵⁾ For all three groups (sham and ranibizumab 0.3 mg and 0.5 mg), the manufacturer reported that patients who did not receive GLP achieved greater improvements in visual acuity outcomes (BCVA and proportion of people achieving improvement of 15 or more letters) compared with those in the same group who received GLP. The analysis presented by Pieramici *et al.*⁽⁵⁵⁾ assesses all those receiving GLP in the treatment (0–6 months) and/or observation (6–12 months) phase; during the observation phase all patients could receive ranibizumab PRN. As part of the clarification process, the ERG requested data on visual acuity outcomes at 1, 2 and 3 months for all patients randomised to the sham injection and ranibizumab 0.5 mg groups. In addition, for the subgroup of patients receiving GLP in the treatment phase, the ERG asked for: the mean BCVA based on last observation immediately prior GLP; data on visual outcomes at month 6; and data on visual outcomes at month 12. The manufacturer supplied the data separately for those receiving GLP at month 3, month 4, or month 5. The ERG notes that few patients receive GLP at months 4 and 5 and so the data are not discussed further.

For patients receiving GLP in the treatment phase, the ERG also requested the number of patients achieving an improvement of ≥ 15 letters and ■■■■■ at 6 and 12 months' follow-up. The manufacturer reported that these analyses are underway, and will be available in July: at the time of writing this report, the ERG had not received these data.

Considering those who received GLP at month 3 (that is, observation at month 2; Table 7), ■■■■■

However, the ERG and manufacturer both note that the results of these analyses should be interpreted with caution: there is a significant selection bias in the analyses because patients were not randomised to GLP; there is considerable disparity in the number of patients in the treatment and control arms; and the sample size in some subgroups is small.

Table 7. Patient visual acuity outcomes for patients who received grid laser photocoagulation treatment at month 3

	Sham	Rani 0.5 mg
Last observation prior to GLP treatment for those patients receiving GLP treatment at month 3		
Number of patients being assessed ^a		
Mean visual acuity		
Mean change in BCVA from baseline		
Outcomes measures at month 6 for those patients who received GLP treatment at month 3		
Number of patients being assessed		
Mean visual acuity		
Mean change in BCVA from baseline		
Outcomes measures at month 12 for those patients who received GLP treatment at month 3		
Number of patients being assessed		
Mean visual acuity		
Mean change in BCVA from baseline		
Abbreviations used in table: BCVA, best corrected visual acuity; GLP, grid laser photocoagulation; Rani, ranibizumab.		

In the MS, the manufacturer states that the addition of GLP at month 3 is representative of UK clinical practice, and is based on the precedent established in the Branch Retinal Vein Study (BVOS).⁽¹⁴⁾ BVOS enrolled patients who had MO secondary to BRVO for a period of 3 to 18 months. Patients were subsequently randomised to either GLP or no treatment. In the MS, the manufacturer states (MS; pg 36) that “rapid treatment of MO secondary to RVO is known to be important in terms of good prognosis, but laser photocoagulation treatment is not recommended for the management of MO within 3 months of the initial BRVO event to allow some reduction in haemorrhage.” The ERG considers it important to clarify that the rationale, as reported in BVOS, for delaying GLP is not to allow for absorption of the haemorrhage but to allow time for spontaneous improvement. The authors of BVOS stated that patients with duration of occlusion of less than 3 months were not eligible because clinical judgement was that spontaneous improvement often occurs during this timeframe.

GLP is typically administered after the initial observation period if most of the haemorrhage has been absorbed. Results from BVOS indicate that the potential benefit of GLP treatment continue to be observed at 3 years after the initial improvement in post-GLP visual acuity.

In the MS (MS; pg 54), the manufacturer highlights that the RCO guidelines⁽¹⁾ do not recommend concomitant use of GLP and pharmacotherapy for the management of BRVO, and the manufacturer does not anticipate ranibizumab regularly being given in conjunction with GLP.

Based on the points outlined above, the ERG notes that concomitant use of GLP starting from month 3 confounds the results of the BRAVO RCT and considers that definitive conclusions cannot be drawn as to the effects of ranibizumab versus sham injection or versus GLP alone. The ERG notes that, for a valid comparison of ranibizumab versus GLP, all patients in the “sham” treatment group should have received GLP at the point of randomisation and no patients in the ranibizumab group should have received GLP. Furthermore, the ERG notes that concomitant use of ranibizumab and GLP does not represent how ranibizumab would necessarily be used in clinical practice. In the MS (MS; pg 24), the manufacturer describes a pilot trial (RABAMES) in MO secondary to BRVO comparing ranibizumab 0.5 mg versus laser photocoagulation versus ranibizumab 0.5 mg plus laser photocoagulation (RABAMES; NCT00562406) over 6 months. The results of RABAMES are scheduled to be released by the end of 2011.⁽⁵⁶⁾ The inclusion criteria for this trial, as listed on the ClinicalTrials.gov entry, stipulate that patients have “chronic (>3months, <18 months) macular edema secondary to branch retinal vein occlusion”. The ERG considers that the results of this trial will better inform the comparison of GLP versus ranibizumab 0.5 mg in the population of interest to this technology appraisal.

4.3.2 Ranibizumab in the treatment of MO secondary to CRVO

In the MS, the manufacturer present data at 6 and 12 months for several visual acuity outcomes for MO secondary to CRVO (MS; Table B18 [6 months], pg 105, and Table B20 [12 months], pg 113), some of which were exploratory outcomes. Here, the ERG has extracted data (Table 8 of the ERG report) on the primary prespecified outcome (mean change in BCVA from baseline). The ERG also extracted data on the prespecified secondary outcome of proportion of patients with an improvement of ≥ 15 letters in BCVA and the *post-hoc* outcome of [REDACTED] as proportion of patients gaining improvement in vision drives the economic model. The manufacturer also carried out a *post-hoc* analysis of percentage of patients with an improvement of ≥ 15 letters in BCVA for day 7, month 1, month 2 and month 3; these data are also presented in Table 8.

Regarding the clinical decision problem of determining the comparative effectiveness of ranibizumab in treating MO secondary to RVO, the ERG considers that data pre-PRN ranibizumab (i.e., at month

6) are potentially the most relevant. The authors of the ROCC RCT (CRVO) state that 6 months' follow-up may be insufficient to determine the long-term effects of ranibizumab: they highlight that "longer follow-up after the last injection, or a longer period with repeated injections, would provide more certainty regarding treatment recommendations".⁽⁴²⁾ The ERG agrees with the authors of the ROCC RCT in this regard.

The CRUISE CONSORT flow diagram for participant flow (MS; Figure B5, pg 85) indicates that, of patients in the sham injection group and ranibizumab 0.5mg, 90% (234/260) completed the study at month 6, and 86% (223/260) completed the study at month 12.

As in BRAVO, the data indicate that the effect of ranibizumab 0.5 mg is seen early on in treatment. Again, as the manufacturer notes, the earliest statistically significant group difference ($p < 0.0001$ vs sham) was detected at day 7 after treatment. For the primary outcome of mean change in BCVA and the key visual outcome of proportion of patients with an improvement in visual acuity of ≥ 15 letters, as the data presented in Table 8 and Figure 2 indicate, the majority of improvement with ranibizumab was observed by 3 months in patients with MO secondary to CRVO.

Table 8. Summary of efficacy data for ranibizumab 0.5 mg in the treatment of MO secondary to CRVO (CRUISE)^(16;44)

Timeframe	Sham (n = 130)	Rani 0.5mg (n = 130)	Significance
Mean (SD) change from baseline in BCVA score (ETDRS letters)			
Month 6	0.8 (16.2) ^a 95% CI: -2.0 to 3.6	14.9 (13.2) ^a 95% CI: 12.6 to 17.2	$p < 0.0001$
Month 12	7.3 (15.9) 95% CI: 4.5 to 10.0	13.9 (14.2) 95% CI: 11.5 to 16.4	–
Patients who gained ≥ 15 ETDRS letters			
Percentage at 7 days	3.8%	26.9%	$p < 0.0001$ (post-hoc analysis)
Percentage at Month 1	5.4%	25.4%	$p < 0.0001$ (post-hoc analysis)
Percentage at Month 2	5.4%	37.7%	$p < 0.0001$ (post-hoc analysis)
Percentage at Month 3	8.5%	36.9%	$p < 0.0001$ (post-hoc analysis)
Proportion at month 6, n (%)	22 (16.9%) ██████████	62 (47.7%) ██████████	$p < 0.0001^b$
Proportion at month 12, n (%)	43 (33.1%) ██████████	66 (50.8%) ██████████	–
Proportion of patients who gained ≥ 10 ETDRS letters			
Month 6, n (%)	██████████	██████████	██████████ ██████████
			██████████ ██████████
Mean █████ change from baseline NEI VFQ-25 Composite Score			
Month 6 ^d	2.8 █████ 95% CI: 0.8 to 4.7 127 patients in analysis	6.2 █████ 95% CI: 4.3 to 8.0 128 patients in analysis	$p < 0.05$ for rani vs sham ^c

the physician. The ROCC RCT noted that all patients in the ranibizumab group responded to treatment (a decrease in central macular thickness and an improvement in BCVA score). The authors of ROCC noted that after the first 3 injections with ranibizumab, 3 patients (out of 15 patients) in the group had a persistent response throughout the study, having a flat macula and improved BCVA score. The 3 patients with persistent response had a mean symptom duration of 73 days and a mean age of 64 years. However, the authors of ROCC went on to report that, in the sham injection group, four patients had a decrease in central macular thickness and an improved BCVA score during the study period, and that the improvements were most pronounced during the first 3 months of the study. The baseline characteristics of these four patients indicate that they are comparatively young and have a short duration of CRVO (mean age of 61 years at baseline, mean symptom duration of 30 days, and a mean BCVA score of 69 ETDRS letters). The authors of ROCC highlight that there could be a rationale for delaying treatment in the hope of spontaneous improvement. They go on to suggest that if there is no resolution of symptoms then “younger patients may require fewer injections to achieve a lasting dry macula and may have a better prognosis following treatment with ranibizumab”.

4.3.3 Long-term effects of ranibizumab in treating MO secondary to RVO

The manufacturer reported results from HORIZON (Cohort 2),⁽⁵²⁾ which is a large open label, single arm extension study that enrolled patients who completed BRAVO and CRUISE. The objective of HORIZON was to assess the long-term safety and efficacy of ranibizumab 0.5 mg PRN. An overview of the trial conduct and exclusion criteria is given in Box 9.

The ERG notes that the rate of follow-up at month 12 of HORIZON (i.e., 24 months after commencement of BRAVO and CRUISE) was low (51.5%–70.2%; Table 9). It is noted in the conference abstract in which HORIZON results were presented that “~88% of patients discontinued due to study termination 30 days after approval of ranibizumab for RVO”. The ERG notes that the low rate of follow-up could increase the risk of bias in the study and so results should be interpreted with caution. In addition, the standard deviation, which is a measure of the variation around the mean value, for the mean changes in BCVA at month 12 in HORIZON were not reported (MS; Table B21, pg 114).

In HORIZON, patients with MO secondary to BRVO (BRAVO) who were initially randomized to sham injection during the treatment phase (0–6 months) and then received ranibizumab 0.5 mg PRN (6–12 months) experienced a mean change in BCVA (ETDRS letters) at month 24 of +15.6 ETDRS letters (change from baseline BCVA at enrolment in BRAVO), whereas patients initially randomized to ranibizumab 0.5 mg in the treatment phase experienced a mean change in BCVA of +17.5 ETDRS letters (change from baseline BCVA at enrolment in BRAVO) (data summarised in Table 9). Following on from the ERG’s earlier comments on concomitant use of GLP in BRAVO (section 4.3.1), and the findings from BVOS that improvements in BCVA were observed at up to 3 years after

GLP,⁽¹⁴⁾ for those patients initially entered into BRAVO, the ERG thinks it important to also highlight separately the mean change in BCVA from baseline BCVA at enrolment in HORIZON (summarised in Table 10). The mean change in BCVA at 12 months' follow-up of HORIZON (i.e., 12 months after the end of BRAVO) from baseline BCVA at entry into the extension study is +0.9 letters with sham/ranibizumab 0.5 mg group compared with -0.7 letters with ranibizumab 0.5 mg group. It is important to note that a larger proportion of patients (67% [65/97] patients) in the group initially randomised to sham injection (sham/0.5 mg column in Table 10) received at least one rescue treatment with GLP during the 12 months' follow-up of BRAVO compared with the group initially randomised to ranibizumab 0.5 mg (36% [37/104] patients). Taken together, these findings could suggest that the improvements in BCVA are observed with GLP in the longer-term, as reported by BVOS.⁽¹⁴⁾ However, it should be noted that the differences between groups in baseline BCVA are small with considerable variation around the mean, and the rate of follow-up is low.

Patients with MO secondary to CRVO (CRUISE) who were initially randomized to sham injection during the treatment phase and subsequently received ranibizumab 0.5mg PRN experienced a mean change in BCVA (ETDRS letters) at month 24 of +7.6 ETDRS letters (change from baseline BCVA at enrolment in CRUISE), whereas those randomized to ranibizumab 0.5 mg in the treatment phase achieved a mean change of +12.0 ETDRS letters (change from baseline BCVA at enrolment in CRUISE) (summarised in Table 10). However, the mean change in BCVA at 12 months' follow-up of HORIZON (i.e., 12 months after the end of CRUISE) was -4.1 letters in the sham/ranibizumab 0.5 mg group compared with -4.2 letters in the ranibizumab 0.5 mg group. The similarity in change in BCVA at month 24 could suggest that delaying treatment to allow time for spontaneous improvement does not have a deleterious effect on visual acuity in the long-term. In addition, as the manufacturer notes, the loss in BCVA could suggest that the PRN dosing regimen is insufficient and a more frequent treatment regime would be required in MO secondary to CRVO to maintain the initial observed benefit.

Box 9. Overview of the protocol for the HORIZON extension study.

Patients from BRAVO and CRUISE who had central subfield thickness ≥ 250 micrometres or MO that affected visual acuity were given ranibizumab 0.5 mg PRN, and followed up at 3 monthly intervals for up to 24 months or until study termination (defined as 30 days after FDA approval of ranibizumab for RVO treatment). People were precluded from entering HORIZON if they met any of the following criteria:

- Concurrent use of systemic anti-VEGF agents
- History of intraocular surgery (including cataract extraction, scleral buckle, etc.) within 1 month prior to Day 0 of this extension study
- Use of RVO treatments not approved by the Food and Drug Administration (FDA) in the study eye
- Use of intravitreal bevacizumab in the study eye and/or fellow eye
- Macular edema in the study eye due to other causes than RVO such as diabetes for Cohort 2

The baseline characteristics of people enrolled into HORIZON is reported in the MS (MS; Table B9, pg 75). In brief, of 263 people enrolled in the sham injection and ranibizumab 0.5 mg groups in BRAVO, 201 people (76.4%) continued into the HORIZON cohort, and of 260 people enrolled in the sham injection and ranibizumab 0.5 mg groups in CRUISE, 197 people (75.8%) continued into the HORIZON cohort. [REDACTED]

In addition to HORIZON,⁽⁵²⁾ the manufacturer identified a smaller (40 people) randomised, but uncontrolled, open-label, dose comparison study of ranibizumab (0.3 mg vs 0.5 mg) treatment for visual impairment due to MO secondary to RVO, with a follow-up of 24 months.^(53;54) The manufacturer included this study as it informs on the long-term effects of treatment with ranibizumab. Results at month 24⁽⁵⁴⁾ (summarised in Table 11) suggest that ranibizumab affords long-term benefit in improving visual acuity in patients with MO secondary to RVO, and in particular those with BRVO. In patients with MO secondary to CRVO, the ERG notes that the results suggest a decline in the initial improvement in BCVA (from 12.0 [2.2 SE] letters at month 3 to 8.5 [3.9 SE] letters at month 24), which mirrors the trend observed in HORIZON. However, the ERG would like to highlight that reported changes in mean BCVA at month 24 are a combined analysis of ranibizumab 0.5 mg and ranibizumab 0.3 mg; data not reported separately for ranibizumab 0.3 mg and 0.5 mg.

Table 9. Retention of patients to HORIZON (reproduced from MS, Table B14, pg 86)

	Initial trial					
	BRAVO			CRUISE		
	Sham/ 0.5 mg (n = 97)	Rani 0.3 mg (n = 103)	Rani 0.5 mg (n = 104)	Sham/ 0.5 mg (n = 98)	Rani 0.3 mg (n = 107)	Rani 0.5 mg (n = 99)
Completed HORIZON Month 12, n (%)	66 (68.0)	66 (64.1)	73 (70.2)	60 (61.2)	70 (65.4)	51 (51.5)
Average duration of follow-up at study completion ^a (years)						
N	■	■	■	■	■	■
Mean (SD)	■	■	■	■	■	■
Median	■	■	■	■	■	■
Range	■	■	■	■	■	■
^a ■						
Abbreviations used in table: Rani, ranibizumab.						

Table 10. Summary of long-term follow-up data from HORIZON

	Initial trial			
	BRAVO		CRUISE	
	Sham/ 0.5 mg (n = 97)	Rani 0.5 mg (n = 104)	Sham/ 0.5 mg (n = 98)	Rani 0.5 mg (n = 99)
Mean (SD) change in BCVA score^a (ETDRS letters) from BRAVO or CRUISE baseline				
Month 12 of HORIZON (24 months from BRAVO/CRUISE baseline) [Number of patients with a VA score at Month 12]	15.6 [66]	17.5 [73]	7.6 [60]	12.0 [51]
Baseline BCVA in study eye at entry into HORIZON				
Mean (SD) BCVA, ETDRS letters	68.1 (15.6)	72.2 (13.8)	59.8 (18.4)	64.7 (16.7)
Mean (SD) change in BCVA score^a (ETDRS letters) from HORIZON baseline				
Month 6 [Number of patients with a VA score at Month 6]	-0.1 (8.1) [88]	-1.3 (7.1) [98]	-3.2 (10.4) [90]	-3.2 (9.7) [91]
Month 9 [Number of patients with a VA score at Month 9]	0.6 (9.5) [84]	-1.8 (7.6) [92]	-4.9 (12.3) [76]	-3.9 (10.9) [75]
Month 12 [Number of patients with a VA score at Month 12]	0.9 (6.9) [66]	-0.7 (7.3) [73]	-4.2 (11.3) [58]	-4.1 (12.9) [50]
^a Summaries based on the observed data; number of patients with observed data varies at each time point and includes patients with data available at that time point and initial study baseline.				
Abbreviations used in table: BCVA, best corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; Rani, ranibizumab; VA, visual acuity.				

Table 11. Summary of long-term follow-up data from Campochiaro^(53;54)

	MO secondary to BRVO (n = 20)	MO secondary to CRVO (n = 20)
Median change in BCVA from baseline at 3 months, ETDRS letters ⁽⁵³⁾	10 (0.3 mg) 18 (0.5 mg)	17 (0.3 mg) 14 (0.5 mg)
Mean (SE) change in BCVA from baseline at 3 months, ETDRS letters ⁽⁵⁴⁾	16.1 (2.3)	12.0 (2.2)
Mean (SE) change in BCVA from baseline at 24 months, ETDRS letters ⁽⁵⁴⁾ [Number of patients included in analysis; number who completed 24 months' follow-up]	17.8 (2.8) [17]	8.5 (3.9) [14]
ITT analysis for mean change in BCVA from baseline at 24 months, ETDRS letters	17.8	9
Proportion of patients improving by 6 lines at 24 months (of those completing 24 months' follow up)	18%	14.4%
Proportion of patients improving by 3 lines at 24 months (of those completing 24 months' follow up)	59%	28.6%
Proportion of patients improving by 2 lines at 24 months (of those completing 24 months' follow up)	76%	42.9%
Proportion of patients with Snellen equivalent BCVA of 20/40 or better at 24 months (n)	58.9% (10)	28.6% (4)
⁽⁵⁴⁾ Data at 3 and 24 months not reported separately for ranibizumab 0.3 mg and ranibizumab 0.5 mg		
⁽⁵⁴⁾ BRVO patients had an average of 2 injections each in year 2 of the study. CRVO patients had an average of 3.5 injections each in year 2 of the study.		
Abbreviations used in table: BCVA, best corrected visual acuity; BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion; ETDR, Early Treatment Diabetic Retinopathy Study; ITT, intention to treat; MS, manufacturer's submission; Rani, ranibizumab; SE, standard error of the mean.		

4.3.4 Adverse effects

In the MS, the manufacturer presents data on adverse effects at 6 and 12 months' follow-up from BRAVO⁽¹⁵⁾ and CRUISE,⁽¹⁶⁾ and from a further 12 months' follow-up from HORIZON⁽⁵²⁾: tables from the MS are supplied in Appendix of the ERG report.

The manufacturer stated that ranibizumab has been found to be safe and well tolerated in patients with MO secondary to RVO in the BRAVO, CRUISE and ROCC trials. The ERG notes that the overall rates of adverse effects reported in BRAVO and CRUISE at month 6 are low. In BRAVO, there were 7 events (5.4%) in the ranibizumab 0.5 mg group compared with 17 (13%) in the sham group, excluding occurrences of raised intraocular pressure (IOP). In CRUISE, there were 13 events (10.1%) in the ranibizumab 0.5 mg group compared with 25 (19.4%) in the sham group, excluding occurrences of raised IOP.

Raised intraocular pressure (IOP) is listed as an adverse effect in the summary of product characteristics of both ranibizumab⁽³¹⁾ and pegaptanib.⁽⁵⁷⁾ Sustained elevations in intraocular pressure can lead to vision problems, including blindness

Results from HORIZON suggest a low rate of serious adverse events (AEs) at month 24. The incidence of study eye SAEs and SAEs potentially related to systemic VEGF inhibition across treatment arms was 2% to 9% and 1% to 6%, respectively (see Tables A3.5 and A3.6 in Appendix).

Supporting information on the safety of ranibizumab comes from an STA assessing ranibizumab and pegaptanib for the treatment of age-related macular degeneration.⁽⁵⁸⁾ Considering the AEs associated with these anti-VEGF agents, the Appraisal Committee concluded that “most adverse events are manageable and serious ones are rare”. The manufacturer reported that “through its licensed use worldwide in patients with wet AMD the cumulative exposure of ranibizumab since its launch in 2006 to 31 June 2010 is 751,000 patient-years” (MS; pg 160).

In the MS, the manufacturer discusses and compares the systemic safety profile of ranibizumab with that of bevacizumab. The manufacturer states that, in patients with AMD, ranibizumab has been found to have an improved safety profile over bevacizumab, and provides data from three large retrospective studies in support of this assertion (reproduced here as Table 12).^(32;33;59) The ERG notes that there are additional factors that should be considered when interpreting these results. All three studies are retrospective analyses, and are therefore inherently susceptible to confounding. Moreover, the studies are comparing bevacizumab and ranibizumab in AMD rather than RVO, and as such the data may not be generalisable to the treatment of MO secondary to RVO. As the manufacturer notes, AMD manifests in later life than RVO, and so the mean age of patients in BRAVO and CRUISE was lower than those reported in the studies in people with AMD.

The largest of the analyses presented by the manufacturer was that reported by Curtis *et al.*⁽³³⁾ (Table 12). Curtis *et al.*⁽³³⁾ assessed the risks of mortality, myocardial infarction, bleeding, and stroke associated with ranibizumab, bevacizumab, pegaptanib, and photodynamic therapy for the treatment of AMD. The manufacturer presented results from a secondary analysis comparing ranibizumab versus unlicensed intravitreal bevacizumab that showed that ranibizumab was associated with a significantly lower risk of stroke (Hazard Ratio [HR] 0.78; 95% CI: 0.64 to 0.96) and all-cause mortality (HR 0.86; 95% CI: 0.75 to 0.98). The ERG notes that Curtis *et al.*⁽³³⁾ carried out two secondary analyses based on two observations. The authors noted that: (i) by the end of the study period, almost all newly treated patients received bevacizumab or ranibizumab as first-line therapy; and (ii) that their primary analysis could be subject to selection bias based on socioeconomic status (people with poorer socioeconomic status are more likely to have received bevacizumab and to have poorer health). One secondary analysis, which was presented by the manufacturer, limited the populations to new users of bevacizumab or ranibizumab between July and December 2006. The ERG think it important to report the results of the second analysis that further limited the study population

to those who received either ranibizumab or bevacizumab in a medical practice that used a single drug exclusively, which was carried out in an attempt to mitigate the effects of confounding by socioeconomic status. This analysis found no significant difference between ranibizumab and bevacizumab in stroke (HR 0.87; 95% CI: 0.61 to 1.24) or all-cause mortality (HR 1.10; 95% CI: 0.85 to 1.41). The absolute numbers for this analysis have been added to Table 12.

A second study⁽⁵⁹⁾ reported by the manufacturer also found that bevacizumab was associated with a statistically significant increased risk of haemorrhagic stroke (HR 1.57; 99% CI: 1.04 to 2.37) and all-cause mortality (HR 1.11; 99% CI: 1.01 to 1.23) compared with ranibizumab. The authors of this study reported that the HRs were adjusted for baseline comorbidities, demographics and socioeconomic status proxies. The study was reported in only abstract form and no further details are available on specific factors for which the analysis has been adjusted. In addition, the authors go on to comment that their study is limited by incomplete information on some important confounding factors, including smoking, and lipid and blood pressure levels.

The manufacturer comments that a safety signal for bevacizumab is indicated by results from a recent head-to-head comparison of bevacizumab and ranibizumab in the treatment of wet AMD (the CATT study),⁽⁶⁰⁾ specifically that bevacizumab was associated with a higher rate of hospitalizations due to serious AEs compared with ranibizumab. The data in support of this as reported in the MS (MS; pg 160) are “a significantly higher rate of hospitalizations due to serious AEs in patients treated with bevacizumab (24.1%) compared to ranibizumab (19.0%) (RR 1.29; 95% CI: 1.01 to 1.66)”. CATT was a multicenter non-inferiority RCT that compared bevacizumab versus ranibizumab in 1208 patients with neovascular AMD. The ERG agrees with the manufacturer that there is a statistically significant difference between bevacizumab and ranibizumab but notes that the RR quoted here is for overall rate of serious systemic adverse effects (includes all-cause mortality, arteriothrombotic events, and venous thrombotic events) and not solely rate of hospitalisation for serious adverse effects. The authors of the study note that hospitalisations accounted for a large proportion of the recorded serious adverse effects (298 hospitalisations from 370 individual serious systemic AEs [80.5%]). In addition, the authors highlight that “the excess numbers of these events were distributed over many different types of conditions, most of which were not identified in cancer trials involving patients who were receiving intravenous doses of bevacizumab that were 500 times those used in intravitreal injections.”

In summary, the ERG notes that ranibizumab appears to be a well-tolerated treatment, but more data on the adverse effect profile of ranibizumab compared with bevacizumab in the treatment of MO secondary to RVO are needed before a definitive conclusion can be drawn on this issue.

Table 12. Overview of retrospective studies comparing ranibizumab to bevacizumab in wet AMD (modified from the MS; Table B37, pg 162)

	Carneiro 2011⁽³²⁾	Curtis 2010⁽³³⁾	Gower 2011⁽⁵⁹⁾ (Abstract only)
Methods	Retrospective chart review of 378 patients diagnosed with a treated for neovascular AMD in a Portuguese hospital December 2006 to January 2010	Retrospective cohort study of 149,942 Medicare beneficiaries aged ≥65 years with a claim for AMD and treated with anti-VEGF therapy or photodynamic therapy July 2006 to December 2006 ^a	Retrospective study of 77,886 Medicare beneficiaries with 1+ neovascular AMD 2005 to 2009
Results^b	<p><u>ATEs:</u> Bevacizumab – 12.4% (12/97) Ranibizumab – 1.4% (3/219)</p> <p>OR – 10.16 (2.80 to 36.93); p <0.0001</p>	<p>Primary analysis (adjusted)^a HR ranibizumab vs photodynamic therapy</p> <p><u>All cause mortality</u> HR: 0.85 (0.75-0.95)</p> <p><u>Incident myocardial infarction</u> HR: 0.73 (0.58 to 0.92)</p> <p><u>Bleeding</u> HR: 0.97 (0.88 to 1.07)</p> <p><u>Stroke</u> HR: 0.83 (0.69 to 0.99)</p> <p>Secondary analysis^a HR ranibizumab vs bevacizumab</p> <p><u>All cause mortality</u> Bevacizumab – 4.7% (833/21,815)</p> <p>Ranibizumab – 4.1% (647/19,026)</p> <p>HR: 0.86 (0.75 to 0.98); p <0.05</p> <p><u>Incident myocardial infarction</u> Bevacizumab – 1.3% (1793/21,815)</p> <p>Ranibizumab – 1.1% (1390/19,026)</p> <p>HR: 0.83 (0.64 to 1.08)</p> <p><u>Bleeding</u> Bevacizumab – 5.6% (2403/21,815)</p> <p>Ranibizumab – 5.8% (2025/19,026)</p> <p>HR: 1.03 (0.92 to 1.16)</p> <p><u>Incident stroke</u> Bevacizumab – 2.2% (1893/21,815)</p> <p>Ranibizumab – 1.8% (1471/19,026)</p>	<p><u>Overall mortality</u> HR: 1.11 (1.01 to 1.23)</p> <p><u>Risk of haemorrhagic cerebrovascular accident</u> HR: 1.57 (1.04 to 2.37)</p> <p>No statistically significant differences for myocardial infarction or ischaemic cerebrovascular accident</p> <p>HR bevacizumab vs ranibizumab</p>

		HR: 0.78 (0.64 to 0.96); p <0.05	
		<p>DATA ADDED BY ERG^c</p> <p>Stroke: Ranibizumab: 2.1% (90/4821) Bevacizumab: 2.4% (129/6147)</p> <p>HR for ranibizumab vs bevacizumab 0.87; 95% CI: 0.61 to 1.24</p> <p>All-cause mortality: Ranibizumab: 4.7% (197/4821) Becavizumab: 4.3% (225/6147)</p> <p>HR for ranibizumab vs bevacizumab: 1.10; 95% CI: 0.85 to 1.41</p> <p>Incident myocardial infarction: Ranibizumab: 1.1% (47/4821) Becavizumab: 1.3% (69/6147)</p> <p>HR for ranibizumab vs bevacizumab: 0.87; 95% CI: 0.53 to 1.41</p> <p>Bleeding: Ranibizumab: 5.3% (225/4821) Becavizumab: 5.2% (279/6147)</p> <p>HR for ranibizumab vs bevacizumab: 1.01; 95% CI: 0.80 to 1.28</p>	
<p>^a In primary analysis patients with higher socioeconomic status may have been more likely to receive these ranibizumab and bevacizumab therapies and therefore the primary analysis may have been subject to selection bias. The primary analysis did not identify a statistically significant relationship between treatment group and bleeding events or stroke. The secondary analysis of full study population (n=40,841) limited to newly treated patients who receive ranibizumab or bevacizumab.</p> <p>^b Hazard ratios and odds ratios presented with 95% confidence intervals for Carneiro 2011 and Curtis 2010. Hazard ratio for Gower 2011 presented with 99% confidence interval.</p> <p>^c Analysis adjusted for age, gender, ethnicity and comorbid conditions.</p> <p>Abbreviations used in table: AMD, age-related macular degeneration; ATEs, arterial thromboembolic events; HR, hazard ratio; OR, odds ratio; VEGF, vascular endothelial growth factor; vs, versus.</p>			

4.4 Additional analysis

4.4.1 Meta-analysis of RCTs identified for ranibizumab in the treatment of MO secondary to CRVO

In addition to the CRUISE RCT,⁽¹⁶⁾ the manufacturer identified a second smaller RCT – the ROCC RCT⁽⁴²⁾ – assessing the effect of ranibizumab in the treatment of MO secondary to CRVO. As discussed in section 4.1.3, the manufacturer carried out a meta-analysis of the two studies, presenting

the data in the appendices (MS; Section 10.1, Appendix 14, pg 351) of the MS. The NICE ‘Guide to the Methods of Technology Appraisal’⁽³⁵⁾ recommends that “Synthesis of outcome data through meta-analysis is appropriate provided there are sufficient relevant and valid data that use measures of outcome that are comparable” (located in section 5.3.9). The ERG notes that it is appropriate to present the results from the meta-analysis for review. The results of the meta-analysis indicate that there is strong evidence ($p < 0.00001$) that, in patients with MO secondary to non-ischaemic CRVO, ranibizumab is more effective than sham injection at improving best corrected visual acuity (as measured by ETDRS score) at month 6.

The manufacturer carried out a fixed effects analysis of the change in mean BCVA from baseline at month 6. The ERG replicated the meta-analysis carried out by the manufacturer and generated approximately the same result (see figure 3 for forest plot from ERG analysis). A minor difference in the mean difference was noted between the manufacturer’s analysis and the ERG analysis, which was possibly the result of a discrepancy in the value used for mean BCVA score at month 6 in the sham arm of the ROCC RCT; the manufacturer used a mean gain of 1 letter, however, in the RCT, the mean change in baseline BCVA was reported to be loss of one letter. This minor discrepancy had little effect on the overall result, and, as expected, favoured the overall effect of ranibizumab. As the manufacturer notes, the analysis is heavily weighted by the CRUISE RCT, and the inclusion of the ROCC RCT has little effect on the overall result. The ERG would like to highlight that the ROCC results were based on a per protocol analysis of 29 patients who completed the study (32 patients were enrolled), and a sample size power calculation was not reported.

Although no heterogeneity was identified between the two studies ($I^2 = 0$), the ERG thinks it useful to present a comparison of the patient characteristics of the populations included in CRUISE and ROCC (Table 13), and the individual results of the outcome assessed in the meta-analysis (mean change in BCVA from baseline at month 6). Data from ROCC for mean change in BCVA score from baseline at months 1 and 3 are also reported in Table 13.

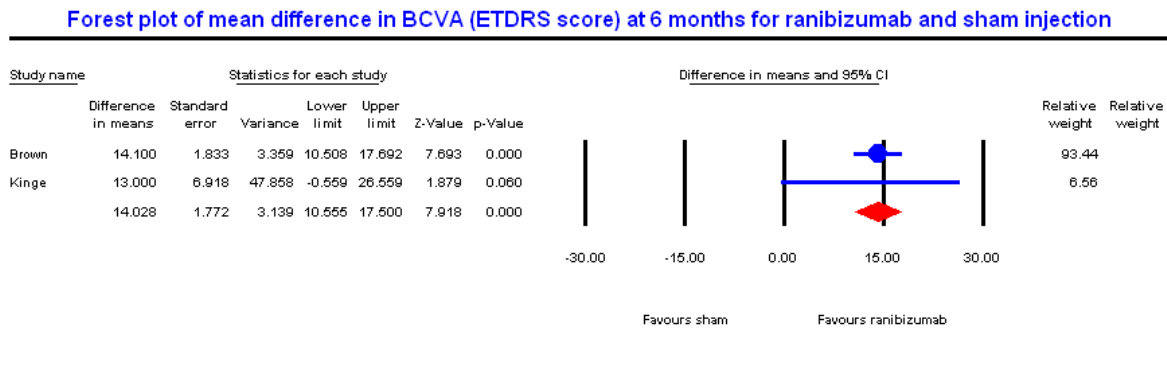
Table 13. Summary of patient demographics and change in mean BCVA from baseline as reported in CRUISE⁽¹⁶⁾ and ROCC⁽⁴²⁾

	ROCC ⁽⁴²⁾		CRUISE ⁽¹⁶⁾	
Patient characteristics				
	Sham (n = 14)	Rani 0.5mg (n = 15)	Sham (n = 130)	Rani 0.5 mg (n = 130)
Mean age (range), years	72 (52–88) (mean age in each arm not reported separately)		65.4 (20–91)	67.6 (40–91)
Gender				
Male, n (%)	16 (55.2)		72 (55.4)	80 (61.5)
Female, n (%)	13 (44.8) (number of men/women in each arm not reported separately)		58 (44.6)	50 (38.5)
Number of patients with ischaemia ^a	4	1	N/A	N/A
Mean duration of CRVO (range) ^b	78 days (10–163 days) (mean duration of CRVO in each arm not reported separately)		2.9 months (0–14 months)	3.3 months (0–27 months)
Mean (SD) baseline BCVA score, ETDRS letters ^c	41 (22) (20/152 Snellen equivalent)	45 (23) (20/126 Snellen equivalent)	49.2 (14.7)	48.1 (14.6)
Mean (SD) central macular thickness, micrometres ^c	587 (154)	661 (161)	N/A	N/A
Mean (SD) central foveal thickness, micrometres	–	–	687.0 (237.6)	688.7 (253.1)
Proportion of patients who required injections after month 3, n (%)	12 (86%)	12 (80%)	N/A	N/A
Mean (SD) number of injections received during the study, up to 6 months	5.5 (1.1)	4.3 (0.9)	5.5 ■	5.6 ■
Results				
Mean (SD) change in BCVA from baseline at month 1, ETDRS letters	–8 (14) (p = 0.055 vs baseline)	12 (12) (p = 0.002 vs baseline)	–	–
Mean (SD) change in BCVA from baseline at month 3, ETDRS letters	–5 (15) (p = 0.261 vs baseline)	16 (14) (p = 0.001 vs baseline; p = 0.001 vs sham group)	–	–
Mean (SD) change in BCVA from baseline at month 6, ETDRS letters	–1 (17) (p = 0.765 vs baseline)	12 (20) (p = 0.04 vs baseline; p = 0.067 vs sham group)	0.8 (16.2)	14.9 (13.2) (p <0.0001 vs sham group)
^a The ROCC RCT did not define ischaemia but recorded the number of patients with “non-perfusion in an area >5 disc areas revealed by fluorescein angiography”. ^b In CRUISE, the duration of CRVO reported is mean number of months from RVO diagnosis to screening. ^c In ROCC, the overall mean (SD) BCVA score was 43 (22) letters (20/138 Snellen equivalent).				

Overall mean (SD) macular thickness was 625 (159) micrometres.

Abbreviations used in table: BCVA, best corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; N/A, not applicable; Rani, ranibizumab.

Figure 3. Forest plot of mean difference in BCVA (ETDRS score) at month 6 in patients with MO secondary to CRVO for ranibizumab versus sham injection.



Meta Analysis

Footnote to Figure 3: **Heterogeneity:** $I^2 = 0\%$, $df(Q) = 1$; $p = 0.878$; **Test for overall effect:** $Z = 7.918$, $p < 0.0001$

4.4.2 Indirect comparisons between ranibizumab and comparators listed in the final scope.

The decision problem issued by NICE⁽²⁹⁾ and reviewed by all stakeholders, including the manufacturer, requests ranibizumab to be compared with:

- For CRVO: best supportive care (ischaemic only), bevacizumab and dexamethasone intravitreal implant;
- For BRVO: best supportive care (ischaemic only), bevacizumab, dexamethasone intravitreal implant, and GLP.

The RCTs presented in the MS (principally CRUISE and BRAVO, but also ROCC) directly compare ranibizumab with:

- CRVO: best supportive care (non-ischaemic only);^(16;42)
- BRVO: best supportive care/GLP (non-ischaemic only).⁽¹⁵⁾

Throughout the MS, the manufacturer consistently highlights that bevacizumab should not be considered an appropriate comparator for ranibizumab as it is currently unlicensed for use in ocular conditions, not routinely used in the NHS, and not considered best practice (MS; pg 121). However, the ERG considers that bevacizumab is used throughout the NHS to treat ocular conditions, albeit infrequently, and should be considered a valid comparator. This aligns with the RCO guidelines⁽¹⁾ and the opinion of clinical specialists who presented their views to the NICE Appraisal Committee for dexamethasone intravitreal implant for the treatment of MO secondary to RVO.⁽³⁶⁾

The ERG has previously commented (section 4.3.1) that the direct comparison with sham/GLP presented within the MS is confounded by the design of BRAVO; that is, for a valid comparison of ranibizumab versus GLP, all patients in the “sham” treatment group should have received GLP at the point of randomisation and no patients in the ranibizumab group should have received GLP. In addition, the trial duration should have been at least 1 year (with long-term follow-up for up to 5 years post randomisation) to capture the long-term benefits of GLP as presented in BVOS.⁽¹⁴⁾ Alternatively, for BRAVO to be a valid comparison of ranibizumab versus sham, no patients in either treatment group should have received GLP. However, this scenario might not be feasible as GLP is considered standard care in patients with MO secondary to BRVO.

As such, the ERG considers the results from BRAVO to be potentially confounded to a degree that they poorly inform a comparison of ranibizumab with sham or GLP. The ERG requested the 3 month data for BRAVO from the manufacturer (i.e., the latest data prior to any patient receiving GLP) to have a true estimate of ranibizumab compared with sham (section 4.3.1).

The ERG’s view is that the manufacturer should have performed an adjusted indirect comparison to produce a valid estimate of ranibizumab compared with bevacizumab, dexamethasone intravitreal implant, and GLP. Based on the evidence presented in the MS, the ERG has performed exploratory analyses for CRVO and BRVO.

CRVO

The manufacturer discusses the feasibility of conducting an indirect comparison of ranibizumab with dexamethasone intravitreal implant or bevacizumab in CRVO. However, the MS presents an argument against each potential comparator. The ERG’s view on these reasons is presented below:

Ranibizumab (CRUISE) versus dexamethasone intravitreal implant (GENEVA)

- Longer period of MO allowed prior to study entry in CRUISE⁽¹⁶⁾ than GENEVA⁽⁶¹⁾:
 - While the inclusion criteria for the GENEVA trials did restrict inclusion to a shorter duration than CRUISE (6 to 9 months vs ≤ 12 months, respectively) this criterion applied to the whole of GENEVA, which consisted of a population of patients with CRVO and BRVO. From the baseline characteristics, the mean duration of MO secondary to CRVO was shorter in CRUISE than in the GENEVA trials (~3 months vs ~5 months). In addition, the manufacturer states that the duration of MO prior to treatment was longer in GENEVA than CRUISE (MS; pg 127);
 - The likely impact of this would potentially favour ranibizumab in any indirect comparison conducted between the trials. As the manufacturer states, “A greater mean duration of RVO tends to result in a poorer response to treatment” (MS; pg 127).

- Different baseline ranges of BCVA and different retinal thicknesses allowed:
 - While the baseline BCVA in CRUISE and the GENEVA trials are numerically different, the mean difference is <5 letters, which is unlikely to be considered clinically meaningful;⁽⁶²⁾
 - The difference in inclusion criteria for CFT (≥ 250 micrometres for CRUISE and ≥ 300 micrometres for GENEVA) does lead to an increase in retinal thickness of ~130 micrometres in GENEVA compared with CRUISE;
 - There is unlikely to be any clinically meaningful impact of the difference in baseline BCVA and the difference in retinal thickness would, if anything, favour ranibizumab in any indirect comparison.
- CRUISE excluded patients who had received GLP 4 months prior to baseline:
 - The GENEVA trials included 8 patients with CRVO that received prior GLP (4 dexamethasone intravitreal implant and 4 sham). This is unlikely to have had a major impact on the overall results as they represent <3% of the patient population for CRVO in the GENEVA trials;
 - The lack of therapeutic benefit with GLP in patients with CRVO is why GLP is not recommended for use in patients with CRVO.⁽¹⁾
- Patients intolerant to steroids were excluded from GENEVA:
 - As dexamethasone intravitreal implant is a steroid it would have been inappropriate for patients intolerant to steroids to have been included in the GENEVA trials;
 - The ERG is unaware of what, if any difference, this would make in an indirect comparison as tolerance or intolerance to steroids is not a recognised prognostic indicator for success or failure in the treatment of RVO.

The ERG would like to raise an issue in addition to those mentioned in the MS. GENEVA did not screen for patients with ischaemic disease. However, the development of neovascularisation in 2.6% of sham patients suggests that at least some patients in GENEVA had ischemic disease.⁽⁶¹⁾ Correspondingly, in CRUISE, patients were screened for APD and, if found, excluded. The presence of ischaemic patients in the GENEVA trials may have led to an underestimation of the treatment effect in GENEVA in perfused patients.⁽⁶¹⁾ This is likely to favour ranibizumab in any indirect comparison.

Overall, the ERG considers that there are differences in the CRUISE and GENEVA trials (Tables 14 and 15), but that the direction of the likely bias would favour ranibizumab in any indirect comparison based on CRUISE and the CRVO patients from GENEVA. The ERG, therefore, considers that an adjusted indirect comparison should have been carried out with a critical assessment of the impact that this bias may have on the results.

Ranibizumab versus bevacizumab

From the information provided in the MS, the ERG agrees it is not possible to perform an adjusted indirect comparison of ranibizumab versus bevacizumab in CRVO.

Table 14. Design of studies informing the indirect comparison for MO secondary to CRVO

Study name	Study design	Comparison	Follow-up
CRUISE ⁽¹⁶⁾	RCT (study design described in detail in Table A1.2 in Appendix 1)	Ranibizumab 0.5 mg (130 patients) versus sham injection (130 patients)	6 months
GENEVA ⁽⁶¹⁾	RCT: two identical, multicenter, blinded, placebo-controlled trials each of which included patients with BRVO and patients with CRVO	Dexamethasone 0.7 mg (136 patients) versus sham injection (147 patients)	6 months

Abbreviations used in table: BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion; MO, macular oedema.

Table 15. Characteristics of populations included in studies informing the indirect comparison for MO secondary to CRVO

Study name	Population	Mean age	Gender	Duration of MO	Percentage of patients with ischaemic RVO	Baseline visual acuity	Visual acuity at follow-up
CRUISE ⁽¹⁶⁾	260 people with MO secondary to CRVO	Rani: 67.6 years Sham: 65.4 years	Rani: 61.5% male Sham: 55.4% male	Mean number of months from RVO diagnosis to screening ^a : Rani: 3.3 Sham: 2.9	2 patients were reported to have ischaemic disease: group allocation not reported	Mean (SD) baseline BCVA, ETDRS score: Rani: 48.1 (14.6) Sham: 49.2 (14.7)	Mean (SD) change in BCVA from baseline, ETDRS letters: Rani: 14.9 (13.2) Sham: 0.8 (16.2)
GENEVA ⁽⁶¹⁾	283 people with MO secondary to CRVO	All patients, includes those with BRVO: Dex: 64.7 years Sham: 63.9 years	All patients, includes those with BRVO: Dex: 50.8% male Sham: 56.3% male	Mean duration of MO, days (all patients, includes those with BRVO) ^a : Dex: 157.6 Sham: 156.1	Not assessed	Mean (SD) ETDRS score (all patients, includes those with BRVO): Dex: 54.3 (9.93) Sham: 54.8 (9.86)	Mean change in BCVA from baseline, ⁽⁶³⁾ ETDRS letters: ^b Dex: 0.1 Sham: -1.8

^a In CRUISE, the number of patients with MO secondary to RVO of ≤ 3 months was 94 (72.3%) in the ranibizumab group and 91 (70.0%) in the sham group. In GENEVA, the number of patients with MO secondary to RVO of ≤ 90 days (all patients, includes those with BRVO) was 70 (16.4%) in the dexamethasone intravitreal implant group and 65 (15.3%) in the sham group.

^b Subgroup analysis: results taken from ERG report for single technology appraisal for dexamethasone in the treatment of MO secondary to RVO.⁽⁶⁴⁾

Abbreviations used in table: BCVA, best corrected visual acuity; BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion; Dex, dexamethasone intravitreal implant; ETDRS, Early Treatment Diabetic Retinopathy Study; MO, macular oedema; Rani, ranibizumab; RVO, retinal vein occlusion.

CRVO exploratory analysis

Ranibizumab versus dexamethasone intravitreal implant

Based on the information presented within the MS, the ERG has performed an adjusted indirect comparison of ranibizumab versus dexamethasone intravitreal implant in CRVO utilising the direct comparisons with sham in CRUISE⁽¹⁶⁾ and GENEVA,⁽⁶¹⁾ respectively, as the common comparator. The outcomes of interest are the primary outcome from the CRUISE trial (≥ 15 ETDRS letters improvement) and the *post-hoc* exploratory outcome used in the economic evaluation in the MS (██████████). While ROCC⁽⁴²⁾ could potentially have been included in this analysis, unfortunately it does not report either of these outcomes of interest.

The method used for the adjusted indirect comparison used by the ERG was originally proposed by Bucher *et al.*⁽⁶⁵⁾ and is one of the methods advocated in the NICE ‘Guide to the Methods of Technology Appraisal’.⁽³⁵⁾ The data for use in the analysis were taken from CRUISE and the CRVO subgroup in the GENEVA trials⁽⁶³⁾ and is presented in Tables 16 and 17, respectively.

The results of the adjusted indirect comparison are presented in Table 18. While these results should be treated with caution, they demonstrate a trend in favour of ranibizumab over dexamethasone intravitreal implant. It should be stressed that the likely bias identified in the trials used is in favour of ranibizumab and so the results may represent an overly optimistic view of its efficacy against dexamethasone intravitreal implant. However, the ERG considers this to represent a more methodologically robust assessment than the naïve indirect comparison presented in the MS and used in the manufacturer’s economic evaluation. The method employed by the manufacturer is discussed later (section 5.4.6).

Table 16. Number of patients with ETDRS letters of improvement (≥ 15 or █████ letters) during the CRUISE trial comparing ranibizumab (130 patients) and sham (130 patients) (MS; reproduced from Table B18)

Outcome	Visit							
	Month 1		Month 2		Month 3		Month 6	
	Rani	Sham	Rani	Sham	Rani	Sham	Rani	Sham
≥ 15 letters improvement, (%)	33 (25.4)	7 (5.4)	49 (37.7)	7 (5.4)	48 (36.9)	11 (8.5)	62 (47.7)	22 (16.9)
██████████	████	████	████	████	████	████	████	████

Abbreviations used in table: ETDRS, Early Treatment Diabetic Retinopathy Study; MS, manufacturer’s submission; NDR, no data reported; Rani, ranibizumab.

Table 17. Number of patients with ETRS letters of improvement (≥ 15 or ≥ 10 letters) during the GENEVA trials (CRVO subgroup) comparing dexamethasone intravitreal implant (136 patients) and sham (147 patients), calculated from the percentages reported in Tables 29 and 32 of the dexamethasone intravitreal implant MS⁽⁶³⁾

Outcome	Visit							
	Month 1		Month 2		Month 3		Month 6	
	Dex	Sham	Dex	Sham	Dex	Sham	Dex	Sham
≥ 15 letters improvement, (%)	29 (21.3)	10 (6.8)	39 (28.7)	13 (8.8)	24 (17.6)	15 (10.2)	25 (18.4)	18 (12.2)
≥ 10 letters improvement, (%)	62 (45.6)	18 (12.2)	67 (49.3)	29 (19.7)	49 (36.0)	34 (23.1)	36 (26.5)	35 (23.8)
Abbreviations used in table: CRVO, central retinal vein occlusion; Dex, dexamethasone intravitreal implant; MS, manufacturer's submission.								

Table 18. Relative risk (RR) of ranibizumab compared with dexamethasone intravitreal implant in patients with CRVO based on an adjusted indirect comparison (RR <1 favours ranibizumab, RR >1 favours dexamethasone intravitreal implant)

	Mean	95% Confidence Interval	
		Lower	Upper
≥ 15 ETRS letters improvement			
Month 1	0.66	0.24	1.87
Month 2	0.46	0.18	1.20
Month 3	0.40	0.17	0.93
Month 6	0.53	0.26	1.07
[REDACTED]			
Month 1	–	–	–
Month 2	–	–	–
Month 3	–	–	–
Month 6	0.40	0.24	0.66
[REDACTED]			
[REDACTED]			
Abbreviations used in table: CRVO, central retinal vein occlusion; ETRS, Early Treatment Diabetic Retinopathy Study; RR, relative risk.			

BRVO

The manufacturer discusses the feasibility of conducting an indirect comparison of ranibizumab with dexamethasone intravitreal implant, bevacizumab, and GLP in BRVO. However, the MS presents an argument against each potential comparator, which the ERG comments on, as follows:

Ranibizumab versus dexamethasone intravitreal implant

- The manufacturer presents the same arguments against performing an indirect comparison in BRVO as in CRVO but in this instance comparing BRAVO with the BRVO subgroup from the GENEVA trials. Please refer to the earlier section (pg 62) for the ERG's critique of this assessment.

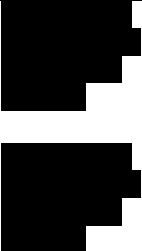
In summary, the ERG considers an adjusted indirect comparison is possible between BRAVO and the BRVO subgroup from the GENEVA trials with the caveat that it is likely to under estimate the likely treatment benefit of dexamethasone intravitreal implant (Tables 19 and 20).

Table 19. Design of studies informing the indirect comparison MO secondary to BRVO

Study name	Study design	Comparison	Follow-up
BRAVO ⁽¹⁵⁾	RCT (study design described in detail in Table A1.1 in Appendix 1)	Ranibizumab 0.5 mg (131 patients) versus sham injection (132 patients)	3 months
GENEVA ⁽⁶¹⁾	RCT: two identical, multicenter, blinded, placebo-controlled trials each of which included patients with BRVO and patients with CRVO	Dexamethasone 0.7 mg (291 patients) versus sham injection (279 patients)	3 months
Moradian ⁽³⁷⁾	RCT: double blind, placebo-controlled	Bevacizumab 1.25 mg (42 eyes) versus sham injection (39 eyes)	12 weeks
Russo ⁽³⁸⁾	Quasi-randomised trial: patients assigned according to clinic chart number), open label	Bevacizumab 1.25 mg (15 patients) versus grid laser photocoagulation (15 patients)	3 months

Abbreviations used in table: BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion; MO, macular oedema.

Table 20. Characteristics of populations included in studies informing the indirect comparison for MO secondary to BRVO

Study name	Population	Mean age	Gender	Duration of MO	Percentage of patients with ischaemic RVO	Baseline visual acuity	Visual acuity at follow-up
BRAVO ⁽¹⁵⁾	263 people with MO secondary to BRVO	Rani: 67.5 years Sham: 65.2 years	Rani: 54.2% male Sham: 56.1% male	Mean number of months from RVO diagnosis to screening ^a : Rani: 3.3 Sham: 3.7	Rani: 0% sham: 0%	Mean (SD) ETDRS score: Rani: 53.0 (12.5) Sham: 54.7 (12.2)	
GENEVA ⁽⁶¹⁾	570 people with MO secondary to BRVO	All patients, includes those with CRVO: Dex: 64.7 years Sham: 63.9 years	All patients, includes those with CRVO): Dex: 50.8% male Sham: 56.3% male	Mean duration of MO, days (all patients, includes those with CRVO): Dex: 157.6 Sham: 156.1	Not assessed	Mean (SD) ETDRS score (all patients, includes those with CRVO): Dex: 54.3 (9.93) Sham: 54.8 (9.86)	Mean change in BCVA from baseline, ⁽⁶³⁾ ETDRS letters: ^b Dex: 8.7 Sham: 5.0
Moradian ⁽³⁷⁾	81 eyes with MO secondary to acute BRVO (less than 3 months duration)	Bev: 58.1 years Sham: 57.2 years	Not reported	Mean (SD) duration of MO, weeks: Bev: 7.5 (4.8) Sham: 4.9 (3.2)	Foveal ischaemia: Bev: 24% (10/42 eyes) Sham: 21% (8/39 eyes)	Mean (SD) logMAR: Bev: 0.74 (0.38) Sham: 0.8 (0.38)	Mean (SD) logMAR: Bev: 0.42 (0.33) Sham: 0.66 (0.56)

Russo ⁽³⁸⁾	30 people with cystoid MO secondary to non-ischemic BRVO (of at least 3 months duration)	Bev: 64.6 years GLP: 65.2 years	Bev: 80% male (12/15) GLP: 73.3% male (11/15)	Mean (SD) duration of onset of BRVO to treatment, months: Bev: 4.7 (0.5) GLP: 4.9 (0.4)	0 Inclusion criteria specifies non-ischaemic BRVO	Mean (SD) BCVA (logMAR): Bev: 0.87 (0.16) GLP: 0.89 (0.13)	Mean (SD) BCVA (logMAR): Bev: 0.55 (0.18) GLP: 0.67 (0.12)
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^a In BRAVO, the number of patients with MO secondary to RVO of ≤ 3 months was 88 (67.2%) in the ranibizumab group and 85 (64.4%) in the sham group. In GENEVA, the number of patients with MO secondary to RVO of ≤ 90 days (all patients, includes those with CRVO) was 70 (16.4%) in dexamethasone group and 65 (15.3%) in the sham group.

^b Subgroup analysis: results taken from ERG report for single technology appraisal for dexamethasone in the treatment of MO secondary to RVO.⁽⁶⁴⁾

Abbreviations used in table: BCVA, best corrected visual acuity; Bev, bevacizumab; BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion; Dex, dexamethasone intravitreal implant; ETDRS, Early Treatment Diabetic Retinopathy Study; GLP, grid laser photocoagulation; MO, macular oedema; Rani, ranibizumab; RVO, retinal vein occlusion.

Subgroup analysis: results taken from ERG report for single technology report for dexamethasone in the treatment of MO secondary to RVO

Ranibizumab versus bevacizumab

- Mean duration of MO different in BRAVO⁽¹⁵⁾ and Moradian 2011⁽³⁷⁾:
 - Moradian 2011 included patients with acute BRVO, that is, < 3 months duration. However, the largest proportion of patients in BRAVO (65.7%) had a duration of MO secondary to RVO from diagnosis to screening of < 3 months duration;
 - In Moradian 2011, the duration of symptoms was 7.5 weeks in the bevacizumab group and 4.9 weeks in the sham group, while in BRAVO the mean was 3.7 months in ranibizumab group and 3.3 months in the sham group;
 - The likely impact of the increased duration of MO in BRAVO compared with Moradian 2011, is likely to bias the results of an indirect comparison in favour of bevacizumab.
- Different numbers of patients with ischaemia in BRAVO and Moradian 2011:
 - The MS confirms that BRAVO had no patients with ischaemia in the ranibizumab 0.5 mg and sham groups while Moradian 2011 had ~20% of patients with foveal ischaemia (MS; pg 139);
 - Moradian 2011⁽³⁷⁾ states that macular ischaemia can prevent improvement in visual acuity regardless of improvements in central foveal thickness;
 - The impact of more patients with ischaemia in Moradian 2011 than BRAVO would bias the result of an indirect comparison in favour of ranibizumab.

- Moradian 2011 trial is much shorter than BRAVO (12 weeks vs 12 months):
 - Trial duration is a potential issue which is resolved by the ERG's view that only results up to month 3 (12 weeks) from BRAVO provide a valid comparison of ranibizumab versus sham.

In summary, the ERG considers an adjusted indirect comparison is possible between ranibizumab and bevacizumab using BRAVO and Moradian 2011 (Tables 19 and 20). There are potential conflicting biases in the assessment but overall these are likely to favour ranibizumab in any indirect comparison with bevacizumab.

Ranibizumab versus grid laser photocoagulation

Ranibizumab could be compared to GLP using the indirect comparison with bevacizumab to link with the trial of bevacizumab versus GLP (Russo 2009⁽³⁸⁾). However, the MS raises the following concerns:

- Difference in trial designs (BRAVO: double-blind, randomised; Russo 2009: unblinded, quasi-randomised):
 - The ERG agrees with the manufacturer that Russo 2009 has the potential for bias in patient allocation;
 - This is likely to lead to an increase in treatment effect with the “new” treatment compared with the established treatment.⁽⁶⁶⁾ In the Russo 2009 trial, bevacizumab could have a larger treatment effect compared with GLP than the effect observed in a trial with appropriate allocation concealment.
- Much smaller trial size (Russo 2009) compared with BRAVO (30 patients vs 397 patients):
 - The ERG agrees that Russo 2009 is smaller than BRAVO, which would affect the precision around the effect estimate that would be captured in any indirect comparison performed.
- Mean CFT higher and mean BCVA lower at baseline in Russo 2009 than BRAVO:
 - There is a mean difference of ~140 micrometres between bevacizumab and ranibizumab in the two trials;
 - There is a mean difference of ~8 ETDRS letters between the two trials;
 - These poorer measures at baseline are likely to lead to less observed benefit in Russo 2009 compared with BRAVO.

In summary, the ERG considers an adjusted indirect comparison is possible between ranibizumab and GLP, using BRAVO, Moradian 2011, and Russo 2009 (Tables 19 and 20). There are potential conflicting biases in the assessment but overall these are likely to favour ranibizumab in any indirect comparison with GLP.

The ERG notes that the rationale provided by the manufacturer for being unable to compare ranibizumab with GLP using sham as a common comparator is due to the sham treatment group being confounded with treatment with GLP (MS, page 137). The ERG agrees with this observation, which is why only the treatment effect at up to month 3 is considered a valid comparison of ranibizumab with sham. The key concern with this comparison is the different durations of trials and reported data (e.g., month 3 for BRAVO compared with 3 year follow-up in BVOS⁽¹⁴⁾).

BRVO exploratory analysis

Ranibizumab versus dexamethasone intravitreal implant

Based on the information presented within the MS, the ERG has performed an adjusted indirect comparison of ranibizumab versus dexamethasone intravitreal implant in BRVO utilising the direct comparisons with sham in BRAVO and GENEVA, respectively, as the common comparator. The outcomes of interest are the primary outcome from the BRAVO trial (≥ 15 ETDRS letters improvement) and the *post-hoc* exploratory outcome used in the economic evaluation in the MS [REDACTED]. As discussed earlier, only the data from BRAVO for months 1, 2 and 3 are considered by the ERG to be a valid comparison of ranibizumab versus sham and only these data are used in the following analysis.

The same method of performing the adjusted indirect comparison employed for CRVO was used here. The data for use in the analysis were taken from BRAVO (only up to month 3) and the BRVO subgroup in the GENEVA trials and are presented in Tables 21 and 22.

The results of the adjusted indirect comparison are presented in Table 23. While these results should be treated with caution, they demonstrate a trend in favour of ranibizumab over dexamethasone intravitreal implant. However, as the likely bias identified in the trials used is in favour of ranibizumab, the results may represent an overly optimistic view of its efficacy against dexamethasone intravitreal implant. It is interesting to note that the results [REDACTED]. The ERG considers this to represent a more methodologically robust assessment than the naïve indirect comparison presented in the MS and used in the manufacturer's economic evaluation. The method employed by the manufacturer is discussed later (Section 5.4.6).

Table 21. Number of patients with ETDRS letters of improvement (≥ 15 or ≥ 10 letters) during the BRAVO trial comparing ranibizumab (131 patients) and sham (132 patients) from the manufacturer's response to Letter of Clarification

Outcome	Visit					
	Month 1		Month 2		Month 3	
	Rani	Sham	Rani	Sham	Rani	Sham
≥ 15 letters improvement, (%)	100	100	100	100	100	100
≥ 10 letters improvement, (%)	100	100	100	100	100	100

Abbreviations used in table: ETDRS, Early Treatment Diabetic Retinopathy Study; Rani, ranibizumab.

Table 22. Number of patients with ETDRS letters of improvement (≥ 15 or ≥ 10 letters) during the GENEVA trials (BRVO subgroup) comparing dexamethasone intravitreal implant (291 patients) and sham (279 patients), calculated from percentages reported in Tables 28 and 31 of the dexamethasone intravitreal implant MS⁽⁶³⁾

Outcome	Visit					
	Day 30		Day 60		Day 90	
	Dex	Sham	Dex	Sham	Dex	Sham
≥ 15 letters improvement, (%)	62 (21.3)	22 (7.9)	86 (29.6)	35 (12.5)	69 (23.7)	41 (14.7)
≥ 10 letters improvement, (%)	124 (42.6)	56 (20.1)	151 (51.9)	82 (29.4)	137 (47.1)	87 (31.2)

Abbreviations used in table: BRVO, branch retinal vein occlusion; Dex, dexamethasone intravitreal implant; ETDRS, Early Treatment Diabetic Retinopathy Study; MS, manufacturer's submission.

Table 23. Relative risk (RR) of ranibizumab compared with dexamethasone intravitreal implant in patients with BRVO based on an adjusted indirect comparison (RR <1 favours ranibizumab, RR >1 favours dexamethasone intravitreal implant)

	Mean	95% Confidence Interval	
		Lower	Upper
≥ 15 ETDRS letters improvement			
Month 1	0.69	0.32	1.48
Month 2	0.99	0.56	1.74
Month 3	0.56	0.33	0.96
≥ 10 ETDRS letters improvement			
Month 1	0.99	0.64	1.54
Month 2	0.79	0.54	1.15
Month 3	0.79	0.56	1.12

Abbreviations used in table: BRVO, branch retinal vein occlusion; ETDRS, Early Treatment Diabetic Retinopathy Study; RR, relative risk.

Ranibizumab versus bevacizumab versus grid laser photocoagulation

Unfortunately the outcome available, from the trials able to supply data for an indirect comparison of ranibizumab compared with bevacizumab (and so with GLP), is based on number of ETDRS letters improved rather than the categories presented for the comparisons with dexamethasone intravitreal

implant. Therefore, a separate adjusted indirect comparison had to be performed with dexamethasone intravitreal implant rather than a mixed treatment comparison including all comparators for BRVO. However, number of ETDRS letters improved was the primary outcome in BRAVO and should provide some insight into how comparable the different treatments are in patients with BRVO.

From the trials reported in the MS, it was possible to construct a linear network of trials using BRAVO (ranibizumab vs sham), Moradian 2011⁽³⁷⁾ (bevacizumab vs sham), and Russo 2009⁽³⁸⁾ (bevacizumab vs GLP). The method of performing the adjusted indirect comparison of this “linear” network of trials was a mixed treatment comparison⁽⁶⁷⁻⁶⁹⁾ using WinBUGS and is one of the methods advocated in the NICE ‘Guide to the Methods of Technology Appraisal’.⁽³⁵⁾ As only a single trial was available for each link, a fixed effects model was used. As discussed earlier, only the data from BRAVO for months 1, 2 and 3 are considered by the ERG to be a valid comparison of ranibizumab versus sham, and only the month 3 data (the latest available data) are used in the following analysis. The data used in the analysis were taken from BRAVO (only month 3), Moradian 2011⁽³⁷⁾ and Russo 2009,⁽³⁸⁾ and are presented in Table 24.

Table 24. Logarithm of minimum angle of resolution (logMAR) change from baseline and number of ETDRS letters change from baseline at month 3 from BRAVO,⁽¹⁵⁾ Moradian 2011,⁽³⁷⁾ and Russo 2009⁽³⁸⁾

Difference from baseline	BRAVO		Moradian 2011 ^a		Russo 2009 ^a	
	Rani	Sham	Bev	Sham	Bev	GLP
logMAR						
Mean	–	–	–0.31	–0.15	–0.32	–0.22
Standard Deviation	–	–	0.3	0.3	0.18	0.12
Number of ETDRS Letters						
Mean	■	■	15.5	7.5	16	11
Standard Deviation	■	■	15	15	9	6
^a ETDRS letters were calculated from logMAR using 0.02 logMAR equivalent to 1 ETDRS letter. ⁽⁶²⁾ Abbreviations used in table: Bev, bevacizumab; ETDRS, Early Treatment Diabetic Retinopathy Study; GLP, grid laser photocoagulation; Rani, ranibizumab.						

The results of the mixed treatment comparison are presented in Table 25. While these results should be treated with caution, as they are likely to be an overly optimistic estimate of the efficacy of ranibizumab, they provide estimates of around 3 letters improvement with ranibizumab over bevacizumab and 8 letters improvement with ranibizumab over GLP at month 3.

Table 25. Mean difference in change in ETDRS letters from baseline, for bevacizumab, GLP, and sham using ranibizumab as the reference treatment in BRVO (negative numbers favour ranibizumab, positive numbers favour the comparator).

Comparator	Mean difference	95% Credible Interval	
		Lower	Upper
Bevacizumab	-2.916	-10.070	4.347
GLP	-7.974	-17.030	1.212
Sham	-10.80	-13.750	-7.832

Abbreviations used in table: BRVO, branch retinal vein occlusion; ETDRS, Early Treatment Diabetic Retinopathy Study; GLP, grid laser photocoagulation.

Overall conclusions

Good practice for an adjusted indirect comparison is to identify any direct comparison between treatments in a related therapy area that might add plausibility to the conclusions of the indirect comparison.⁽⁶⁷⁻⁶⁹⁾ The ERG did not have the capacity to perform a systematic review of the literature to inform this exploratory work and had to rely on the information supplied in the MS. As such, the ERG is unaware of any direct comparisons of ranibizumab versus dexamethasone intravitreal implant in a related therapeutic indication. The results of the indirect comparison with dexamethasone intravitreal implant cannot be corroborated with other evidence from RCTs.

With regards to ranibizumab versus bevacizumab, the recently published CATT trial⁽⁶⁰⁾ does directly compare ranibizumab and bevacizumab in patients with neovascular age-related macular degeneration. This was a large (1,208 patients) multicentre, single blind, randomised non-inferiority trial conducted in the USA. It concluded that “At 1 year, bevacizumab and ranibizumab had equivalent effects on visual acuity when administered according to the same schedule”. The non-inferiority limit was set at 5 letters and the mean difference in letters at 1 year for monthly ranibizumab versus monthly bevacizumab was 0.5 letters (95% CI: -3.9 to 2.9). This direct comparison supports the view that ranibizumab and bevacizumab may have similar efficacy in BRVO, as indicated by the results of the mixed treatment comparison, where the mean difference at month 3 was -2.9 letters (95% credible interval [CrI]: -10.1 to 4.3).

With regards to the comparison of ranibizumab versus GLP, the indirect comparison favours ranibizumab with a mean difference at month 3 of -8.0 letters (95% CrI: -17.0 to 1.2). However, the benefit of GLP is not in the short-term but in the long-term and for up to 3 years.⁽¹⁴⁾ The ERG is aware of the RESTORE trial in patients with diabetic MO, which compared ranibizumab monotherapy or combined with GLP versus GLP monotherapy.⁽⁷⁰⁾ This was a multicentre, double blind, randomised controlled trial in 345 patients. This trial identified a significant mean difference in ranibizumab monotherapy compared with GLP monotherapy (5.3 ETDRS letters at month 12, p <0.0001). This

direct comparison supports the view that ranibizumab may have increased benefit compared with GLP in BRVO, as indicated by the results of the mixed treatment comparison. A direct comparison of ranibizumab versus GLP in BRVO (the RABAMES⁽⁵⁶⁾ RCT) is currently underway with results due for release by the end of 2011.

4.5 Subgroup analysis

Subgroups of interest listed in the final scope were:

- type of RVO (BRVO and CRVO);
- the presence or absence of ischaemia;
- baseline visual acuity;
- baseline structural damage to the central fovea;
- perfusion at the back of the eye;
- duration of macular oedema (time since diagnosis).

Within BRAVO⁽¹⁵⁾ and CRUISE,⁽¹⁶⁾ of the subgroups of interest, the manufacturer was able to carry out analysis for baseline BCVA, baseline central foveal thickness and duration of macular oedema from diagnosis to screening and presented data for these subgroups on the primary outcome of change in mean BCVA from baseline and the secondary outcome of proportion of patients with an improvement of ≥ 15 letters (see Table 26 and 27 [BRAVO], and Tables 28 and 29 [CRUISE] for a summary of the subgroup analyses presented in the MS). The results of the subgroup analyses mirror the overall results in BRAVO and CRUISE, with patients treated with ranibizumab having greater improvements at month 6 compared with sham injection. The ERG notes that the results do not seem to suggest that duration of MO secondary to RVO, or baseline VA or CFT are prognostic factors in the effectiveness of ranibizumab for the treatment of MO secondary to BRVO or CRVO.

The manufacturer was unable to carry out a subgroup analysis based on presence or absence of ischaemia as, primarily as a result of exclusion of people with brisk afferent pupillary defect, people with ischaemia were not included either RCT. It follows that the results of BRAVO and CRUISE could be interpreted to be the subgroups of MO secondary to non-ischaemic BRVO and CRVO, respectively.

Table 26. Summary of subgroup analysis for mean change from baseline BCVA at month 6 in patients with MO secondary to BRVO (MS; taken from Table B22, pg 115)

Subgroup	Number of patients Sham (0.5 mg)/0.5 mg	Mean change from baseline BCVA in ETDRS letters at month 6		
		Sham	Rani 0.5 mg	
		Mean [95% CI for mean]	Mean [95% CI for mean]	
Baseline BCVA, ETDRS letter score				
≤34	9/13	13.6 [2.3 to 24.9]	30.7 [25.9 to 35.5]	
35–54	50/49	8.9 [5.0 to 12.9]	21.8 [17.8 to 25.8]	
≥55	73/69	5.4 [2.6 to 8.2]	13.4 [10.8 to 16.1]	
Baseline CFT, μm				
<450	61/48	8.0 [5.4 to 10.5]	13.8 [10.2 to 17.5]	
≥450	71/83	6.8 [3.2 to 10.4]	20.9 [18.0 to 23.7]	
Time from BRVO diagnosis to screening (months)				
<3	71/75	8.2 [5.0 to 11.4]	19.9 [16.9 to 23.0]	
≥3	61/56	6.3 [3.1 to 9.4]	16.1 [12.6 to 19.5]	
<p>The last-observation-carried-forward method was used to impute missing data.</p> <p>Abbreviations used in table: BCVA, best-corrected visual acuity; BRVO, branch retinal vein occlusion; CFT, central foveal thickness; CI, confidence interval; ETDRS, Early Treatment Diabetic Retinopathy Study; Rani, ranibizumab.</p>				

Table 27. Summary of subgroup analysis for proportion of patients who gained ≥15 ETDRS letters at month 6 in patients with MO secondary to BRVO (MS; taken from Table B23, pg 116)

Subgroup	Number of patients Sham (0.5 mg)/0.5 mg	Proportion of patients who gained ≥15 ETDRS letters at month 6		
		Sham	Rani 0.5 mg	
		n (%) [95% CI for %]	n (%) [95% CI for %]	
Baseline BCVA, ETDRS letter score				
≤34	9/13	(33.3%)	(100%)	
35–54	50/49	(36.0%)	(63.3%)	
≥55	73/69	(23.3%)	(52.2%)	
Baseline CFT, μm				
<450	61/48	(24.6%)	(47.9%)	
≥450	71/83	(32.4%)	(68.7%)	
Time from BRVO diagnosis to screening (months)				
<3	71/75	(32.4%)	(69.3%)	
≥3	61/56	(24.6%)	(50.0%)	
<p>The last-observation-carried-forward method was used to impute missing data.</p> <p>Abbreviations used in table: BCVA, best-corrected visual acuity; BRVO, branch retinal vein occlusion; CFT, central foveal thickness; CI, confidence interval; ETDRS, Early Treatment Diabetic Retinopathy Study; Rani, ranibizumab.</p>				

Table 28. Summary of subgroup analysis for mean change from baseline BCVA at month 6 in patients with MO secondary to CRVO (MS; taken from Table B24, pg 117)

Subgroup	Number of patients in each arm sham /ranibizumab 0.5 mg	Mean change from baseline BCVA in ETDRS letters at month 6		
		Sham/0.5 mg	Ranibizumab 0.5 mg	
		Mean [95% CI for mean]	Mean [95% CI for mean]	
Baseline BCVA, ETDRS letter score				
≤34	26/30	5.7 [0.3 to 11.2]	18.4 [12.4 to 24.4]	
35–54	49/50	2.4 [-2.2 to 7.1]	15.7 [12.1 to 19.4]	
≥55	55/50	-3.0 [-7.5 to 1.5]	11.9 [8.7 to 15.1]	

Baseline CFT, μm				
<450	20/19	-1.7 [-12.5 to 9.1]	10.2 [5.3 to 15.0]	
\geq 450	109/111	1.2 [-1.6 to 4.0]	15.7 [13.2 to 18.2]	
Time from CRVO diagnosis to screening (months)				
<3	80/74	1.1 [-2.9 to 5.1]	14.3 [11.1 to 17.5]	
\geq 3	50/56	0.4 [-3.4 to 4.1]	15.7 [12.4 to 18.9]	
<p>The last-observation-carried-forward method was used to impute missing data.</p> <p>Abbreviations used in table: BCVA, best-corrected visual acuity; BRVO, branch retinal vein occlusion; CFT, central foveal thickness; CI, confidence interval; ETDRS, Early Treatment Diabetic Retinopathy Study</p>				

Table 29. Summary of subgroup analysis for proportion of patients who gained \geq 15 ETDRS letters at month 6 in patients with MO secondary to CRVO (MS; taken from Table B25, pg 118)

Subgroup	Number of patients in each arm sham /ranibizumab 0.5 mg	Proportion of patients who gained \geq 15 ETDRS letters at month 6		
		Sham/0.5 mg	Ranibizumab 0.5 mg	
		n (%) [95% CI for %]	n (%) [95% CI for %]	
Baseline BCVA, ETDRS letter score				
\leq 34	26/30	(19.2%)	(53.3%)	
35–54	49/50	(28.6%)	(50.0%)	
\geq 55	55/50	(5.5%)	(42.0%)	
Baseline CFT, μm				
<450	20/19	(25.0%)	(31.6%)	
\geq 450	109/111	(15.6%)	(50.5%)	
Time from CRVO diagnosis to screening (months)				
<3	80/74	(18.8%)	(51.4%)	
\geq 3	50/56	(14.0%)	(42.9%)	
<p>The last-observation-carried-forward method was used to impute missing data.</p> <p>Abbreviations used in table: BCVA, best-corrected visual acuity; BRVO, branch retinal vein occlusion; CFT, central foveal thickness; CI, confidence interval; ETDRS, Early Treatment Diabetic Retinopathy Study.</p>				

4.6 Conclusions

4.6.1 Summary of results

- The main sources of evidence cited in the MS are the BRAVO⁽¹⁵⁾ and CRUISE⁽¹⁶⁾ RCTs.
- BRAVO and CRUISE were three armed RCTs assessing the effects of two doses of ranibizumab (0.3 mg and 0.5 mg) and sham injection. For the purposes of the decision problem that is the focus of this single technology appraisal, only ranibizumab 0.5 mg is of interest as this is the licensed dose.
- BRAVO enrolled patients with MO secondary to BRVO (263 patients), whereas CRUISE enrolled patients with MO secondary to CRVO (260 patients). In both RCTs, MO had been diagnosed within 12 months of study initiation.
- In both BRAVO and CRUISE, the mean improvement in BCVA from baseline (ETDRS letters) was significantly higher at month 6 in the ranibizumab 0.5 mg groups compared with the sham injection groups:
 - BRAVO: 18.3 with ranibizumab vs 7.3 with sham injection ($p < 0.0001$);
 - CRUISE: 14.9 with ranibizumab vs 0.8 with sham injection ($p < 0.0001$).
- The proportion of patients achieving an improvement of 15 letters was also statistically significantly larger with ranibizumab than with sham injection:
 - BRAVO: 61.1% with ranibizumab vs 28.8% with sham injection ($p < 0.0001$);
 - CRUISE: 47.7% with ranibizumab vs 16.9% with sham injection ($p < 0.0001$).
- In BRAVO, data suggest that there is some improvement without treatment at month 3:
 - In the sham injection group, 17.4% of patients (■/132) reached the prespecified outcome of improvement of 15 or more letters from baseline score at month 3, rising to 28.8% (■/132) at month 6.
- The number of AEs was low in both BRAVO and CRUISE.
- Data from the single-arm extension study (HORIZON) indicate a deterioration in BCVA at month 24 in people with MO secondary to CRVO, which could suggest that the PRN dosing regimen is insufficient in this population and a more frequent treatment regime would be required to maintain the initial observed benefit.

4.6.2 Clinical issues

- Only one large RCT is available for each of MO secondary to BRVO and to CRVO.
- People with brisk afferent pupillary defect (APD) were excluded:
 - APD is an indicator of retinal ischaemia and people with ischaemic RVO are unlikely to have been included in BRAVO and CRUISE;
 - It follows that the populations in which ranibizumab has been assessed are limited to people with MO secondary to non-ischaemic BRVO and non-ischaemic CRVO.
- In BRAVO, GLP was added at month 3, which the ERG thinks confounds the results from BRAVO.
 - The ERG notes that the RCT does not present a direct comparison of ranibizumab versus either sham injection or GLP alone for people with MO secondary to BRVO.
- Although long-term data (24 months' follow-up) are available, these data are from an extension study in which everyone received ranibizumab PRN. There are no long-term data on how ranibizumab compares with other active treatments listed in the decision problem.
- No indirect comparisons in either clinical condition for ranibizumab versus dexamethasone intravitreal implant or bevacizumab, both of which were listed as comparators of interest in the final scope.

5 ECONOMIC EVALUATION

5.1 Introduction

This section provides a structured description and critique of the systematic literature review and *de novo* economic evaluation submitted by the manufacturer. The manufacturer provided a written submission of the economic evidence along with an electronic version of the Microsoft® EXCEL-based economic model. Table 30 summarises the location of the key economic information within the manufacturer's submission (MS).

Table 30. Summary of key information within the MS

Information	Section (MS)
Details of the systematic review of the economic literature	6.1
Model structure	6.2.2 to 6.2.5
Technology	6.2.7 to 6.2.8
Clinical parameters and variables	6.3
Measurement and valuation of health effects and adverse events	6.4
Resource identification, valuation and measurement	6.5
Sensitivity analysis	6.6
Results	6.7
Validation	6.8.1
Subgroup analysis	6.9
Strengths and weaknesses of economic evaluation	6.10.3 to 6.10.4

5.2 Overview of the manufacturer's review of cost-effectiveness evidence

The manufacturer provides a brief description of the review of published cost-effectiveness evidence. The databases searched and the search terms used appear to be reasonable and both inclusion and exclusion criteria are explicitly stated. The search identified only one cost-utility study by Brown *et al.*⁽⁷¹⁾ of GLP in macular oedema (MO) secondary to retinal vein occlusion (RVO). This study was not considered relevant to the decision problem, since it was entirely US-based and therefore not easily generalisable to the UK population.

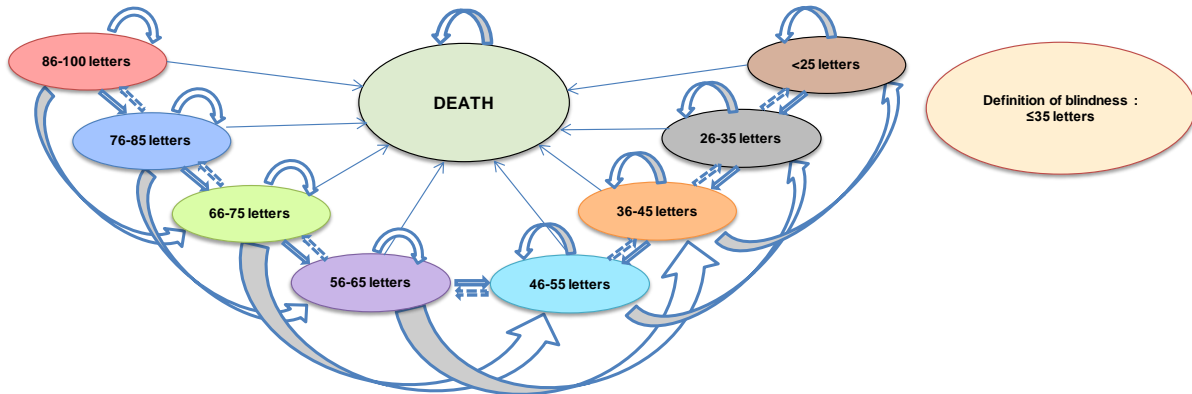
5.3 Summary of manufacturer's economic evaluation

The manufacturer developed a *de novo* cost utility model to analyse the cost effectiveness of ranibizumab monotherapy in the treatment of patients with visual impairment due to MO secondary to RVO.

5.3.1 Model structure

The *de novo* cost utility analysis uses a Markov state transition model to evaluate the clinical and economic outcomes of a hypothetical cohort of 1000 patients, with a starting age of approximately 66 years, over a 15 year time horizon. The structure of the model is displayed in figure 4.

Figure 4: Model structure



The model consists of eight different best corrected visual acuity (BCVA) health states and the absorbing state of death; the BCVA health states are defined as bands of 10 Early Treatment Diabetic Retinopathy Study (ETDRS) letters (2 lines) based on the assumption that a change in visual acuity of two lines is clinically significant. Patients are initially distributed across the BCVA health states to reflect the baseline distribution of patients in the BRAVO and CRUISE trials for MO secondary to branch RVO (BRVO) and central RVO (CRVO), respectively. Thus, all BRVO and CRVO patients are eligible for treatment with ranibizumab and the manufacturer assumes that all BRVO patients with MO of longer than 3 months are eligible for grid laser photocoagulation (GLP), if they meet the prespecified criteria listed in section 4.3.1. In the base case, it is assumed that patients remain on treatment for a maximum of two years.

Each BCVA health state has an associated utility and mortality risk, depending on whether the better-seeing eye (BSE) or worse-seeing eye (WSE) is treated. In the base case analysis, it is assumed that all patients are treated in their BSE. Patients transition through the model in monthly cycles, accumulating the utility associated with each health state they enter, together with the costs of treatment and subsequent monitoring. In addition, patients experiencing AEs have an associated cost and disutility applied, and patients considered to be blind accumulate the additional costs of blindness; blindness is assumed to occur when patients have a visual acuity of ≤ 35 letters in their BSE.

5.3.2 Population

The economic evaluation is based on the clinical effectiveness and patient characteristics of all patients included in the BRAVO⁽¹⁵⁾ and CRUISE⁽¹⁶⁾ trials. The manufacturer also conducted subgroup analyses on clinically relevant subgroups, which were identified *a priori*. Table 31 shows the patient

numbers for each population modelled. The manufacturer highlights that no patients in BRAVO⁽¹⁵⁾ and only two patients in CRUISE⁽¹⁶⁾ were ischaemic and hence subgroup analysis of ischaemic patients was not possible. The manufacturer also states that some subgroups have small numbers of patients and the results of these analyses should be interpreted with caution.

Table 31. Patient numbers in BRAVO⁽¹⁵⁾ and CRUISE⁽¹⁶⁾

Patient group	N
BRAVO	
Base case (all patients)	■
Baseline BCVA of <54 letters	■
Baseline BCVA of >54 letters	■
Time since diagnosis of <3 months	■
Time since diagnosis of 3–<6 months	■
Time since diagnosis of ≥6 months	■
CRUISE	
Base case (all patients)	■
Baseline BCVA of <54 letters	■
Baseline BCVA of >54 letters	■
Time since diagnosis of <3 months	■
Time since diagnosis of 3–<6 months	■
Time since diagnosis of ≥6 months	■
Abbreviations used in table: BCVA, best corrected visual acuity.	

5.3.3 Interventions and comparators

The main comparators for ranibizumab in the economic evaluation are GLP (standard care) and best supportive care for MO secondary to BRVO and CRVO, respectively. In addition, an exploratory indirect comparison with dexamethasone intravitreal implant is conducted in both BRVO and CRVO, but no comparison with bevacizumab was submitted. The manufacturer’s rationale for excluding bevacizumab is that bevacizumab use in the NHS is neither routine nor best practice and that it is unlicensed in ocular conditions (MS; p37).

5.3.4 Model parameters

Tables 32 to 35 present a summary of the parameters and values used in the manufacturer’s economic model.

Table 32. Indication specific parameters used in the economic model

Input parameter	Base case value: BRVO	Base case value: CRVO	Source
Baseline age (years)	66.43	67.61	BRAVO ⁽¹⁵⁾ /CRUISE ⁽¹⁶⁾
Baseline health state distribution (BCVA letter score)			
86–100	0.00%	0.00%	Ibid
76–85	0.40%	0.00%	Ibid
66–75	17.20%	13.50%	Ibid
56–65	33.60%	26.90%	Ibid
46–55	26.00%	21.20%	Ibid
36–45	13.70%	16.20%	Ibid
26–35	7.30%	15.00%	Ibid
<25	1.90%	7.30%	Ibid
Transition probabilities^a			
Month 1			
Ranibizumab: gain at least 4 lines	████	████	BRAVO/CRUISE (data on file)
Ranibizumab: gain between 2 and 4 lines	████	████	Ibid
Ranibizumab: no change	████	████	Ibid
Ranibizumab: lose between 2 and 4 lines	████	████	Ibid
Ranibizumab: lose at least 4 lines	████	████	Ibid
Standard care: gain at least 4 lines	████	████	Ibid
Standard care: gain between 2 and 4 lines	████	████	Ibid
Standard care: no change	████	████	Ibid
Standard care: lose between 2 and 4 lines	████	████	Ibid
Standard care: lose at least 4 lines	████	████	Ibid
Months 2 to 6			
Ranibizumab: gain at least 4 lines	████	████	Ibid
Ranibizumab: gain between 2 and 4 lines	████	████	Ibid
Ranibizumab: no change	████	████	Ibid
Ranibizumab: lose between 2 and 4 lines	████	████	Ibid
Ranibizumab: lose at least 4 lines	████	████	Ibid
Standard care: gain at least 4 lines	████	████	Ibid
Standard care: gain between 2 and 4 lines	████	████	Ibid
Standard care: no change	████	████	Ibid
Standard care Lose between 2 and 4 lines	████	████	Ibid
Standard care: lose at least 4 lines	████	████	Ibid

Months 7 to 12^b			
Ranibizumab: gain at least 4 lines	████	████	Ibid
Ranibizumab: gain between 2 and 4 lines	████	████	Ibid
Ranibizumab: no change	████	████	Ibid
Ranibizumab: lose between 2 and 4 lines	████	████	Ibid
Ranibizumab: lose at least 4 lines	████	████	Ibid
Standard care: gain at least 4 lines	████	████	Ibid
Standard care: gain between 2 and 4 lines	████	████	Ibid
Standard care: no change	████	████	Ibid
Standard care Lose between 2 and 4 lines	████	████	Ibid
Standard care: lose at least 4 lines	████	████	Ibid

^a Variation: All transition probabilities were varied using a multiplier, assigned to a lognormal distribution with an assumed variation 0.1.

^b Assumption: the data was pooled across both treatment arms for months 7 to 12 to generate month 7 to 12 transition probabilities for BRVO and the month 2-6 transition probabilities were reapplied for months 7-12 for CRVO.

Abbreviations used in table: BCVA, best corrected visual acuity; BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion; ETDRS, Early Treatment Diabetic Retinopathy Study.

Table 33. Parameter values independent of indication used in the economic model

Input parameter	Base case value	Source
Model structure		
Time horizon	15 years	Assumption; NICE Reference case
Discount rate costs	3.50%	NICE Reference case
Discount rate benefits	3.50%	NICE Reference case
% BSE at baseline	100%	Assumption
% BSE at 12 months	100%	Assumption
Duration of treatment	2 years	Assumption
Adverse events (events per patient, %)		
Ranibizumab: cataracts	6.60%	BRAVO/CRUISE Data on file
Ranibizumab: IOP increased (treated with drug)	10.00%	BRAVO/CRUISE Data on file
Ranibizumab: IOP increased (treated with surgery)	0.00%	BRAVO/CRUISE Data on file
Ranibizumab: stroke	0.05%	Assumption; RR of stroke in RVO applied to annual haemorrhagic stroke rate
Standard care BRVO (GLP): cataracts	0.00%	Assumption
Standard care BRVO (GLP): IOP increased (treated with drug)	0.00%	Assumption
Standard care BRVO (GLP): IOP increased (treated with surgery)	0.00%	Assumption
Standard care BRVO (GLP): stroke	0.05%	Assumption; RR of stroke in RVO applied to annual haemorrhagic stroke rate
Standard care CRVO (observation): cataracts	0.00%	Assumption
Standard care CRVO (observation): IOP increased (treated with drug)	0.00%	Assumption
Standard care CRVO (observation): IOP increased (treated with surgery)	0.00%	Assumption
Standard care CRVO (observation): stroke	0.05%	Assumption; RR of stroke in RVO applied to annual haemorrhagic stroke rate

Dexamethasone intravitreal implant: cataracts	14.80%	Shyangdan 2011 ⁽⁶⁴⁾
Dexamethasone intravitreal implant: IOP increased (treated with drug)	50.40%	Shyangdan 2011 ⁽⁶⁴⁾
Dexamethasone intravitreal implant: IOP increased (treated with surgery)	1.40%	Shyangdan 2011 ⁽⁶⁴⁾
Dexamethasone intravitreal implant: stroke	0.05%	Assumption; RR of stroke in RVO applied to annual haemorrhagic stroke rate
Risk ratio for mortality, by VA status		
86–100	1	Assumption, Christ 2008 ⁽⁷²⁾
76–85	1	Assumption, Christ 2008 ⁽⁷²⁾
66–75	1	Assumption, Christ 2008 ⁽⁷²⁾
56–65	1	Assumption, Christ 2008 ⁽⁷²⁾
46–55	1.23	Christ 2008 ⁽⁷²⁾
36–45	1.23	Christ 2008 ⁽⁷²⁾
26–35	1.54	Christ 2008 ⁽⁷²⁾
<25	1.54	Christ 2008 ⁽⁷²⁾
BSE utility scores		
VA 86–100 letters	0.92	Brown 1999 ⁽⁷³⁾
VA 76–85 letters	0.88	Brown 1999 ⁽⁷³⁾
VA 66–75 letters	0.77	Brown 1999 ⁽⁷³⁾
VA 56–65 letters	0.755	Brown 1999 ⁽⁷³⁾
VA 46–55 letters	0.67	Brown 1999 ⁽⁷³⁾
VA 36–45 letters	0.665	Brown 1999 ⁽⁷³⁾
VA 26–35 letters	0.645	Brown 1999 ⁽⁷³⁾
VA<25 letters	0.51	Brown 1999 ⁽⁷³⁾
WSE utility scores (all BCVA health states)	0.85	Assumption
Death	0	Assumption
Cataracts	-0.14	Brown 2007 ⁽⁷⁴⁾
IOP increased (treated with drug)	-0.01	Vaahoranta-Lehtonen 2007 ⁽⁷⁵⁾
IOP increased (treated with surgery)	-0.01	Vaahoranta-Lehtonen 2007 ⁽⁷⁵⁾
Stroke	-0.26	Schwander 2009 ⁽⁷⁶⁾
Abbreviations used in table: BRVO, branch retinal vein occlusion; BSE, better-seeing eye; CRVO, central retinal vein occlusion; GLP, grid laser photocoagulation; IOP, intraocular pressure; VA, visual acuity.		

Table 34. Resource use; base case values

Input parameter	BRVO	CRVO	Source
Ranibizumab injection frequency year 1	8	9	BRAVO ⁽¹⁵⁾ /CRUISE ⁽¹⁶⁾
Ranibizumab follow up visit frequency year 1	4	3	Assumption; SPC (based on a total of 12 visits of any type per year)
Ranibizumab injection frequency year 2	2.5	3.8	HORIZON (data on file)
Ranibizumab follow up visit frequency year 2	3.5	6.2	Assumption; HORIZON ⁽⁵²⁾ , expert opinion
Ranibizumab injection frequency year 3	0	0	Assumption; expert opinion
Ranibizumab follow up visit frequency year 3	2	4	Assumption; expert opinion (based on a total of 4 visits of any type per year)
GLP administration frequency year 1	1.5	0	SCORE study ⁽⁷⁷⁾
GLP/SC follow up visit frequency year 1	2.5	6	Assumption; expert opinion
GLP/SC administration frequency year 2	1	0	SCORE study ⁽⁷⁷⁾
GLP/SC follow up visit frequency year 2	3	4	Assumption; expert opinion
GLP/SC administration frequency year 3	0	0	Assumption; expert opinion
GLP/SC follow up visit frequency year 3	2	4	Assumption; expert opinion (based on a total of 4 visits of any type per year)

Dexamethasone intravitreal implant injection frequency year 1	2	2	Shyangdan 2011 ⁽⁶⁴⁾
Dexamethasone intravitreal implant follow up visit frequency year 1	6	6	Assumption
Dexamethasone intravitreal implant injection frequency year 2	2	2	Shyangdan 2011 ⁽⁶⁴⁾
Dexamethasone intravitreal implant follow up visit frequency year 2	6	6	Assumption
Dexamethasone intravitreal implant injection frequency year 3	0	0	Assumption; expert opinion
Dexamethasone intravitreal implant follow up visit frequency year 3	2	4	Assumption; expert opinion
GLP applies to BRVO while standard care (SC) applies to CRVO.			
Abbreviations used in table: BRVO, branch retinal vein occlusion; BSE, better-seeing eye; CRVO, central retinal vein occlusion; GLP, grid laser photocoagulation; IOP, intraocular pressure; SC, standard care; VA, visual acuity.			

Table 35. Costs

Input parameter	Base case value	Source
Technology costs		
Ranibizumab: technology cost (without PAS)	£742.17	Novartis Pharmaceuticals UK Ltd
Ranibizumab: technology cost (with PAS)	██████	Novartis Pharmaceuticals UK Ltd ⁽³⁹⁾
Ranibizumab: administration cost	£192.00	NHS Reference Costs 2009/10 ⁽⁷⁸⁾ : (78) [outpatient procedure (£137) + OCT (£55)]
Ranibizumab: follow up visit cost	£151.00	NHS Reference Costs 2009/10 ⁽⁷⁸⁾ : outpatient procedure (£137) + OCT (£55).
GLP (BRVO): technology cost	£0.00	Assumption; capital expenditure and maintenance costs are excluded
GLP (BRVO): administration cost	£110.59	NHS Reference Costs 2009/10 ⁽⁷⁸⁾ : outpatient procedure (£137) + OCT (£55). 57% of patients incur GLP costs as per control arm of BRAVO
GLP (BRVO): follow up visit cost	£151.00	NHS Reference Costs 2009/10 ⁽⁷⁸⁾ : outpatient procedure (£137) + OCT (£55).
Observation (CRVO): technology cost	£0.00	n/a
Observation (CRVO): administration cost	£0.00	n/a
Observation (CRVO): follow up visit cost	£151.00	NHS Reference Costs 2009/10 ⁽⁷⁸⁾ : outpatient procedure (£137) + OCT (£55).
Dexamethasone intravitreal implant: technology cost	£870.00	BNF ⁽⁷⁹⁾
Dexamethasone intravitreal implant: administration cost	£295.25	NHS Reference Costs 2009/10 ⁽⁷⁸⁾ : outpatient/daycase procedure (£240) Weighted average of day case [25%] and outpatient [75%] + OCT (£55)
Dexamethasone intravitreal implant: follow up visit cost	£151.00	NHS Reference Costs 2009/10 ⁽⁷⁸⁾ : outpatient procedure (£137) + OCT (£55).
Costs of blindness		
First year cost	£6,286.10	Shyangdan 2011, ⁽⁶⁴⁾ based on Meads and Hyde 2003 ⁽⁸⁰⁾
Subsequent annual costs	£6,067.93	Shyangdan 2011, ⁽⁶⁴⁾ based on Meads and Hyde 2003 ⁽⁸⁰⁾
Technology costs treating of adverse events		
Cataract	£800	NHS Reference Costs 2009/10 ⁽⁷⁸⁾ : BZ02Z: NHS Trusts Day Cases HRG Data= £800 (Phacoemulsification Cataract Extraction & Lens Implant)

IOP increased (treated with drug)	£31.67	Shyangdan 2011 ⁽⁶⁴⁾
IOP increased (treated with surgery)	£872.63	Shyangdan 2011 ⁽⁶⁴⁾
Abbreviations used in table: BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion; GLP, grid laser photocoagulation; IOP, intraocular pressure, HRG, healthcare resource group.		

5.3.5 Treatment effectiveness

Ranibizumab, grid laser photocoagulation (standard care) and best supportive care

Individual patient level data from BRAVO⁽¹⁵⁾ and CRUISE⁽¹⁶⁾ were used to populate the transition probability matrices of the main comparisons in the submitted economic model for MO secondary to BRVO and CRVO, respectively. Probabilities were calculated for the following transitions:

- Gaining at least 4 lines;
- Gaining between 2 and 4 lines;
- No change;
- Losing between 2 and 4 lines;
- Losing at least 4 lines.

Two sets of probabilities were calculated based on different assumptions: (i) transitions are independent of current visual acuity; and (ii) transitions are dependent on current visual acuity. The model allows the user to choose which assumption forms the basis for the transition probability matrices. The manufacturer's base case uses probabilities calculated on the assumption of independence as, due to small patient numbers, the transitions derived from assuming dependence were unreliable in extreme visual acuity states. The manufacturer considers this a conservative assumption as the effect of ranibizumab estimated under this assumption is lower than that observed in the trials (MS; Tables B70 and B71).

Transition probabilities are determined monthly and subsequently used to calculate overall monthly transition probabilities for the following time periods:

- Month 0 to 1;
- Months 2 to 6;
- Months 7 to 12.

In both BRAVO⁽¹⁵⁾ and CRUISE⁽¹⁶⁾ patients entered an observation period after 6 months, where ranibizumab could be given to any participants on a *pro re nata* (PRN) basis (see section 4.2.2 for more detail), therefore there is no data for GLP (standard care in MO secondary to BRVO) or best supportive care (standard care in MO secondary to CRVO) past 6 months. Table 36 summarises the transition probabilities used for each time period of the model from baseline to 2 years.

Table 36. Source of transition probabilities

Source of transition probabilities (BRVO)		
Months	Ranibizumab	Grid laser photocoagulation (standard care)
0–1	Ranibizumab arm of BRAVO; month 0 to 1	Sham arm of BRAVO: month 0 to 1
2–6	Ranibizumab arm of BRAVO; months 2 to 6	Sham arm of BRAVO: months 2 to 6
7–12	Pooled ranibizumab and sham arm of BRAVO; months 7 to 12	Pooled ranibizumab and sham arm of BRAVO; months 7 to 12
13–24	Pooled ranibizumab and sham arm of BRAVO; months 7 to 12	Pooled ranibizumab and sham arm of BRAVO; months 7 to 12
Source of transition probabilities (CRVO)		
	Ranibizumab	Best supportive care
0–1	Ranibizumab arm of CRUISE; month 0 to 1	Sham arm of CRUISE: month 0 to 1
2–6	Ranibizumab arm of CRUISE; months 2 to 6	Sham arm of CRUISE: months 2 to 6
7–12	Ranibizumab arm of CRUISE; months 7 to 12	Sham arm of CRUISE: months 2 to 6
13–24	Ranibizumab arm of CRUISE; months 7 to 12	Sham arm of CRUISE: months 2 to 6

Abbreviations used in table: BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion.

In CRVO, the probabilities derived from the sham arm of the CRUISE trial for months 2 to 6 applied at months 2 to 6, 7 to 12 and 13 to 24 in the best supportive care arm of the model, due to the absence of any comparator data after month 6. However, in BRVO, the probabilities for months 7 to 12 are pooled from both trial arms of BRAVO and applied at months 7 to 12 and months 13 to 24 to both arms of the model. The manufacturer states that this approach is to account for the impact of GLP in the comparator arm and considers this a conservative approach (MS; pg 194).

Dexamethasone intravitreal implant

Dexamethasone intravitreal implant is incorporated into the model by the application of relative risks (RRs) derived from an exploratory indirect comparison, using data from Allergan’s submission to NICE for dexamethasone intravitreal implant in MO secondary to RVO.⁽⁶³⁾

The manufacturer constructs normal approximations of the distribution of the mean change from baseline for dexamethasone intravitreal implant and sham at month 1 using the data below (reported on page 59 of Allergan’s submission⁽⁶³⁾):

- the mean change in BCVA from baseline at month 1 for dexamethasone intravitreal implant;
- the mean change in BCVA from baseline at month 1 for sham;
- the 95% confidence interval (constructed using a Normal approximation) for the difference in mean change from baseline between dexamethasone intravitreal implant and sham.

The probability of each transition used in the economic model was estimated from the respective distributions for dexamethasone intravitreal implant and sham. The RR of each of these transitions for dexamethasone intravitreal implant versus sham was then calculated by taking the ratio of the probabilities (see Appendix for calculation details). Table 37 displays the RRs used in the economic

model; these risks are applied to the comparator arm transition probabilities at month 1 for BRVO and CRVO.

Table 37. RR for dexamethasone intravitreal implant versus sham at month 1 (reproduced from Table B46 of the MS)

Transition	BRVO	CRVO
Gain at least 4 lines		
Gain between 2 and 4 lines		
No change ^a		
Lose between 2 and 4 lines		
Lose at least 4 lines		
^a In the model these transitions are assumed to be 1–(all other transitions). Abbreviations used in table: BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion; N/A, not applicable; RR, relative risk.		

After 1 month, the transition probabilities for dexamethasone intravitreal implant are assumed not to vary from those of GLP (standard care) or best supportive care in BRVO and CRVO, respectively; it is assumed all the benefit of dexamethasone intravitreal implant is received in month 1.

Long-term disease progression

From year 3 and beyond, the manufacturer introduces a monthly natural rate of deterioration of 0.031% calculated from the Beaver Dam Eye study⁽⁸¹⁾ that is applied to all modelled arms beginning at year 3.

5.3.6 Health related quality of life

The BRAVO⁽¹⁵⁾ and CRUISE⁽¹⁶⁾ trials collected vision-related quality-of-life data using the National Eye Institute (NEI) Visual Functioning Questionnaire (VFQ)-25 questionnaire. The manufacturer states that NEI VFQ-25 is not a preference-based questionnaire and does not include a direct estimation of utility weights. However, both trials reported a significant ($p < 0.005$ and $p < 0.05$ for BRAVO and CRUISE respectively). difference between ranibizumab and the sham arm in NEI-VFQ-25 score at month 6 (see section 4.3). The manufacturer conducted a systematic review to identify utility values reported in the literature for populations with visual impairment due to RVO, with priority given to populations with MO secondary to BRVO or CRVO. The manufacturer states that consideration would have been given to patients with diabetic MO or age-related macular degeneration (AMD) if utility values for RVO could not be identified (MS; pg 208). Seven studies were identified. Brown *et al.*⁽⁷³⁾ was chosen as the source for utilities as this was the only study for which utility values by visual acuity were reported. Brown *et al.*⁽⁷³⁾ is a US study assessing preferences for different levels of visual acuity in a population of patients with vision loss due to various causes, 7% of whom had RVO (MS; Table B52).

The manufacturer’s model applies different utility values to each BCVA health state, depending on whether the BSE or WSE is treated. Brown *et al.*⁽⁷³⁾ presented separate utility values for visual acuity in the BSE and WSE; however, the manufacturer only used the utility values for visual acuity in the BSE and assumed a flat curve of 0.85 for utility associated with visual acuity in the WSE. The rationale for this was that there were inconsistencies between the WSE utilities reported in Brown *et al.*⁽⁷³⁾ and the significant impact of visual impairment (VI) in the WSE on vision related QoL reported elsewhere^(3;4) and observed in BRAVO⁽¹⁵⁾ and CRUISE.⁽¹⁶⁾ BSE utility values were reported for a greater number of visual acuity levels than those used in the manufacturer’s model, therefore the manufacturer made some simplifying assumptions in order to utilize these data (Table 38). Utilities are not adjusted for age and the WSE is not considered in the base case.

Table 38. BSE Utility values used in the economic analysis

Visual acuity (Brown <i>et al.</i> ⁽⁷³⁾)	n	TTO Utility (SD)	Visual acuity (manufacturer’s model)	Utility	Assumptions
20/20	32	0.92 (0.13)	86–100 letters = 20/16–20/10	0.92	The highest utility value was used
20/25	50	0.87 (0.19)	76–85 letters = 20/32–20/20	0.88	The average of 20/20 and 20/30
20/30	44	0.84 (0.19)	66–75 letters = 20/64–20/40	0.77	The average of 20/40 and 20/70
20/40	54	0.80 (0.22)	56–65 letters = 20/80–20/50	0.76	The average of 20/50 and 20/70
20/50	31	0.77 (0.20)	46–55 letters = 20/125–20/80	0.67	Equivalent to 20/100
20/70	40	0.74 (0.21)	36–45 letters = 20/200–20/125	0.67	Average of 20/100 and 20/200
20/100	18	0.67 (0.21)	26–35 letters = 20/320–20/200	0.65	Average of 20/200 and 20/300
20/200	16	0.66 (0.23)	<25 letters = <20/320	0.51	Average of 20/300, 20/400, counting fingers and hand motions-or perception of light
20/300	13	0.63 (0.16)			
20/400	9	0.54 (0.17)			
Counting fingers	12	0.52 (0.29)			
Hand motions-no light perception	6	0.35 (0.29)			
Abbreviations used in table: BSE, best seeing-eye; TTO, time trade off.					

Adverse event disutility

The rationale for inclusion of AEs presented by the manufacturer is a combination of relative prevalence and severity. Endophthalmitis and retinal tear were excluded due to low incidence in BRAVO⁽¹⁵⁾ and CRUISE.⁽¹⁶⁾ No rationale for the exclusion of vitreous haemorrhage was given;

however, the manufacturer states that the exclusion of vitreous haemorrhage is conservative, because, in BRAVO⁽¹⁵⁾ and CRUISE,⁽¹⁶⁾ the incidence of vitreous haemorrhage was higher in the sham arms than in the ranibizumab arms. Table 39 shows the AEs included in the model and their associated disutility; disutilities were applied once at the start of the first cycle and weighted by their respective prevalence and duration.

Table 39. Adverse events included in the model

Adverse event	Disutility	Source	Duration (months)	Source
Cataracts	-0.14	Brown <i>et al.</i> ⁽⁷⁴⁾	6.00	Assumption
IOP increased (treated with drug)	-0.01	Vaahoranta-Lehtonen <i>et al.</i> ⁽⁷⁵⁾	0.03 (one day)	Assumption
IOP increased (treated with surgery)	-0.01	Vaahoranta-Lehtonen <i>et al.</i> ⁽⁷⁵⁾	6.00	Assumption
Stroke	-0.26	Schwander <i>et al.</i> ⁽⁷⁶⁾ 2009	Lifetime	Assumption

Abbreviations in table: IOP, intraocular pressure.

The manufacturer does not include safety data from the HORIZON⁽⁵²⁾ study in the model, but states that there were low incidences of serious AEs during follow-up, with serious AEs occurring in 2% to 9% of study eyes across the treatment groups and serious AEs potentially associated with systemic vascular endothelial growth factor (VEGF) treatment occurring in 1% to 6% of study eyes (HORIZON⁽⁵²⁾; MS; pg 165).

5.3.7 Mortality

The model structure is highly flexible regarding the assumptions around mortality, and allows simultaneous accounting for mortality risks associated with: all cause mortality; treatment; RVO; and visual acuity. However, the manufacturer's base case analyses include only all-cause and visual-acuity-related mortality risks. All-cause mortality rates were sourced from life tables for England and Wales; the male and female rates were averaged and converted into the monthly rates required for the model using standard formulae (England & Wales Life Tables 2007–2009⁽⁸²⁾).

Excess mortality risk associated with visual impairment is taken from a study by Christ *et al.*⁽⁷²⁾, which reports HRs of 1.54 and 1.23 associated with severe and “some” visual impairment, respectively. Severe visual impairment is defined as blind in both eyes. “Some” visual impairment is defined as either:

- VI in both eyes;
- Blind in one eye, visually impaired in the other eye;
- Blind or visually impaired in only one eye, with the other eye having good vision or not mentioned.

The manufacturer applies the severe visual impairment HR to patients who have a visual acuity of less than 35 ETDRS letters in their BSE and the HR associated with “some” visual impairment to patients who have visual acuity of between 36 and 55 ETDRS letters in their BSE (MS; Table B47, pg 199).

The manufacturer’s rationale for assuming no excess mortality from treatment is the low mortality rates observed in BRAVO⁽¹⁵⁾ and CRUISE.⁽¹⁶⁾ Similarly, the manufacturer argues that, although there is evidence of a higher risk of cardiovascular mortality associated with RVO (Cugati 2007⁽²⁴⁾, Xu 2007⁽²⁵⁾, Tsaloumas 2000⁽²⁶⁾, Martin 2002⁽²⁷⁾), the low mortality rates observed in BRAVO⁽¹⁵⁾ and CRUISE,⁽¹⁶⁾ taken together with evidence from studies by Christoffersen *et al.*⁽⁸³⁾ and Curtis *et al.*⁽³³⁾, indicate that there is no significant difference in the risk of mortality between patients with RVO and the general population (MS; pg 199).

5.3.8 Resources and costs

In the economic evaluation, the manufacturer identifies three key types of cost: intervention and comparator costs; health state costs; and AE costs. These are summarised in Tables B59 to B66 in the MS (MS; pg 235–240). With the exception of ranibizumab treatment costs, all costs were obtained from published sources and referenced.

Intervention and comparator costs

In the case of BRVO, there are no direct treatment costs for GLP and, as such, only an administration cost and the cost of optical coherence tomography (OCT) were applied. Administration and OCT costs were also applied to the ranibizumab and dexamethasone intravitreal implant model arms, in addition to the direct cost of treatment.

The manufacturer states (MS; pg 228) that administration of GLP and ranibizumab as a monotherapy would be costed as a Vitreous Retinal Procedures – category 1 (HRG code: BZ23Z) – and therefore applies the same administration cost to the ranibizumab and GLP arms of the model, with the cost of administration of GLP weighted by the proportion of patients receiving GLP (■■■■). Administration of dexamethasone intravitreal implant is generally more involved than that of ranibizumab or GLP, due to the size of the needle. The manufacturer adopted the approach taken by Allergan in their submission to NICE for dexamethasone intravitreal implant in MO secondary to RVO, which uses a weighted average of an outpatient procedure (25%) and a day case procedure (75%) (Allergan 2010⁽⁶³⁾).

The cost of OCT was estimated to be the same as an outpatient diagnostic procedure coded as an ultrasound scan of less than 20 minutes (HRG code: RA23Z). The manufacturer states that the cost of OCT may well be accounted for in the administration cost, however in order to take a conservative approach the manufacturer applied this cost in addition to the cost of administration.

Health state costs: cost of blindness

The only health state with an associated cost was that of blindness; defined as those patients whose visual acuity is below 35 letters in the BSE. The costs of blindness were drawn from Colquitt *et al.*⁽⁵⁸⁾ and applied using the same methodology as that used by the ERG responsible for reviewing Allergan's submission to NICE for dexamethasone intravitreal implant in MO secondary to RVO.⁽⁶⁴⁾ Costs were inflated to 2010 using the Personal and Social Services Research Unit (PSSRU) Health and Social Care Services (HSCS) index.⁽⁸⁴⁾

Although the model allows the user the option to apply the cost of blindness to any eye falling below a visual acuity of 35 ETDRS letters, the base case assumption is that the costs of blindness are only applied when visual acuity in the BSE falls below 35 letters. The MS states that these costs were applied only in the first year of blindness, which is in accordance with other evaluations conducted in RVO. However, the manufacturer acknowledges that this strategy may underestimate the costs as the costs of low vision aids and low vision rehabilitation would in fact be biannual according to the Royal National Institute of Blind People (RNIB) (MS; p238).

Adverse event costs

As observed by the manufacturer, the incidence of AEs was low in both the BRAVO⁽¹⁵⁾ and CRUISE⁽¹⁶⁾ trials. The manufacturer included cataracts, intraocular pressure (IOP) and stroke in the analyses. Costs of cataracts were taken from NHS reference costs 2009/10,⁽⁷⁸⁾ while those of stroke were taken from a cost utility study in primary and secondary prevention of cardiovascular events by Schwander *et al.*⁽⁷⁶⁾. The costs for IOP (requiring treatment with drug or with surgery) were derived from Allergan's submission to NICE for dexamethasone intravitreal implant in the treatment of MO secondary to RVO.⁽⁶³⁾

5.3.9 Perspective, time horizon and discounting

The economic evaluation was undertaken from the perspective of the NHS and Personal and Social Services (PSS) in England and Wales. The time horizon used in the model is 15 years. Both costs and benefits were discounted at 3.5% per annum.

5.3.10 Cost effectiveness results

The manufacturer submitted an approved patient access scheme (PAS) price of ranibizumab of [REDACTED] (£742.17 [REDACTED])⁽³⁹⁾ in parallel to the main submission which provided base case results for the incremental cost per quality-adjusted life year (QALY) gained for the following comparisons: ranibizumab versus GLP in MO secondary to BRVO (Table 40), ranibizumab versus best supportive care in MO secondary to CRVO (Table 41) and incremental results of ranibizumab versus GLP and dexamethasone intravitreal implant (Table 42) and ranibizumab versus best

supportive care and dexamethasone intravitreal implant (Table 43) for patients with MO secondary to BRVO and CRVO respectively. All the results presented in this section are based on the PAS price of ranibizumab. The cost effectiveness planes and cost effectiveness acceptability curves of ranibizumab in MO secondary to BRVO and CRVO are presented in figures 5 and 8 respectively and the probabilities of cost effectiveness at thresholds of £20,000 and £30,000 are summarised in Table 44 for both indications.

The MS presents a series of tables (Tables 45 to 48) showing detailed disaggregated costs and benefits for ranibizumab versus GLP (standard care) and best supportive care in BRVO and CRVO, respectively. No disaggregated tables for the comparison versus dexamethasone intravitreal implant were provided.

Table 40. Base case cost-effectiveness results of ranibizumab versus grid laser photocoagulation (standard care): MO secondary to BRVO (adapted from MS with PAS; Table 3b)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
GLP	£11,990	12.561	7.705	–	–	–	–
Ranibizumab	██████	██████	██████	██████	██████	██████	£20,494

Abbreviations used in table: BRVO, branch retinal vein occlusion; GLP, grid laser photocoagulation; ICER, incremental cost-effectiveness ratio; LYG, life years gained; MO, macular oedema; PAS, patient access scheme; QALYs, quality-adjusted life years.

Table 41. Base case cost-effectiveness results of ranibizumab versus best supportive care: MO secondary to CRVO (adapted from MS with PAS; Table 3d)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
BSC	£20,727	12.149	7.061	–	–	–	–
Ranibizumab	██████	██████	██████	██████	██████	██████	£8,643

Abbreviations used in table: CRVO, central retinal vein occlusion; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; MO, macular oedema; PAS, patient access scheme; QALYs, quality-adjusted life years.

Figure 6. BRVO cost effectiveness acceptability curve: ranibizumab versus GLP (reproduced from MS with PAS; Figure 1a)



Figure 7. [REDACTED]

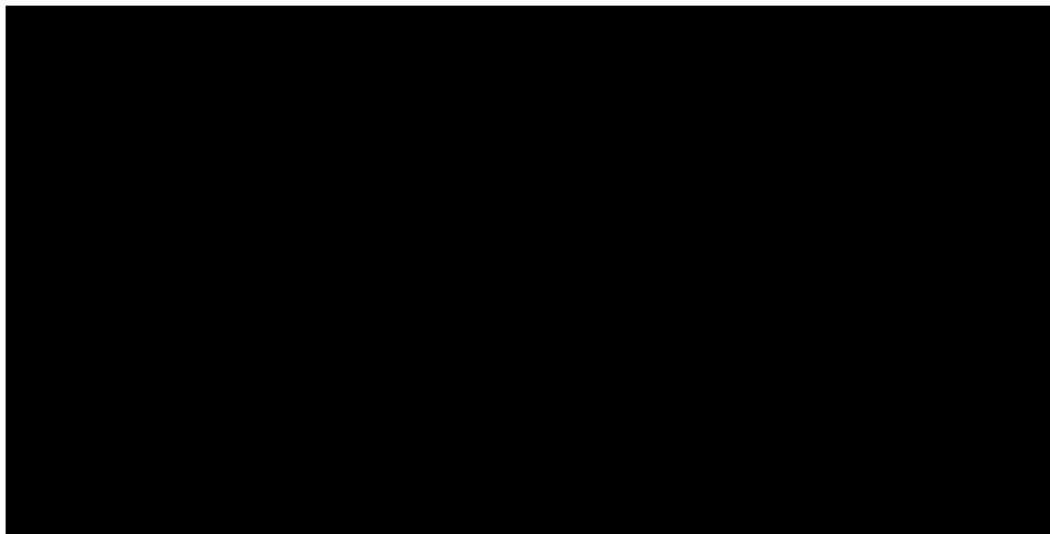


Figure 8. CRVO cost effectiveness acceptability curve: ranibizumab versus BSC (reproduced from MS with PAS; Figure 2a)

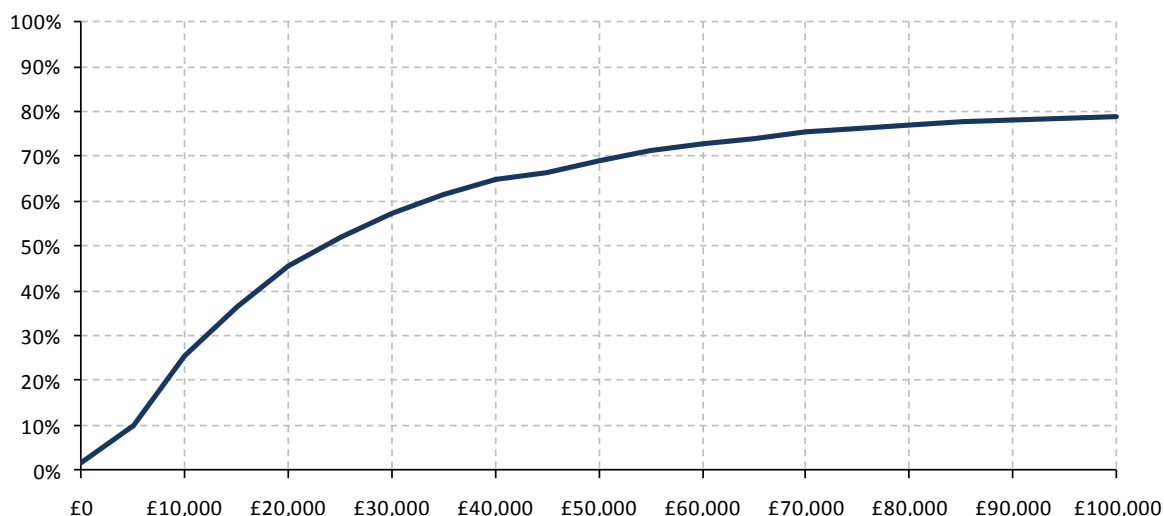


Table 44. Probability of cost effectiveness (reproduced from MS with PAS; Table 6)

	WTP = £0	WTP = £20,000	WTP = £30,000
BRVO: ranibizumab vs GLP	1.6%	45.5%	57.2%
CRVO: ranibizumab vs best supportive care	10.3%	74.5%	83.3%

Abbreviations used in table: BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion; PAS, patient access scheme; WTP, willingness to pay.

Table 45. Summary of QALY gain by health state: BRVO (reproduced from the MS; Table B77)

Health state	QALY intervention (ranibizumab)	QALY comparator (GLP)	Increment	Absolute increment	% Absolute increment
86–100	2.350	1.865	0.484	0.484	33.85%
76–85	1.681	1.411	0.270	0.270	18.86%
66–75	1.256	1.158	0.098	0.098	6.85%
56–65	1.000	1.039	-0.039	0.039	2.74%
46–55	0.667	0.783	-0.116	0.116	8.13%
36–45	0.488	0.642	-0.154	0.154	10.75%
26–35	0.332	0.481	-0.149	0.149	10.42%
<25	0.212	0.327	-0.116	0.116	8.08%
Loss due to adverse events	-0.007	-0.002	-0.005	0.005	0.33%
Total	■	7.705	■	1.431	100.00%

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.⁽⁸⁵⁾

Abbreviations used in table: BRVO, branch retinal vein occlusion; GLP, grid laser photocoagulation; QALY, quality-adjusted life year.

Table 46. Summary of QALY gain by health state: CRVO (reproduced from the MS; Table B78)

Health state	QALY intervention (ranibizumab)	QALY comparator (best supportive care)	Increment	Absolute increment	% Absolute increment
86–100	1.910	1.114	0.796	0.796	34.77%
76–85	1.364	0.969	0.395	0.395	17.24%
66–75	1.123	0.931	0.193	0.193	8.41%
56–65	0.979	0.973	0.006	0.006	0.28%
46–55	0.735	0.860	-0.125	0.125	5.45%
36–45	0.618	0.843	-0.225	0.225	9.81%
26–35	0.474	0.758	-0.284	0.284	12.40%
<25	0.355	0.616	-0.262	0.262	11.43%
Loss due to adverse events	-0.007	-0.002	-0.005	0.005	0.20%
Total	■	7.061	■	2.290	100.00%

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee⁽⁸⁵⁾.

Abbreviations used in table: CRVO, central retinal vein occlusion; QALY, quality-adjusted life year.

Table 47. Summary of predicted resource use by category of cost: BRVO with PAS (adapted from the MS; Table B79)

Item	Costs intervention (ranibizumab)	Costs comparator (GLP)	Increment	Absolute increment	% Absolute increment
Treatment costs	£■	£0	£■	£■	56.80%
Administration costs	£1,941	£264	£1,677	£1,677	14.94%
Follow-up	£3,522	£3,218	£304	£304	2.71%
Cost of adverse events	£61	£5	£56	£56	0.50%
Cost of blindness	£5,691	£8,503	-£2,811	£2,811	25.05%
Total	£■	£11,990	£■	£■	100.00%

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.⁽⁸⁵⁾

Abbreviations used in table: BRVO, branch retinal vein occlusion; GLP, grid laser photocoagulation; MS, manufacturer's submission; PAS, patient access scheme.

Table 48. Summary of predicted resource use by category of cost: CRVO with PAS (adapted from the MS; Table B80)

Item	Costs intervention (ranibizumab)	Costs comparator (best supportive care)	Increment	Absolute increment	% absolute increment
Treatment costs	£■■■■	£0	£■■■■	£■■■■	48.18%
Administration costs	£2,354	£0	£2,354	£2,354	14.66%
Follow-up	£6,052	£6,128	-£76	£76	0.48%
Cost of adverse events	£61	£5	£56	£56	0.35%
Cost of blindness	£8,763	£14,595	-£5,832	£5,832	36.33%
Total	£■■■■	£20,727	£■■■■	£■■■■	100.00%

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.⁽⁸⁵⁾

Abbreviations used in table: CRVO, central retinal vein occlusion; PAS, patient access scheme; QALY, quality-adjusted life year.

5.3.10 Sensitivity analyses

Extensive sensitivity analyses and probabilistic sensitivity analyses (PSAs) were carried out by the manufacturer. The results of these analyses (without the inclusion of the PAS) are presented in Section 4.13 of the manufacturer's PAS submission.⁽³⁹⁾ Base case results (with PAS) in patients with MO secondary to BRVO patients generate costs per QALY of £20,494 for ranibizumab versus GLP and £5,486 versus dexamethasone intravitreal implant. In patients with MO secondary to CRVO ranibizumab versus best supportive care, base case results (with PAS) generate a cost per QALY of £8,643 and £7,174 for ranibizumab versus dexamethasone intravitreal implant, respectively. When an incremental analysis was done including all the comparators, dexamethasone intravitreal implant is ruled out by extended dominance for patients' with MO secondary to either BRVO or CRVO. PSAs demonstrate a high level of uncertainty around the base case results for both indications. However, there is a slightly higher likelihood of falling below the cost-effectiveness threshold in CRVO (see figures 5 and 7 above).

Two different types of deterministic sensitivity analysis have been carried out:

- One way deterministic sensitivity analysis on pre-specified model parameters;
- Scenario/structural analyses of: utility source, potential stopping rule and involvement of WSE.

The results of one way deterministic sensitivity analyses are provided for all comparisons made within the model. Parameters that are varied to an upper and lower limit are presented in tabular form (manufacturer's PAS submission; Tables 5b and 5c) and parameters that are varied across a range are

presented graphically (MS; Figures B21–B52). The manufacturer concludes in section 6.7.10 of the submission that the direction of the results of the deterministic analysis followed prior expectations.

Scenario analyses are conducted on the base case comparisons of ranibizumab versus GLP and BSC in MO secondary to BRVO and CRVO respectively. The results of these are summarised in Table 49, changing the source of utility, using utilities from Sharma *et al.* (reference not provided by the manufacturer), decreased the ICERs by £3,972 and £1,290, implementing a stopping rule for poor responders decreased the ICERs by £5,483 and £1,291 in BRVO and CRVO, respectively.

Table 49. Scenario analysis: BRVO (adapted from the MS; Table 5 with PAS)

Scenario	BRVO		
	Incremental costs	Incremental QALYs	Incremental cost per QALY
Base case	£ [REDACTED]	[REDACTED]	£20,494
Utilities for BSE, Sharma 2000 utilities (univariate)	£ [REDACTED]	0.339	£16,522
Stopping rule for poor responders	N/R	N/R	£15,011
Abbreviations used in table: BRVO, branch retinal vein occlusion; BSE, better-seeing eye; N/R, not reported; PAS, patient access scheme; QALYs, quality-adjusted life years.			

Table 50. Scenario analysis: CRVO (adapted from the MS; Table 5 with PAS)

Scenario	CRVO		
	Incremental costs	Incremental QALYs	Incremental cost per QALY
Base case	£ [REDACTED]	[REDACTED]	£8,643
Utilities for BSE, Sharma 2000 utilities (univariate)	£ [REDACTED]	0.576	£7,353
Stopping rule for poor responders	N/R	N/R	£7,352
Abbreviations used in table: BSE, better-seeing eye; CRVO, central retinal vein occlusion; N/R, not reported; PAS, patient access scheme; QALYs, quality-adjusted life years.			

The model was especially sensitive to the involvement of the WSE. The manufacturer analysed the assumptions surrounding the involvement of the WSE in a layered manner as follows:

- The manufacturer used two scenarios regarding the proportion of WSE involvement at baseline and 12 months:
 - **Scenario 1** (trial based): 5.2% BSE at baseline, 7.1% BSE at month 12;
 - **Scenario 2** (expected in clinical practice [assumption]): 10% BSE at baseline, 20% BSE at month 12.
- Using each scenario the manufacturer then varied the slope of the WSE utility curve, which was assumed to be flat (i.e., no benefit gained from treating the WSE) in the base case.

The results of these analyses (with PAS) are displayed in figures 9 to 12 below; the costs of blindness are applied only to patients who are blind in the BSE.

Figure 9. Deterministic sensitivity of slope of WSE utility curve in scenario 1 (BRVO)

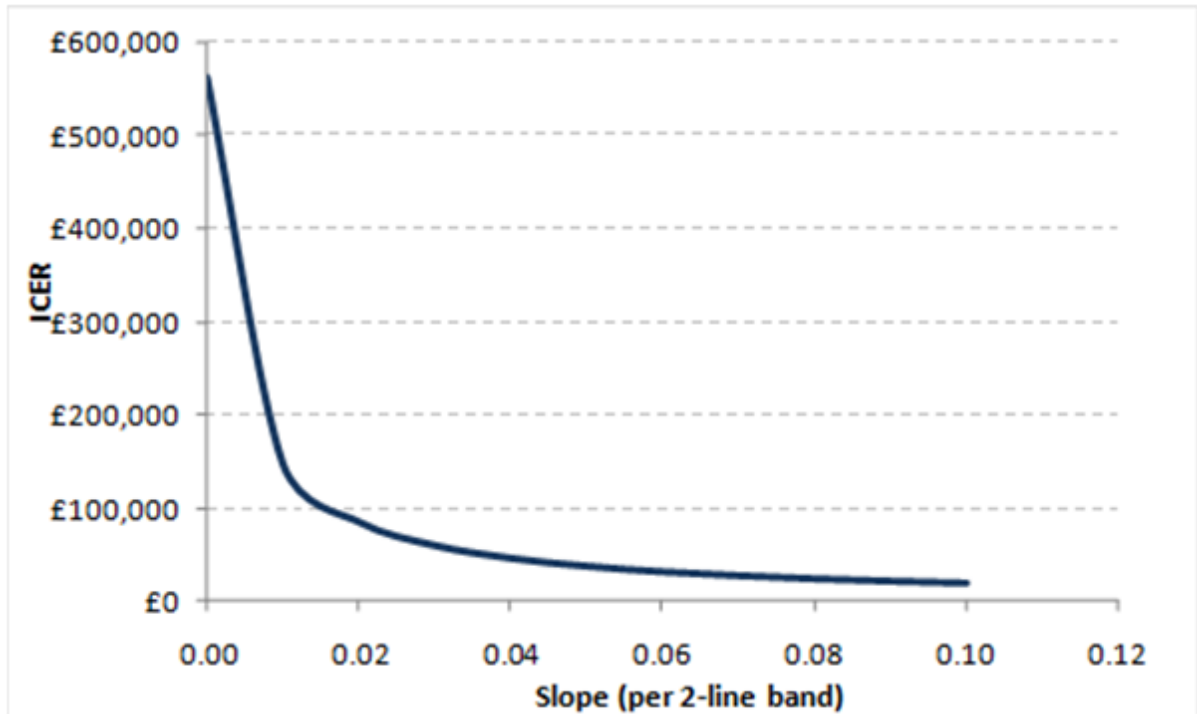
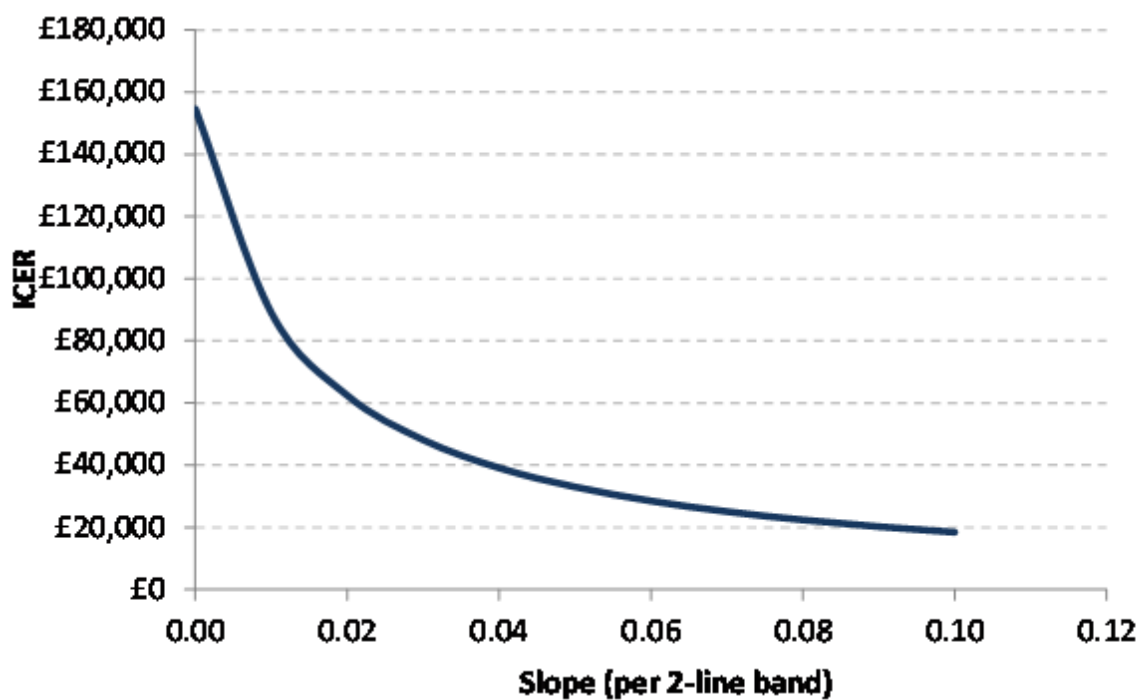


Figure 10. Deterministic sensitivity analysis of slope of WSE utility curve for scenario 2 (BRVO)



In MO secondary to BRVO, the incremental cost effectiveness ratios (ICERs) varied from £530,361 to £18,251 in scenario 1 and from £154,610 to £18,462 in scenario 2, with an ICER of below £30,000 being achieved with slopes of greater than 0.06, translating to a utility difference of approximately 0.4 from the best BCVA health state to the worst.

In MO secondary to CRVO, the ICERs varied from £301,603 to £12,038 in scenario 1 and from £92,047 to £11,745 in scenario 2, with an ICER below £30,000 being achieved with slopes of greater than 0.04, translating to a utility difference of approximately 0.28 from the best BCVA health state to the worst.

Figure 11. Deterministic sensitivity analysis of slope of WSE utility curve for scenario 1 (CRVO)

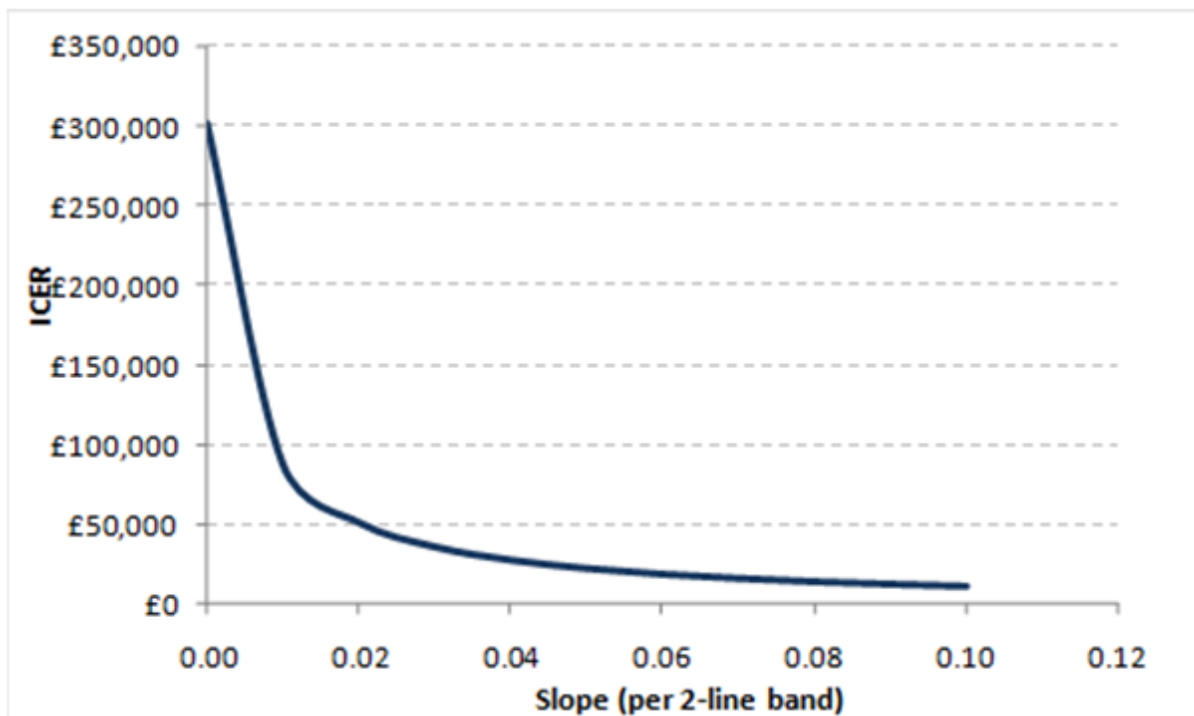
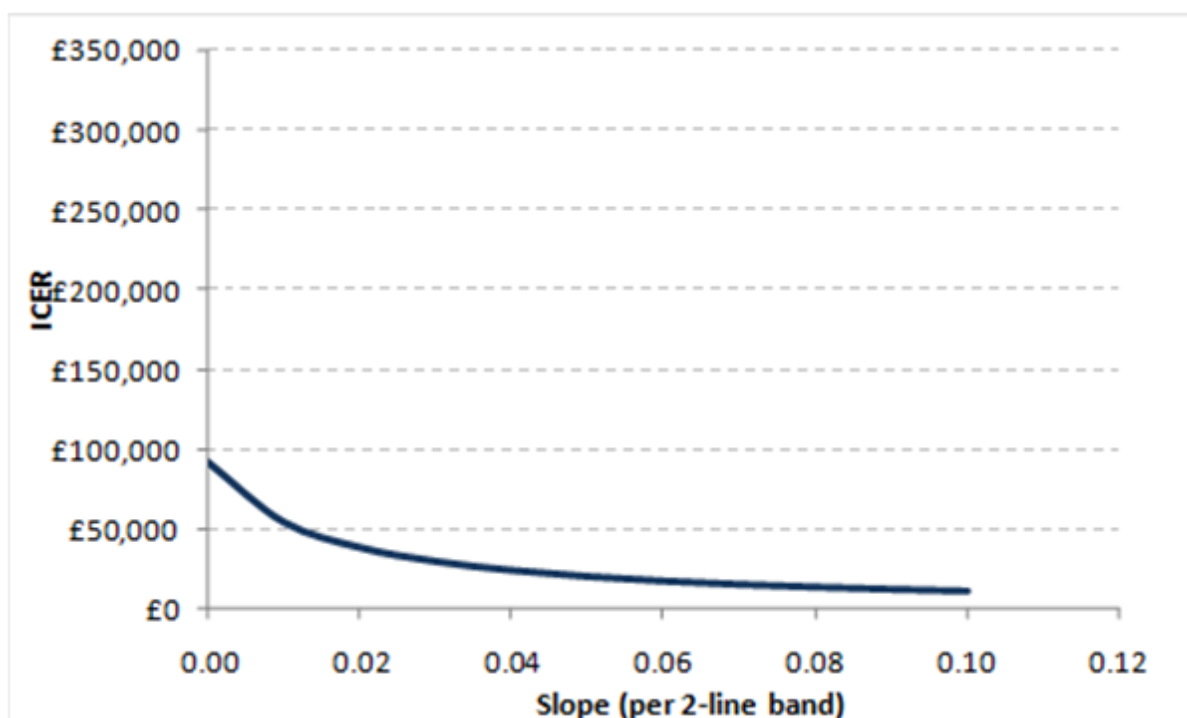


Figure 12. Deterministic sensitivity analysis of slope of WSE utility curve for scenario 2 (CRVO)



5.3.11 Model validation

The manufacturer reports that the methodological approach to economic modelling adopted in the manufacturer model was validated by two external reviewers, who undertook extensive analysis to assess the model for internal and external validity.

5.4 Critique of manufacturer’s economic evaluation

The manufacturer’s model is constructed in Microsoft® EXCEL with Visual Basic for Applications used for navigation and PSA. The model is generally well constructed, with appropriate calculation methods used throughout. The model is very flexible, allowing numerous scenario analyses to be conducted, using new and existing data. However, there were many hidden sheets and unlabelled tables, that reduced the transparency of the model and the use of data tables to generate the deterministic sensitivity analysis and the screen updating the PSA led to a slow running model in which it was difficult to see the impact of the probabilistic mode on the ICER.

5.4.1 NICE reference case checklist

Tables 51 and 52 summarise the ERG’s assessment of the manufacturer’s economic evaluation against the requirements set out in the NICE reference case checklist for a base case analysis. Generally, the manufacturer’s base case economic evaluation matches the reference case set out in the NICE ‘Guide to the Methods of Technology Appraisal’.⁽³⁵⁾ However, the decision problem described

in the final scope by NICE lists bevacizumab as a comparator; the manufacturer did not include bevacizumab as a comparator in the base case economic evaluation. The decision problem also lists an analysis of ischaemic patients and the assessment of the visual acuity of the whole person as an outcome; the manufacturer was unable to provide either of these.

Table 52 summarises the ERG’s appraisal of the manufacturer’s economic evaluation, using the Phillips checklist.⁽⁸⁶⁾ The ERG is of the opinion that the base case analysis is not applicable to the patient population, due to the assumption of a BSE patient population and the highly confounded nature of the data used to inform the comparison with GLP in MO secondary to BRVO.

Table 51. NICE reference case

Attribute	Reference case	Does the <i>de novo</i> economic evaluation match the reference case?
Decision problem	The scope developed by the National Institute for Health and Clinical Excellence	Broadly yes, but omits the following: <ul style="list-style-type: none"> analysis of ischaemic patients; comparison with bevacizumab; assessment of the visual acuity of the whole person
Comparator(s)	Alternative therapies routinely used in the NHS	Yes
Perspective costs	NHS and Personal Social Services	Yes
Perspective benefits	All health effects on individuals	Yes
Form of economic evaluation	Cost-utility analysis	Yes
Time horizon	Sufficient to capture differences in costs and outcomes	Yes
Synthesis of evidence on outcomes	Systematic review	The manufacturer used evidence from the results of systematic review. They did not perform meta-analysis or a network meta-analysis citing lack of homogeneous evidence. ERG could not verify the transition probabilities used by the manufacturer as the data used to calculate them were provided without accompanying explanation of the abbreviations used and also at a late stage in the appraisal process
Outcome measure	Quality adjusted life years	Yes
Health states for QALY	Described using a standardised and validated instrument	Partial. The manufacturer uses values from published literature that have been used in previous STAs. However, the ERG notes that the manufacturer did not use the recommended source of utilities from TA155 ⁽⁵⁸⁾
Benefit valuation	Time-trade off or standard gamble	Yes
Source of preference data for valuation of changes in HRQoL	Representative sample of the public	No. The sample was from people with various ocular conditions, of which 7% of the sample had RVO
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
Sensitivity analysis	Probabilistic sensitivity analysis	Yes. Sensitivity analysis, scenario analysis and probabilistic sensitivity analysis were all performed by the manufacturer
Abbreviations used in table: ERG, evidence review group; NHS, National Health Service; QALY, quality-adjusted life year; RVO, retinal vein occlusion; STA, single technology appraisal.		

Table 52. Phillips checklist

Dimension of quality	Yes/No	Comments
Structure		
S1: Statement of decision problem/objective	Yes	Clearly stated
S2: Statement of scope/perspective	Yes	The ERG notes that in the base case analysis the model assumes all patients are treated in the BSE, despite the fact that 91.7% and 90% of patients in BRAVO and CRUISE, respectively, were treated in their WSE. The ERG also notes that ischaemic patients are not included in this analysis
S3: Rationale for structure	Yes	The ERG considers the model to be overly complicated, with more health states than necessary to capture patient outcomes. The manufacturer assumed no excess mortality due to RVO, the ERG disagrees with this assumption
S4: Structural assumptions		The manufacturer assumed no excess mortality due to RVO; the ERG disagrees with this assumption. The ERG notes that the exploratory approach to the inclusion of dexamethasone may be biased towards ranibizumab
S5: Strategies/comparators		The ERG feels that the reasons given for excluding bevacizumab are inadequate. Also the ERG is of the opinion that a comparison of ranibizumab alone versus GLP is not possible based solely on evidence from BRAVO since the results are confounded by the use of GLP in both arms
S6: Model type		Correct
S7: Time horizon		15 years is long enough
S8: Disease states/pathways		The ERG suggests that fewer health states that correspond to the BCVA categories used at randomisation, which are: ≤ 34 letters, 35–54 letters, and ≥ 55 letters would be more appropriate
S9: Cycle length		Correct (one month)
Data		
D1: Data identification		This was clearly described, including where expert opinion was sought
D2: Premodel data analysis		Correctly described except for minor typographical errors on some formulae
D2a: Baseline data		Baseline data were taken from the BRAVO and CRUISE trials. Half-cycle correction was correctly implemented
D2b: Treatment effects		The ERG is concerned that the transition probabilities were derived from individual patient data, which the ERG was unable to validate. The ERG was also unable to validate the calculations of the RRs of treatment with dexamethasone, and is concerned that these are biased towards ranibizumab. The ERG is also concerned that by assuming the effect of treatment will decline at the same rate between GLP and ranibizumab the manufacturer has failed to recognise that the effects of GLP will last longer than suggested. It is unclear from the data whether the effect of treatment will continue as assumed in the base case, however the manufacturer has conducted sensitivity analysis around this
D2d: Quality of life weights (utilities)		Derived from literature and well referenced. However, the ERG notes that the manufacturer did not use data from Brazier <i>et al.</i> ⁽⁴⁰⁾ , a source that was recommended for ocular conditions in TA155 ⁽⁵⁸⁾

D3: Data incorporation		The use of unpublished patient level data prevented validation of the majority of the data used in the model, also the method process of incorporating dexamethasone relative effect were not described in enough detail to be validated
D4: Assessment of uncertainty		A few minor errors in the formulae. However, the assessment of sensitivity was thorough and robust
D4a: Methodological		The ERG suggested the manufacturer consider use the primary endpoint of 15 letters in place of 10 letters, which the manufacturer did not carry out
D4b: Structural		Deterministic sensitivity analysis and scenario analysis were described in detail by the manufacturer
D4c: Heterogeneity		This was addressed by considering people with different visual acuity levels
D4d: Parameter		Probabilistic sensitivity analysis was done to the satisfaction of the ERG
Consistency		
C1: Internal consistency		The model seems to be mathematically sound
C2: External consistency		The model has been calibrated against the results of BRAVO and CRUISE and the ERG is satisfied that any inconsistencies have been explained and justified
Abbreviations used in table: BCVA, best corrected visual acuity; BSE, better-seeing eye; ERG, evidence review group; GLP, grid laser photocoagulation; MO, macular oedema; RVO, retinal vein occlusion; WSE, worse-seeing eye.		

5.4.2 Model structure

The ERG considers the model structure to be overly complicated, with more health states than necessary to capture patient outcomes and therefore the potential to overestimate utility gains. As part of the clarification process, the ERG requested scenario analysis in which the model uses the pre-specified trial outcome of a gain/loss of ≥ 15 letters rather than the analysis of 10 or more letters. The manufacturer failed to provide the requested analysis, citing time constraints.

The ERG conducted a scenario analysis using utilities from Brazier *et al.*⁽⁴⁰⁾, which reports four utility values for mild, moderate and severe visual impairment (discussed further in section 5.4.4). Applying fewer utility differences across the health states inflated the ICER, adding weight to the theory that health benefits may be over estimated. However, this supposition cannot be confirmed without recalibration of the model with the utility values of Brazier *et al.*⁽⁴⁰⁾, which would require patient level data.

5.4.3 Population

Ischaemic patients

The manufacturer highlights that most ischaemic patients were excluded from the BRAVO⁽¹⁵⁾ and CRUISE⁽¹⁶⁾ trials, as a result of the exclusion criteria of brisk afferent pupillary defect (MS; pg 171); which they state equates to severe retinal ischaemia. As such, the ERG considers that the results of this economic analysis are applicable to only patients with MO secondary to non-ischaemic RVO (see section 4.2.2 for more details).

Worse-seeing eye patients

In the base case analysis, the model assumes all patients are treated in the BSE, despite the fact that 91.7% and 90.0% of patients in BRAVO⁽¹⁵⁾ and CRUISE,⁽¹⁶⁾ respectively, were treated in their WSE. The manufacturer's rationale for this approach to modelling is two-fold. Firstly, the manufacturer argues that whilst considerable HRQoL gains (assessed with the NEI-VFQ 25 questionnaire) were observed in both BRAVO⁽¹⁵⁾ and CRUISE,⁽¹⁶⁾ the paucity of data for WSE utility along with the unavailability of utility data from the trials means that utility changes in the WSE eye cannot be accurately modelled. Secondly, the manufacturer uses the STAs in AMD: TA155⁽⁵⁸⁾ and TA068⁽⁸⁷⁾ as precedents for using a BSE model as a framework for decision making in the WSE. The manufacturer acknowledges that the rate of bilateral involvement in RVO is substantially lower than in wet AMD, but alleges that RVO patients are at risk of other ocular conditions and therefore the precedents of TA155⁽⁵⁸⁾ and TA068⁽⁸⁷⁾ hold (MS; pg 186).

The ERG is unaware of any evidence suggesting that patients with RVO are at higher risk of developing ocular conditions compared with the general population. Furthermore, MO secondary to RVO is predominantly a unilateral condition, as opposed to wet AMD, where approximately 70% of patients present with both eyes affected.⁽⁵⁸⁾ For these reasons, the ERG considers it inappropriate to use either TA155⁽⁵⁸⁾ or TA068⁽⁸⁷⁾ as a precedent for this indication. The ERG agrees that there is a need for further research into the impact of visual acuity in the WSE on utility; however, it is not reasonable to assume equivalent gains in utility and reductions in costs as that seen in treating a patient in their BSE.

5.4.4 Health related quality of life

Better seeing eye/worse-seeing eye

In the base case, the manufacturer assumes that 100% of patients receive treatment in their BSE. As mentioned above, the ERG does not accept the use of a BSE model to inform decisions around treatment of the WSE. However, the manufacturer has designed the model to be fully flexible with regard to the analysis of BSE/WSE and allows the user to assume any distribution of patients across BSE and WSE classifications. The assumptions surrounding the application of costs of blindness and method of utility calculation are also fully flexible and ERG notes that the excess risk of mortality associated with visual impairment in the BSE correctly applied.

Consequently, the ERG was able to conduct several scenario analyses involving the assumptions surrounding the costs and utilities of treating the BSE/WSE, based on the BSE/WSE distributions used by the manufacturer in their deterministic analysis of WSE utility (MS; pg 285).

Table 55 lists all the scenario analyses considered by the ERG around the sources, assumptions and distributions of the BSE/WSE.

Better-seeing eye utilities

The utility values for visual acuity in the BSE are taken from Brown *et al.*⁽⁷³⁾ rather than the study by Brazier *et al.*⁽⁴⁰⁾ previously recommended by NICE in TA155.⁽⁵⁸⁾ The systematic search conducted by the manufacturer for HRQoL data did not include the study by Brazier *et al.*⁽⁴⁰⁾, due to the search being limited to RVO (see section 4.1.1 for more details). Upon request, the manufacturer confirmed that Brown *et al.*⁽⁷³⁾ was chosen as the source for BSE utility values since Brazier *et al.*⁽⁴⁰⁾ is specific to visual impairment arising from wet AMD; however, only 7% of the patient population in Brown *et al.*⁽⁷³⁾ had RVO as their underlying ocular condition.

The ERG is of the opinion that the Brazier *et al.*⁽⁴⁰⁾ study should be used as the source for utility associated with visual acuity in the BSE in this assessment, since expert clinical opinion from both the manufacturer and the ERG concur that the utility associated with visual acuity is applicable across vision disorders (MS; pg 226). Indeed Brown *et al.*⁽⁷³⁾ also conclude that “utility values are much more dependent on the level of visual loss in the better-seeing eye than on the underlying ocular disease process itself”.

Superseded – see
erratum

Table 53. Better-seeing eye utility values (Brazier *et al.*⁽⁴⁰⁾)

Visual acuity	TTO value
≥20/40	0.706
20/40 to 20/80	0.681
20/80 to 20/400	0.511
≤20/400	0.314

Abbreviations used in table: TTO, time trade off.

The ERG conducted scenario analyses (Table 55) using the utility values from Brazier *et al.*⁽⁴⁰⁾ (displayed in Table 53). Some simplifying assumptions were made surrounding the application of a smaller set of utility values to a larger number of health states; these assumptions are summarised in Table 54.

Table 54. The implementation of utility values from Brazier *et al.*⁽⁴⁰⁾

Visual acuity health state	Base case utility	Brazier utility
86–100 letters (20/16–20/10)	0.920	0.706
76–85 letters (20/32–20/20)	0.880	0.706
66–75 letters (20/64–20/40)	0.770	0.681
56–65 letters (20/80–20/50)	0.755	0.681
46–55 letters (20/125–20/80)	0.670	0.511

36–45 letters (20/200–20/125)	0.665	0.511
26–35 letters (20/320–20/200)	0.645	0.511
<25 letters (<20/320)	0.510	0.314

The manufacturer also conducted a scenario analysis using utility values from Brazier *et al.*⁽⁴⁰⁾, although the assumptions surrounding the application of the Brazier utilities were not specified.

Worse-seeing eye utilities

The manufacturer’s model assumes a flat curve for utility associated with visual acuity in the WSE, that is, no benefit is afforded from treating the WSE. The ERG does not consider this to be a fair reflection of the benefit associated with treating a patient in their WSE. A previous STA has suggested a 0.1 decrement in utility associated with blindness in the WSE.⁽⁵⁸⁾ The ERG conducted several scenario analyses in which it was assumed that the utility associated with visual acuity of 86–100 in the WSE is equivalent to the utility associated with visual acuity of 86–100 in the BSE and that the slope of the WSE utility curve of 0.014 thereafter (equivalent to an overall utility loss of 0.1, listed in Table 55).

Scenario analyses

The ERG conducted extensive scenario analysis around the utility sources, assumptions and distribution of patients requiring treatment in their BSE or WSE. Table 55 summarises the scenarios considered by the ERG.

Table 55. Better-seeing eye/worse-seeing eye scenario analyses

Scenario	% BSE at baseline	% BSE at 12 months	BSE utility source	Slope of WSE utility curve	Utility assumption used	Costs of blindness
Testing the impact of BSE/WSE distribution on the base case						
A	10	20	Brown	Flat	Combination of BSE and WSE	Applied to only BSE
B	10	20	Brown	Flat	BSE only	Applied to only BSE
C	5.2	7.1	Brown	Flat	Combination of BSE and WSE	Applied to only BSE
D	5.2	7.1	Brown	Flat	BSE only	Applied to only BSE
Testing the impact of Brazier utilities on the base case						
E	100	100	Brazier	Flat	BSE only	Applied to only BSE
Testing the impact of BSE/WSE distribution on the model using Brazier utilities						
F	10	20	Brazier	Flat	Combination of BSE and WSE	Applied to only BSE
G	10	20	Brazier	Flat	BSE only	Applied to only BSE
H	5.2	7.1	Brazier	Flat	Combination of BSE and WSE	Applied to only BSE
I	5.2	7.1	Brazier	Flat	BSE only	Applied to only BSE

Testing the impact of the assumption of a 0.1 overall benefit of treating the WSE						
J	10	20	Brown	0.014 ^a	Combination of BSE and WSE	Applied to only BSE
K	5.2	7.1	Brown	0.014 ^a	Combination of BSE and WSE	Applied to only BSE
Testing the effect of the assumption of a 0.1 overall benefit of treating the WSE on the model using Brazier utilities						
L	10	20	Brazier	0.014 ^a	Combination of BSE and WSE	Applied to only BSE
M	5.2	7.1	Brazier	0.014 ^a	Combination of BSE and WSE	Applied to only BSE
^a Assuming a 0.014 slope of the WSE utility curve translates to an overall utility decrement of 0.1 between the best and worst health BCVA in the WSE. Abbreviations used in table: BSE, better-seeing eye; WSE, worse-seeing eye.						

The results of these and all other scenario analyses are reported in section 6.

Age adjustment

The manufacturer's model assumes utilities are independent of age and the manufacturer states that age adjustment is expected to have minimal impact on resultant ICERs. As part of the clarification process, the ERG requested an updated economic model in which utilities are age adjusted. In their response to clarification questions, the manufacturer presented arguments against performing such an adjustment maintaining that there would be minimal impact to ICERs. To support this argument, the manufacturer provided a standardised table, based on UK population norm utilities,⁽⁸⁸⁾ using the mean age reported in the Brown *et al.*⁽⁷³⁾ study as an index (Table 56).

Table 56. Standardised utility proposed by the manufacturer

Age (years)	UK population norm utilities ⁽⁸⁸⁾	Utility indexed on mean age ^{(73)a}
<25	0.94	1.21
25–34	0.93	1.19
35–44	0.91	1.17
45–54	0.85	1.09
55–64	0.80	1.03
65–74	0.78	1.00
75 and over	0.73	0.94
^a Utility indexed on mean age reported in Brown <i>et al.</i> ⁽⁷³⁾ (67.5 years = 1.00).		

The manufacturer states in their clarification response that the slight downward adjustment that would be required once the cohort reaches 75 would have minimal impact on the ICER.

The ERG is concerned that the manufacturer's standardisation approach to age adjustment would fail to account for the difference between the UK and US patient populations: Brown *et al.*⁽⁷³⁾, BRAVO⁽¹⁵⁾ and CRUISE⁽¹⁶⁾ are largely based in the US. A standard multiplicative approach to age adjustment would be more applicable. The ERG notes that age adjustment of the utilities values presented by Brazier *et al.*⁽⁴⁰⁾ is not necessary since age is adjusted for in the analysis.

Adverse events

Based on the evidence presented by the manufacturer, the ERG agrees with the manufacturer that the overall incidence of serious AEs was low in both the treatment and comparator arms of BRAVO,⁽¹⁵⁾ CRUISE⁽¹⁶⁾ and HORIZON⁽⁵²⁾ and that AEs were correctly incorporated in the model. However, the ERG is concerned that the manufacturer did not use safety data from the HORIZON extension study in the model, citing low incidence of events. HORIZON reports a slightly higher incidence of AEs than BRAVO⁽¹⁵⁾ and CRUISE,⁽¹⁶⁾ particularly transient ischaemic attack and myocardial infarction, suggesting that RVO patients may indeed be at a higher risk of cardiovascular death than the general population (this is discussed further in section 5.4.7).

5.4.5 Interventions and comparators

The ERG notes that by not attempting to carry out a comparison with bevacizumab the manufacturer has not conformed to the scope of the decision problem issued by NICE (29). The manufacturer's rationale for the exclusion of a comparison with bevacizumab is based on various factors: (i) the manufacturer states that the guidelines published by the RCO do not recommend bevacizumab in BRVO or CRVO; (ii) bevacizumab is not routinely used in clinical practice in the NHS; and (iii) there are no reliable efficacy data for bevacizumab in MO secondary to either BRVO or CRVO.

On the first point, the ERG refers to the RCO guidelines, which state that, in relation to the use of bevacizumab in CRVO, "GMC Guidelines on 'Good Medical Practice' as it relates to the use of both off-label and unlicensed medications and the manufacturer's advice should guide physician directed intraocular use" and, in relation to the use of bevacizumab in BRVO, "No recommendations on the use of intravitreal bevacizumab can be made at this time".⁽¹⁾ The ERG is of the opinion that the RCO guidelines are not making recommendations based on the current evidence, rather than stating that bevacizumab is not recommended.

In relation to the point that bevacizumab is not routinely used in the NHS, the RCO guidelines⁽¹⁾ also state on page 43 that "it [bevacizumab] has been used extensively in clinical practice with some success, for the management of many retinal conditions that have a VEGF driven pathophysiology, despite a lack of randomised controlled, clinical trial evidence". The ERG responsible for reviewing the manufacturer's submission to NICE for ranibizumab in DMO⁽⁸⁹⁾ also expressed the opinion that bevacizumab is used sufficiently in the NHS to warrant comparison.

The ERG agrees with the manufacturer that an indirect comparison with bevacizumab in MO secondary to CRVO is not possible with the data currently available from RCTs and that there are differences in the trials identified in MO secondary to BRVO, but disagrees that these differences preclude qualified comparison. As discussed in section 4.4.2 the ERG has conducted an exploratory

indirect comparison of ranibizumab versus bevacizumab as part of a mixed treatment comparison. The direction of bias for this comparison is thought to be towards ranibizumab and results in a 3 letter improvement of ranibizumab over bevacizumab at month 3. The ERG is of the opinion that this translates to a difference between ranibizumab and Bevacizumab that is not clinically meaningful. Additionally, the safety concerns raised by the manufacturer around bevacizumab (MS; pg 160), are discussed in section 4.3.4. The ERG notes that there is insufficient evidence to suggest a difference in the safety profile of ranibizumab and bevacizumab in RVO and considers that it is reasonable to assume equivalent safety profiles for ranibizumab and bevacizumab. Consequently, the ERG have conducted a cost minimisation analysis of ranibizumab versus bevacizumab, using the price of £50 per month used in the report of the ERG responsible for reviewing Allergan's submission to NICE for dexamethasone intravitreal implant in diabetic MO⁽⁸⁹⁾ and the PAS price of ranibizumab⁽³⁹⁾. In addition to this the ERG conducted a threshold analysis to investigate the level of efficacy required of ranibizumab to result in ICERs of £30,000, by applying a range of treatment effect multipliers to the baseline efficacy of ranibizumab at month 1 and at months 2 to 6 (see section 6 for results).

5.4.6 Treatment effectiveness

As mentioned in section 5.3.5, the transition probabilities used in the economic evaluation were calculated from the unpublished individual patient level data of BRAVO⁽¹⁵⁾ and CRUISE.⁽¹⁶⁾ These data were not present in the submitted Microsoft[®] EXCEL version of the model and the manufacturer was asked to provide them for the purposes of validation. The manufacturer initially provided these data in non-standard statistical software (SAS) and later in EXCEL. The data in EXCEL have no accompanying explanation, which made it difficult for the ERG to evaluate the data. Consequently, the ERG was unable to validate any of the transition probabilities used in the model.

Critique of the manufacturer's approach to modelling ranibizumab versus grid laser photocoagulation (standard care) in MO secondary to BRVO

As discussed in section 4.3.1, the ERG notes that a comparison of ranibizumab alone versus GLP from the results presented in BRAVO is not possible for the following reasons:

- The effects of GLP and ranibizumab are confounded by the use of GLP in both arms;
- The use of GLP in the sham arm does not represent the use of GLP in clinical practice as all patients in the sham arm would have been eligible for GLP after having MO for 3 months;
- There is insufficient evidence to conclude that GLP has no effect in the ranibizumab arm;
- The treatment period of the BRAVO trial is insufficient to capture any benefits of GLP on patient outcomes.

The implication of using patient level data from the BRAVO trial to inform an economic evaluation of ranibizumab versus GLP (standard care in MO secondary to BRVO) is that the treatment effect of ranibizumab may be overestimated, as a consequence of the use of GLP in [REDACTED] of patients in the ranibizumab group. Conversely, the effect of GLP may be underestimated as only [REDACTED] of patients received GLP in the sham arm, resulting in an overall bias towards ranibizumab.

The manufacturer attempts to account for the effect of GLP by pooling the transition probabilities calculated during the observation phase of the trial (months 7 to 12). The ERG notes that such pooling would have an inflationary effect on the efficacy of ranibizumab, because the benefit seen in patients in the sham arm who received ranibizumab therapy would be added to the continued effect of ranibizumab therapy in those patients initially randomised to receive ranibizumab, a point also raised in the manufacturer’s response to clarification. Similarly, the reapplication of these pooled probabilities to months 13 to 24 would continue to inflate the efficacy of ranibizumab. It is unclear whether this approach would underestimate or overestimate the effect of GLP.

As part of the clarification process, the manufacturer was asked to provide the unpooled transition probabilities for both arms for months 7 to 12; these are displayed in Table 57. The ERG conducted sensitivity analyses to assess the effect on the overall ICER of using unpooled transition probabilities at:

1. Months 7 to 12;
2. Months 13 to 24;
3. Months 7 to 12 and 13 to 24.

The ICER obtained for ranibizumab versus GLP (standard care) in MO secondary to BRVO rose to £52,004 in the first analysis and ranibizumab was dominated in the remaining analyses. This confirmed the supposition that this approach inflated the effect of ranibizumab. However, the impact of this approach on the effect of GLP remains unknown.

Table 57. 7 to 12 month transition probabilities from BRAVO patient level data

Transition	Probabilities		
	Ranibizumab	Sham	Pooled
Gain >4 lines	[REDACTED]	[REDACTED]	[REDACTED]
Gain 2 to 4 lines	[REDACTED]	[REDACTED]	[REDACTED]
No change	[REDACTED]	[REDACTED]	[REDACTED]
Lose 2 to 4 lines	[REDACTED]	[REDACTED]	[REDACTED]
Lose >4 lines	[REDACTED]	[REDACTED]	[REDACTED]

The ERG notes that the application of the same natural deterioration rate to both arms at the same time would underestimate the effect of GLP, as there is evidence suggesting that improvements in visual acuity post GLP may continue to be seen for as long as 3 years post treatment.⁽¹⁴⁾ The ERG

conducted a sensitivity analysis that delayed the application of natural deterioration to patients in the sham arm for one year, which resulted in a marginally higher ICER of £20,675.

In summary, the ERG does not consider the manufacturer's model to represent a comparison between ranibizumab monotherapy and GLP (standard care) in MO secondary to BRVO. The ERG conducted an indirect comparison of ranibizumab versus GLP at month 3, via the bevacizumab versus sham analysis of Moradian *et al.*⁽³⁷⁾ (see section 4.4.2 for more details). The direction of bias in this analysis was likely to be towards ranibizumab and the result was an improvement of 8 letters for ranibizumab at month 3 compared with GLP. However, the benefit of GLP is seen in the long rather than the short term.⁽¹⁴⁾

The structure of the model is such that it is not possible to incorporate the results of the indirect comparison (which uses improvement in 15 letters rather than the 10 letter used in the base case model) and consequently a valid comparison of ranibizumab with GLP has not been established in this indication. The pilot trial of RABAMES⁽⁵⁶⁾ (discussed in section 4.3.1) may provide further information that could be used to inform this comparison, at least in the short term.

The ERG's proposed model application of immediate versus delayed ranibizumab treatment

The ERG notes that a model based solely on evidence from the BRAVO trial may be best used to inform decisions regarding the delay of treatment with ranibizumab alongside rescue GLP. To evaluate further the cost effectiveness of immediate versus delayed ranibizumab therapy with concomitant GLP, the ERG conducted an additional analysis using the unpooled transition probabilities provided by the manufacturer. In this analysis, the ERG:

1. Applied the 7 to 12 month transition probabilities from the ranibizumab arm of the BRAVO trial to the ranibizumab arm of the model;
2. Assumed no transitions for month 13 to 24;
3. Added the cost of GLP administration in the [REDACTED] of patients from the ranibizumab arm of BRAVO receiving GLP, to the ranibizumab arm of the model;
4. Collated the costs and QALYs obtained from the ranibizumab arm under conditions 1 to 3 under the heading of immediate treatment;
5. Applied the transition probabilities from the sham arm of the BRAVO trial for months 0 to 1, 2 to 6 and 7 to 12 to the ranibizumab arm of the model;
6. Assumed no transitions for months 13 to 24;
7. Adjusted the number of ranibizumab injections to be the mean number received by patients in the sham arm of the BRAVO trial;

8. Added the cost of GLP administration in the [REDACTED] of patients from the sham arm of BRAVO receiving GLP to the ranibizumab arm of the model;
9. Collated the costs and QALYs obtained from the ranibizumab arm under conditions 5 to 7 under the heading of delayed treatment;
10. Calculated the ICER.

The results of this analysis are presented in section 6.

Continuation of treatment

The ERG notes that the unpooled transition probabilities revealed a decline in effect of ranibizumab when patients switched to receiving ranibizumab PRN (Table 58), suggesting that continuous treatment may be required for longer than 6 months, or perhaps a longer duration of treatment overall. This concern was also raised in the ERG report for ranibizumab in diabetic MO⁽⁸⁹⁾ and would of course have serious cost implications. The ERG investigated the sensitivity of the immediate versus delayed treatment model proposed above to the maintenance of PRN treatment for up to 15 years.

Table 58. A comparison of ranibizumab transition probabilities of continuous versus PRN treatment in MO secondary to BRVO

Transitions	Rani continuous (months 2 to 6)	Rani PRN (months 7 to 12)
Gain >4 lines	[REDACTED]	[REDACTED]
Gain 2 to 4 lines	[REDACTED]	[REDACTED]
No change	[REDACTED]	[REDACTED]
Lose 2 to 4 lines	[REDACTED]	[REDACTED]
Lose >4 lines	[REDACTED]	[REDACTED]
Abbreviations used in table: BRVO, branch retinal vein occlusion; MO, macular oedema; PRN, <i>pro re nata</i> ; Rani, ranibizumab.		

Ranibizumab versus best supportive care in MO secondary to CRVO

The ERG has few concerns regarding the manufacturer’s approach to evaluating the comparative treatment effect of ranibizumab versus best supportive care in MO secondary to CRVO. The ERG notes that the approach taken is as comprehensive as the evidence allows. The ERG considers the reapplication of transition probabilities for months 2–6 to months 7–24 is conservative as CRVO patients may spontaneously resolve in the first 3 months (see section 2.1 for more detail).

The principal concern the ERG has regarding the analysis of CRVO relates to assumed cessation of therapy at two years, since, as with MO secondary to BRVO, the transition probabilities of continuous ranibizumab therapy compared with PRN therapy suggest a decline in treatment effect (Table 59). The ERG conducted a sensitivity analysis around the maintenance of PRN therapy in MO secondary to CRVO for up to 15 years.

Table 59. A comparison of ranibizumab transition probabilities of continuous versus PRN treatment in MO secondary to CRVO

Transitions	Rani continuous (months 2 to 6)	Rani PRN (months 7 to 12)
Gain >4 lines		
Gain 2 to 4 lines		
No change		
Lose 2 to 4 lines		
Lose >4 lines		
Abbreviations used in table: CRVO, central retinal vein occlusion; MO, macular oedema; PRN, <i>pro re nata</i> ; Rani, ranibizumab.		

The ERG also notes that the assumption employed by the manufacturer in the base case analysis, that transitions are independent of current visual acuity is not conservative, since whilst the effect of ranibizumab is underestimated, so is the effect of best supportive care, but to a larger extent (Table 60). The manufacturer’s model is flexible regarding this assumption and allows the user to employ transition probabilities calculated on the assumption that transitions are dependent on current visual acuity, which yields an ICER of £13,249 for patients with MO secondary to CRVO.

Table 60. Summary of model results compared with clinical data (adapted from Table B71 of MS)

Outcome	Clinical trial result	Model result	Difference (Model result – Clinical trial result)
Visual acuity at baseline – ranibizumab	48.1	52.52	+4.42
Visual acuity at baseline – observation	49.2	48.43	-0.77
Visual acuity at month 6 – ranibizumab	63.0	61.79	-1.21
Visual acuity at month 6 – observation	50.0	50.55	+0.55
Visual acuity at month 12 – ranibizumab	62.0	62.40	+0.4
Visual acuity at month 12 – observation	56.5	52.11	-4.39
Visual acuity at month 24 – ranibizumab	57.9	62.98	+5.08
Visual acuity at month 24 – observation	52.3	54.24	+1.94

The ERG considers that the evidence available from CRUISE could also be used to analyse the impact of delaying treatment with ranibizumab in patients with MO secondary to CRVO. However, without access to IPD the ERG was unable to formulate the month 7 to 12 transition probabilities for the sham arm required to permit this analysis.

Ranibizumab versus dexamethasone intravitreal implant in MO secondary to BRVO and CRVO

The ERG agrees with the manufacturer that the inclusion of dexamethasone intravitreal implant in this analysis is exploratory and should be treated with caution. As part of the clarification process the manufacturer provided a detailed description of the methodology used to calculate the RRs of treatment effect for dexamethasone intravitreal implant in comparison with sham injection. However, the manufacturer did not provide sufficient detail of the application of this methodology for the ERG to replicate the calculation of the RRs used in the model. However, the RRs calculated by the ERG based on the manufacturer’s description of the methodology were higher than those used by the manufacturer and as such the ERG is concerned that the manufacturer has not been conservative in their approach (Tables 61 and 62).

Table 61. Relative risks (RR) for dexamethasone intravitreal implant: BRVO

Transition	BRVO			
	RR used in the model	ERG RR		
		Month 1	Month 2	Month 3
Gain >4 lines	████	3.54	2.80	3.43
Gain 2 to 4 lines	████	1.78	1.51	N/A
Lose 2 to 4 lines	████	0.24	0.27	N/A
Lose >4 lines	████	0.23	0.15	1

Abbreviations used in table: BRVO, branch retinal vein occlusion; ERG, evidence review group; N/A, not available; RR, relative risk.

Table 62. Relative risks (RR) for dexamethasone intravitreal implant: CRVO

Transition	CRVO			
	RR used in the model	ERG RR		
		Month 1	Month 2	Month 3
Gain >4 lines	████	2.04	2.12	1.42
Gain 2 to 4 lines	████	1.37	1.44	1.15
Lose 2 to 4 lines	████	0.60	0.59	0.80
Lose >4 lines	████	0.41	0.38	0.69

Abbreviations used in table: CRVO, central retinal vein occlusion; ERG, evidence review group; RR, relative risk.

The ERG conducted an indirect comparison of ranibizumab versus dexamethasone intravitreal implant, which provided relative risks of an improvement of 10 letters or more (2 lines) for patients with MO secondary to BRVO and to CRVO (see section 4.4.2 more details). The model structure did not lend itself to inclusion of the results from this indirect comparison. However, the ERG compared the relative risks obtained from the indirect comparison with the relative probability of improving between 2 and 4 lines presented in the manufacturer’s model, these are summarised in Table 63.

Table 63. Relative risk (RR) of ranibizumab compared with dexamethasone intravitreal implant in patients (RR <1 favours ranibizumab, RR >1 favours dexamethasone intravitreal implant)

		Probability of gaining 10 letters (2 lines) or more		RR
		Ranibizumab	Dexamethasone	
BRVO	Manufacturer's model	0.31	0.17	0.55
	ERG indirect comparison	–	–	0.79
CRVO	Manufacturer's model	0.23	0.07	0.30
	ERG indirect comparison	–	–	0.4

Abbreviations used in table: BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion; ERG, evidence review group; RR, relative risk.

The relative risks calculated from the manufacturer's model are more favourable to ranibizumab in both BRVO and CRVO, than the relative risks calculated from the ERG's indirect comparison. Considering the fact that the ERG's indirect comparison was known to be biased towards ranibizumab, this suggests the manufacturer's approach to modelling dexamethasone was largely biased towards ranibizumab.

5.4.7 Mortality

The ERG notes that the evidence of no significant risk of increased mortality attributable to RVO presented by the manufacturer is inconclusive. The study by Christoffesen *et al.*⁽⁸³⁾ in Danish patients with BRVO reports a statistically non-significant difference in mortality between BRVO patients and the general population. However, a range of results have been previously reported: the Beijing eye study by Xu *et al.*⁽²⁵⁾ reported a 95% CI of 0.995 to 8.26 for the mortality rate of patients with RVO and who were less than 70 years of age, and the US based analysis by Cugati *et al.*⁽²⁴⁾ reported a HR of cardiovascular mortality associated with RVO of 2.5 (95% CI: 1.2 to 5.2) in patients younger than 70 (Mean age of patients in BRAVO and CRUISE is in the range of 65.2-67.6 at baseline). The UK-based study of Tsaloumas *et al.*⁽²⁶⁾ found that patients with RVO were at a statistically significant greater risk of death from myocardial infarction than the general population (23.1% in RVO population vs 14.4% in general population, $p < 0.05$, translating to a RR of 1.6). The ERG considers that the RR of 1.6 reported in Tsaloumas *et al.*⁽²⁶⁾ is the most applicable to the UK population and should be implemented in the base case model.

The ERG also notes that the mortality risk associated with "some" visual impairment reported in Christ *et al.*⁽⁷²⁾ should be applied to patients experiencing visual impairment in their WSE, in accordance with the definition of "some" visual impairment used in the study, which includes patients "Blind or visually impaired in one eye only, with the other eye having good vision or not mentioned".

5.4.8 Time horizon

The manufacturer’s model adopts a 15-year time horizon in this indication, with the justification that “15 years is considered a sufficient period to reflect the time to reach, or avoid, severe visual impairment and blindness and for the impact on costs and quality of life to be assessed” (MS; pg 190). The ERG agrees with the manufacturer that this is an appropriate time horizon considering the mean age of patients in BRAVO⁽¹⁵⁾ and CRUISE⁽¹⁶⁾ is lower than that of MARINA⁽⁹⁰⁾ and ANCHOR⁽⁹¹⁾ (66 years vs 77 years).

5.4.9 Resources and costs

The manufacturer was transparent with respect to the resource use and costs applied in the model, providing HRG codes were necessary. The ERG is satisfied that the correct costs were used and the assumptions surrounding resource use were reasonable.

5.4.10 Sensitivity analyses

The manufacturer conducted extensive deterministic and structural sensitivity analysis, the most useful of which were those assessing the sensitivity of the model to the assumptions surrounding the utility associated with the WSE. The only point the ERG would like to raise concerning the manufacturer’s approach to sensitivity analysis relates to the PSA. The ERG notes that the sensitivity of the model to the utility differences between the BCVA health states should have been assessed. The manufacturer varied each health state utility by a multiplier sampled from a Normal distribution; $N(1,0.05)$, which effectively varied the utility value of each health state by the same amount and in the same direction for each probabilistic iteration.

To incorporate an assessment of utility differences into the PSA, the ERG sampled the difference in utility between each health state from a Normal distribution, the mean of which was assumed to be the deterministic value, and the standard error assigned to be 10% of the mean (Table 64).

Table 64. Utility decrement distributions

Health state transition	Distribution
From VA 86–100 letters to VA 76–85 letters	$N(0.04,0.004)$
From VA 76–85 letters to VA 66–75 letters	$N(0.11,0.011)$
From VA 66–75 letters to VA 56–65 letters	$N(0.015,0.0015)$
From VA 56–65 letters to VA 46–55 letters	$N(0.085,0.0085)$
From VA 46–55 letters to VA 36–45 letters	$N(0.005,0.0005)$
From VA 36–45 letters to VA 26–35 letters	$N(0.02,0.002)$
From VA 26–35 letters to VA <25 letters	$N(0.135,0.0135)$
Abbreviations used in table: VA, visual acuity.	

The ERG found some minor discrepancies between the aspects of the PSA reported in the MS, and those implemented in the model. Namely that the number of treatment visits for GLP in year 1 and 2

was not included in the PSA, and the variation around the percentage of BSE patients at baseline and month 12 was not functioning due to zero values for beta in the gamma distribution.

The ERG corrected these errors and reran the PSA for the base case comparisons, and found the probability of being cost effective increased slightly. However, the combined effect of the corrections and amendment of the utility sampling was not significant.

5.4.11 Minor issues

Base case incremental analysis results including dexamethasone intravitreal implant

The incremental results that include dexamethasone intravitreal implant reported in section 6.7.6 of the MS are incorrect, as dexamethasone intravitreal implant is ruled out by extended dominance; the ERG notes that the comparison should be between ranibizumab and GLP in MO secondary to BRVO and ranibizumab and best supportive care in MO secondary to CRVO.

Long-term disease progression formula

The ERG notes an error in the formula converting the 20 year probability into a monthly probability (MS; pg 198). The formula multiplies rather than divides by 12. The error applies only to the written submission and not to the model.

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6 ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

6.1 Immediate versus delayed treatment in BRVO

The ERG considered that data from the BRAVO trial alone was insufficient to inform an economic evaluation of ranibizumab monotherapy and GLP (standard care). Also, the ERG agreed with the manufacturer that no indirect comparison versus GLP could be used in the economic model. Therefore, as discussed in section 5.4.6, the ERG used the manufacturer's model to inform an exploratory analysis comparing immediate monthly ranibizumab therapy plus concomitant GLP versus delayed ranibizumab PRN therapy plus concomitant GLP. Table 65 presents the results of this analysis.

Table 65. Immediate versus delayed ranibizumab treatment results in BRVO

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Delayed PRN ranibizumab	£16,484	12.578	7.714	–	–	–	–
Immediate monthly ranibizumab	£17,680	12.62	7.898	£1196	0.042	0.184	£6,500

Abbreviations used in table: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PRN, *pro re nata*; QALYs, quality-adjusted life years.

Table 66. Breakdown of costs for immediate versus delayed treatment in BRVO

Technologies	Costs					
	Treatment	Administration	Follow up	Adverse events	Blindness	Total
Immediate monthly ranibizumab	£6,376	£2,237	£3,521	£61	£5,485	£17,680
Delayed PRN ranibizumab	£3,671	£1,577	£4,159	£61	£7,016	£16,484

Abbreviations used in table: PRN, *pro re nata*.

6.1.1 Scenario analysis of the better-seeing eye/worse-seeing eye

The ERG conducted extensive scenario analysis around the assumptions and sources regarding treatment of the BSE/WSE. The impact of each scenario analysis on the ranibizumab versus best supportive care ICER in MO secondary to CRVO is presented in Table 67.

Table 67. Results of BSE/WSE scenario analysis (ranibizumab vs BSC in CRVO)

Scenario	% BSE at baseline	% BSE at month 12	BSE utility source	Slope of WSE utility curve	Utility assumption used	Costs of blindness	ICER (£/QALY)
Testing the impact of BSE/WSE distribution on the base case							
A	10	20	Brown	Flat	Combination of BSE and WSE	Applied to only BSE	£92,047
B	10	20	Brown	Flat	BSE only	Applied to only BSE	£19,868
C	5.2	7.1	Brown	Flat	Combination of BSE and WSE	Applied to only BSE	£301,603
D	5.2	7.1	Brown	Flat	BSE only	Applied to only BSE	£21,922
Testing the impact of Brazier utilities on the base case							
E	100	100	Brazier	Flat	BSE only	Applied to only BSE	£9,515
Testing the impact of BSE/WSE distribution on the Brazier utility model							
F	10	20	Brazier	Flat	Combination of BSE and WSE	Applied to only BSE	£98,733
G	10	20	Brazier	Flat	BSE only	Applied to only BSE	£21,437
H	5.2	7.1	Brazier	Flat	Combination of BSE and WSE	Applied to only BSE	£323,648
I	5.2	7.1	Brazier	Flat	BSE only	Applied to only BSE	£23,566
Testing the impact of the assumption of a 0.1 overall benefit of treating the WSE							
J	10	20	Brown	0.014 ^a	Combination of BSE and WSE	Applied to only BSE	£19,868
K	5.2	7.1	Brown	0.014 ^a	Combination of BSE and WSE	Applied to only BSE	£21,922
Testing the effect of the assumption of a 0.1 overall benefit of treating the WSE on the Brazier utility model							
L	10	20	Brazier	0.014 ^a	Combination of BSE and WSE	Applied to only BSE	£49,323
N	5.2	7.1	Brazier	0.014 ^a	Combination of BSE and WSE	Applied to only BSE	£70,632
^a A 0.014 slope for the WSE utility curve, translates to a 0.1 difference between the best and worst BCVA in the WSE Abbreviations used in table: BSE, better-seeing eye; WSE, worse-seeing eye.							

The ERG considers that scenario L is the most accurate representation of the decision problem with respect to the treatment of BSE/WSE.

6.1.2 Model modifications

As detailed in section 5.4, the ERG recommends the addition of an increased risk of mortality associated with RVO and visual impairment in the WSE to any base case analysis. Analyses based on utilities from Brown *et al.*⁽⁷³⁾ should also be adjusted for age using a standard multiplicative approach. Tables 68 to 78 present the results of these amendments to the manufacturer's model using the manufacturer's base case scenario for BSE/WSE and the ERG's recommended BSE/WSE scenario L for:

- ranibizumab versus best supportive care in CRVO;

- ranibizumab versus dexamethasone intravitreal implant in CRVO;
- ranibizumab versus dexamethasone intravitreal implant in BRVO;
- immediate versus delayed treatment in BRVO.

The collective impact of these amendments is reported as the ERG's revised model on the fourth line of each table. In addition, the sensitivity of the ERG's revised model to the adoption of a 10-year time horizon is reported in the tables. The sensitivity of each model to treatment continuation is presented graphically in Figures 13 to 15.

Table 68. Results of ERG modifications for ranibizumab versus best supportive care in MO secondary to CRVO

	Rani total costs	BSC costs	Utility (QALYs)		Incremental		ICER
			Rani	BSC	Costs	QALYs	
Submitted model (with PAS)	£■■■■	£20,727	■■■■	7.061	£■■■■	■■■■	£8,643
+RVO Mortality	£23,299	£18,474	6.863	6.391	£4,824	0.473	£10,204
+WSE VI mortality	Not relevant here as only BSE is considered						
+Age adjustment	£24,963	£20,727	5.888	5.507	£4,235	0.381	£11,111
ERG scenario	£18,107	£9,263	6.555	6.376	£8,844	0.179	£49,323
+RVO Mortality	£17,333	£8,457	5.992	5.823	£8,876	0.169	£52,502
+WSE VI mortality	£17,980	£9,085	6.493	6.288	£8,895	0.206	£43,280
+Age adjustment	Not relevant since Brazier <i>et al.</i> utilities are used						
ERG amended model 1	£17,161	£8,219	5.908	5.704	£8,942	0.204	£43,760
Abbreviations used in table: BSC, best supportive care; BSE, better-seeing eye; CRVO, central retinal vein occlusion; ERG, Evidence Review Group; ICER, Incremental cost-effectiveness ratio; MO, macular oedema; PAS, patient access scheme; QALY, quality-adjusted life year; Rani, ranibizumab; RVO, retinal vein occlusion; WSE, worse-seeing eye.							

Table 69. Costs associated with ranibizumab in MO secondary to CRVO

	Tx	Admin	Follow up	AEs	Cost of blindness	Total
Submitted model (with PAS)	£7,734	£2,354	£6,052	£61	£8,763	£■■■■
+RVO Mortality	£7,666	£2,333	£5,499	£61	£7,740	£23,299
+WSE VI mortality	Not relevant here as only BSE is considered					
+Age adjustment	£7,734	£2,354	£6,052	£61	£8,763	£24,963
ERG scenario	£7,745	£2,357	£6,142	£61	£1,802	£18,107
+RVO Mortality	£7,684	£2,339	£5,619	£61	£1,631	£17,333
+WSE VI mortality	£7,737	£2,355	£6,079	£61	£1,749	£17,980
+Age adjustment	Not relevant since Brazier <i>et al.</i> utilities are used					

ERG amended model 1	£7,671	£2,335	£5,534	£61	£1,560	£17,161
Abbreviations used in table: Admin, administration; AEs, adverse events; BSE, better-seeing eye; CRVO, central retinal vein occlusion; ERG, Evidence Review Group; MO, macular oedema; PAS, patient access scheme; RVO, retinal vein occlusion; WSE, worse-seeing eye.						

Table 70. Costs associated with best supportive care in MO secondary to CRVO

	Tx	Admin	Follow up	AEs	Cost of blindness	Total
Submitted model (with PAS)	£0	£0	£6,128	£5	£14,595	£20,727
+RVO Mortality	£0	£0	£5,558	£5	£12,911	£18,474
+WSE VI mortality	Not relevant here as only BSE is considered					
+Age adjustment	£0	£0	£6,128	£5	£14,595	£20,727
ERG scenario	£0	£0	£6,264	£5	£2,994	£9,263
+RVO Mortality	£0	£0	£5,739	£5	£2,714	£8,457
+WSE VI mortality	£0	£0	£6,174	£5	£2,906	£9,085
+Age adjustment	Not relevant since Brazier <i>et al.</i> utilities are used					
ERG amended model 1	£0	£0	£5,618	£5	£2,596	£8,219
Abbreviations used in table: Admin, administration; AEs, adverse events; BSE, better-seeing eye; CRVO, central retinal vein occlusion; ERG, Evidence Review Group; MO, macular oedema; PAS, patient access scheme; RVO, retinal vein occlusion; WSE, worse-seeing eye.						

Figure 13. The sensitivity of the amended model 1 to treatment continuation (ranibizumab versus best supportive care)

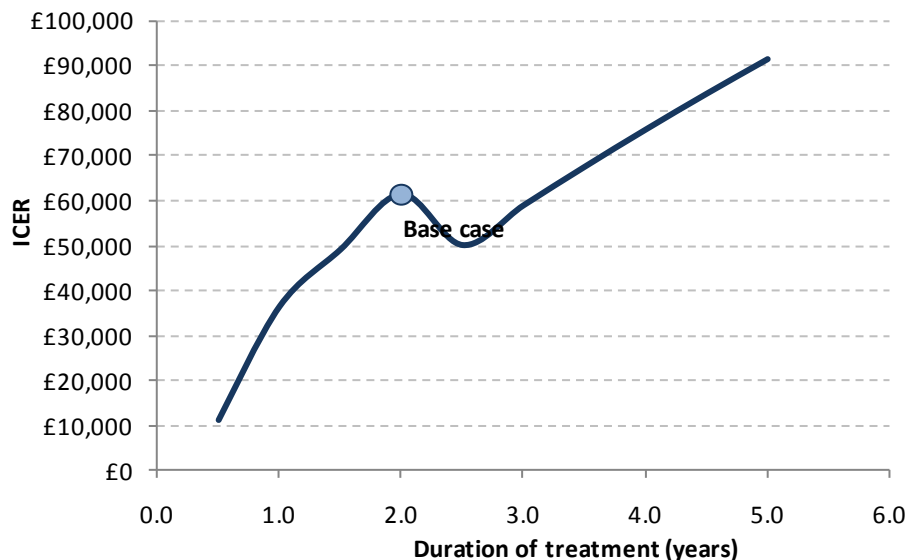


Table 71. Results of ERG modifications for ranibizumab versus dexamethasone intravitreal implant in MO secondary to CRVO

	Rani total costs	Dex total costs	Utility (QALYs)		Incremental		ICER
			Rani	Dex	Costs	QALYs	
Submitted model (with PAS)	£■■■■	£22,945	■■■■	7.270	£■■■■	■■■■	£7,174
+RVO Mortality	£23,299	£20,974	6.863	6,590	£2,324	0.274	£8,490
+WSE VI mortality	Not relevant here as only BSE is considered						
+Age adjustment	£24,963	£22,945	5.888	5.668	£2,018	0.221	£9,143
ERG scenario	£18,107	£13,564	6.555	6.448	£4,543	0.108	£42,147
+RVO Mortality	£17,333	£12,767	5.992	5.890	£4,566	0.103	£44,462
+WSE VI mortality	£17,980	£13,407	6.493	6.370	£4,574	0.123	£37,247
+Age adjustment	Not relevant since Brazier <i>et al.</i> utilities are used						
ERG amended model 2	£17,161	£12,554	5.908	5.785	£4,607	0.123	£37,443
Abbreviations used in table: BSE, better-seeing eye; CRVO, central retinal vein occlusion; Dex, dexamethasone intravitreal implant; ERG, Evidence Review Group; ICER, Incremental cost-effectiveness ratio; MO, macular oedema; PAS, patient access scheme; QALYs, quality-adjusted life years; Rani, ranibizumab; RVO, retinal vein occlusion; WSE, worse-seeing eye.							

Table 72. Costs associated with dexamethasone intravitreal implant in MO secondary to CRVO

	Tx	Admin	Follow up	AEs	Cost of blindness	Total
Submitted model (with PAS)	£3,295	£1,118	£6,432	£152	£11,948	£■■■■
+RVO Mortality	£3,258	£1,106	£5,865	£152	£10,594	£20,974
+WSE VI mortality	Not relevant here as only BSE is considered					
+Age adjustment	£3,295	£1,118	£6,432	£152	£11,948	£22,945
ERG scenario	£3,304	£1,121	£6,548	£152	£2,439	£13,564
+RVO Mortality	£3,271	£1,110	£6,021	£152	£2,213	£12,767
+WSE VI mortality	£3,298	£1,119	£6,470	£152	£2,368	£13,407
+Age adjustment	Not relevant since Brazier <i>et al.</i> utilities are used					
ERG amended model 2	£3,262	£1,107	£5,915	£152	£2,118	£12,554
Abbreviations used in table: Admin, administration; AEs, adverse events; BSE, better-seeing eye; CRVO, central retinal vein occlusion; ERG, Evidence Review Group; MO, macular oedema; PAS, patient access scheme; RVO, retinal vein occlusion; TX, treatment; WSE, worse-seeing eye.						

Figure 14. The sensitivity of the amended model 2 to treatment continuation (ranibizumab versus dexamethasone intravitreal implant)

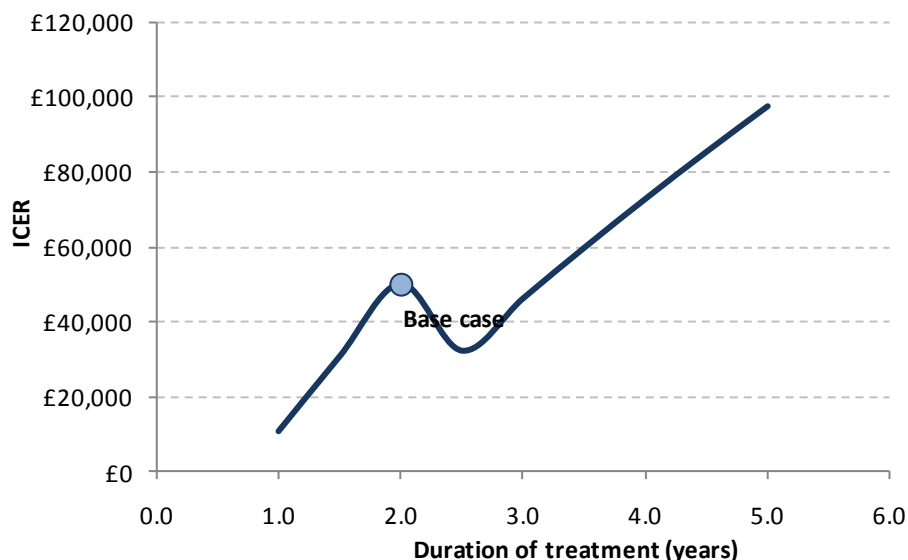


Table 73. Results of ERG modifications for ranibizumab versus dexamethasone intravitreal implant in MO secondary to BRVO

	Rani total costs	Dex total costs	Utility (QALYs)		Incremental		ICER
			Rani	Dex	Costs	QALYs	
Submitted model (with PAS)	£████	£16,448	████	7.769	£████	████	£5,486
+RVO Mortality	£16,658	£15,314	7.337	7.134	£1,343	0.203	£6,614
+WSE VI mortality	Not relevant here as only BSE is considered						
+Age adjustment	£17,592	£16,448	6.221	6.057	£1,144	0.164	£6,978
ERG scenario	£13,111	£10,363	6.778	6.698	£2,747	0.079	£34,598
+RVO Mortality	£12,713	£9,940	6.256	6.180	£2,772	0.076	£36,498
+WSE VI mortality	£13,052	£10,289	6.735	6.646	£2,764	0.089	£30,899
+Age adjustment	Not relevant since Brazier <i>et al.</i> utilities are used						
ERG amended model 3	£12,632	£9,837	6.197	6.107	£2,795	0.090	£31,122

Abbreviations used in table: BSE, better-seeing eye; BRVO, branch retinal vein occlusion; Dex, dexamethasone intravitreal implant; ERG, Evidence Review Group; ICER, Incremental cost-effectiveness ratio; MO, macular oedema; PAS, patient access scheme; QALYs, quality-adjusted life years; Rani, ranibizumab; RVO, retinal vein occlusion; WSE, worse-seeing eye.

Table 74. Costs associated with ranibizumab in MO secondary to BRVO

	Tx	Admin	Follow up	AEs	Cost of blindness	Total
Submitted model (with PAS)	£6,376	£1,941	£3,522	£61	£5,691	£████
+RVO Mortality	£6,332	£1,927	£3,270	£61	£5,067	£16,658
+WSE VI mortality	Not relevant here as only BSE is considered					
+Age adjustment	£6,376	£1,941	£3,522	£61	£5,691	£17,592
ERG scenario	£6,381	£1,942	£3,552	£61	£1,175	£13,111

+RVO Mortality	£6,340	£1,930	£3,311	£61	£1,072	£12,713
+WSE VI mortality	£6,377	£1,941	£3,530	£61	£1,143	£13,052
+Age adjustment	Not relevant since Brazier <i>et al.</i> utilities are used					
ERG amended model 3	£6,334	£1,928	£3,281	£61	£1,028	£12,632
Abbreviations used in table: Admin, administration; AEs, adverse events; BRVO, branch retinal vein occlusion; BSE, better-seeing eye; ERG, Evidence Review Group; MO, macular oedema; PAS, patient access scheme; RVO, retinal vein occlusion; Tx, treatment; WSE, worse-seeing eye.						

Table 75. Costs associated with dexamethasone intravitreal implant in MO secondary to BRVO

	Tx	Admin	Follow up	AEs	Cost of blindness	Total
Submitted model (with PAS)	£3,306	£1,122	£4,156	£152	£7,713	£16,448
+RVO Mortality	£3,274	£1,111	£3,894	£152	£6,884	£15,314
+WSE VI mortality	Not relevant here as only BSE is considered					
+Age adjustment	£3,306	£1,122	£4,156	£152	£7,713	£16,448
ERG scenario	£3,310	£1,123	£4,195	£152	£1,584	£10,363
+RVO Mortality	£3,281	£1,114	£3,947	£152	£1,447	£9,940
+WSE VI mortality	£3,307	£1,122	£4,167	£152	£1,541	£10,289
+Age adjustment	Not relevant since Brazier <i>et al.</i> utilities are used					
ERG amended model 3	£3,276	£1,112	£3,909	£152	£1,389	£9,837
Abbreviations used in table: Admin, administration; AEs, adverse events; BRVO, branch retinal vein occlusion; ERG, Evidence Review Group; MO, macular oedema; PAS, patient access scheme; RVO, retinal vein occlusion; Tx, treatment; WSE, worse-seeing eye.						

Figure 15. The sensitivity of the revised model 6 to treatment continuation (ranibizumab versus dexamethasone intravitreal implant)

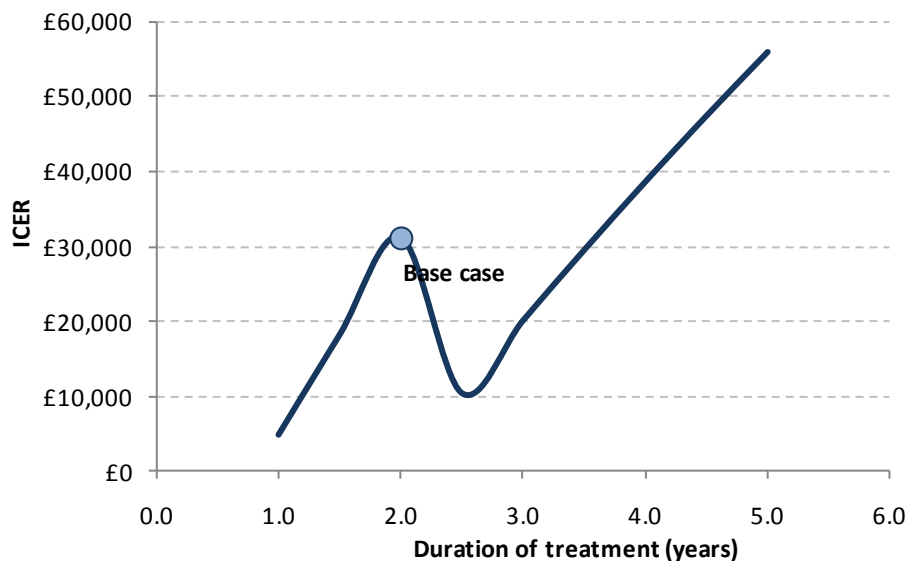


Table 76. Results of ERG modifications for immediate versus delayed treatment in MO secondary to BRVO (using ERG's recommended BSE/WSE scenario model)

	Immediate treatment costs	Delayed treatment costs	Utility (QALYs)		Incremental		ICER
			Immediate	Delayed	Costs	QALYs	
ERG scenario	£13,369	£10,952	6.756	6.690	£2417	0.066	£36,621
+RVO Mortality	£12,973	£10,542	6.236	6.172	£2431	0.064	£37,984
+WSE VI mortality	£13,310	£10,879	6.711	6.635	£2431	0.076	£31,986
+Age adjustment	Not relevant since Brazier <i>et al.</i> utilities are used						
ERG amended model 5	£12,891	£10,441	6.174	6.096	£2450	0.078	£31,410

Abbreviations used in table: BRVO, branch retinal vein occlusion; ERG, Evidence Review Group; ICER, Incremental cost-effectiveness ratio; MO, macular oedema; PAS, patient access scheme; QALYs, quality-adjusted life years; RVO, retinal vein occlusion; WSE, worse-seeing eye.

Table 77. Costs associated with immediate treatment in MO secondary to BRVO (using ERG's recommended BSE/WSE scenario model)

	Tx	Admin	Follow up	AEs	Cost of blindness	Total
ERG scenario	£6,381	£2,239	£3,552	£61	£1,137	£13,369
+RVO Mortality	£6,340	£2,224	£3,311	£61	£1,038	£12,973
+WSE VI mortality	£6,377	£2,237	£3,529	£61	£1,106	£13,310
+Age adjustment	Not relevant since Brazier <i>et al.</i> utilities are used					
ERG amended model 5	£6,333	£2,222	£3,279	£61	£995	£12,891

Abbreviations used in table: Admin, administration; AEs, adverse events; BRVO, branch retinal vein occlusion; ERG, Evidence Review Group; PAS, patient access scheme; RVO, retinal vein occlusion; TX, treatment; WSE, worse-seeing eye.

Table 78. Costs associated with delayed treatment in MO secondary to BRVO (using ERG's recommended BSE/WSE scenario model)

	Tx	Admin	Follow up	AEs	Cost of blindness	Total
ERG scenario	£3,676	£1,579	£4,197	£61	£1,439	£10,952
+RVO Mortality	£3,647	£1,566	£3,952	£61	£1,316	£10,542
+WSE VI mortality	£3,672	£1,577	£4,169	£61	£1,400	£10,879
+Age adjustment	Not relevant since Brazier <i>et al.</i> utilities are used					
ERG amended model 5	£3,641	£1,564	£3,913	£61	£1,262	£10,441

Abbreviations used in table: Admin, administration; AEs, adverse events; BRVO, branch retinal vein occlusion; BSE, better-seeing eye; ERG, Evidence Review Group; MO, macular oedema; PAS, patient access scheme; Rani, ranibizumab; RVO, retinal vein occlusion; TX, treatment; WSE, worse-seeing eye.

6.2 Cost minimisation and threshold analysis of bevacizumab

The cost minimisation analysis conducted by the ERG, resulted in the dominance of bevacizumab over ranibizumab, with the incremental costs of ranibizumab treatment of [REDACTED] and [REDACTED] for patients' with MO secondary to BRVO and CRVO respectively. Analysis of the ICER equation revealed the number of additional QALYs required for ranibizumab to obtain an ICER of £30,000.

These are displayed in Table 79 for the manufacturer’s model and ERG amended model for patients with MO secondary to BRVO and CRVO.

Table 79. Additional QALYs required for ranibizumab to reach an ICER of £30,000

Model	Incremental QALYs required
BRVO	
Manufacturer’s	0.196
ERG amended	0.194
CRVO	
Manufacturer’s	0.237
ERG amended	0.235
Abbreviations used in table: BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion; QALYs, quality-adjusted life years.	

The results of threshold analyses, increasing the efficacy of ranibizumab at month 1 and months 2 to 6 (using a treatment effect multiplier for ranibizumab) are displayed in figures 16 to 19 for the manufacturer’s and ERG’s amended models in MO secondary to BRVO and CRVO.

Figure 16. Threshold analysis of manufacturer’s model for ranibizumab versus bevacizumab in MO secondary to BRVO

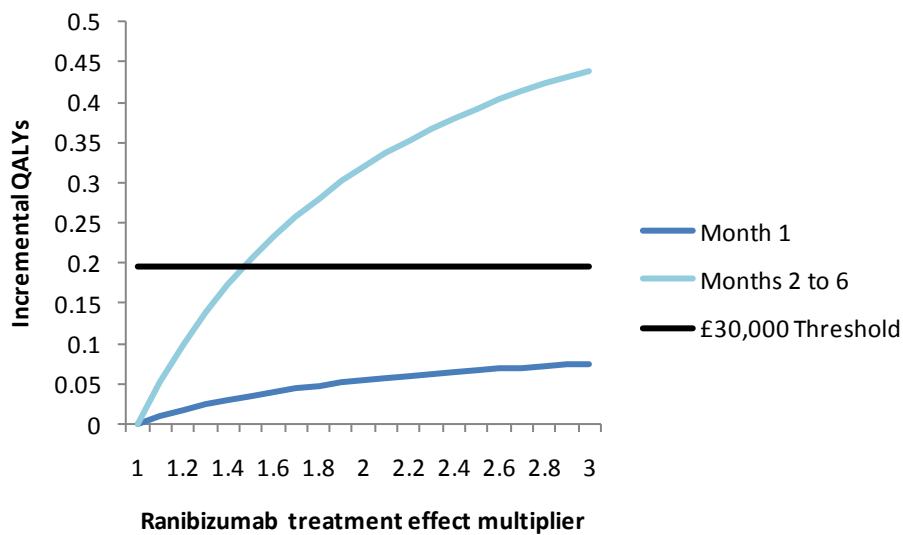


Figure 17. Threshold analysis of ERGs amended model for ranibizumab versus bevacizumab in MO secondary to BRVO

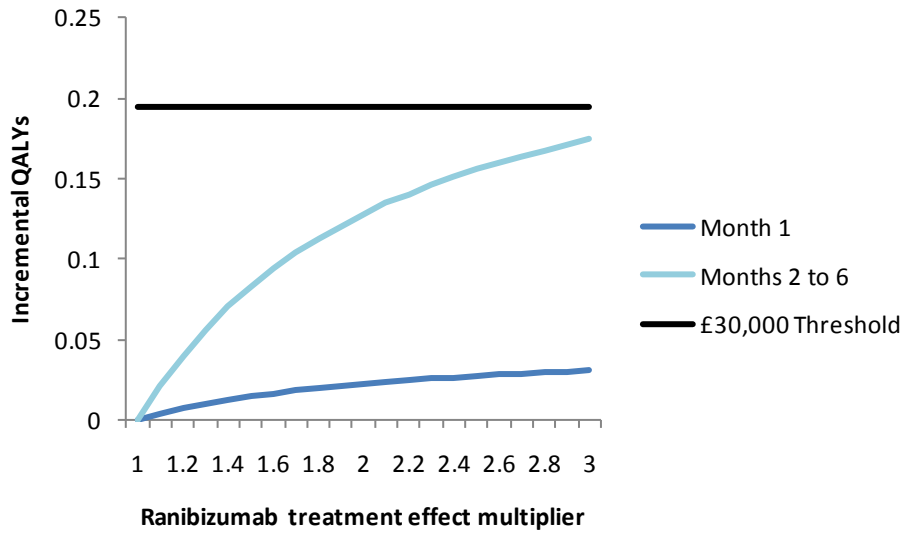


Figure 18. Threshold analysis of manufacturer's model for ranibizumab versus bevacizumab in MO secondary to CRVO

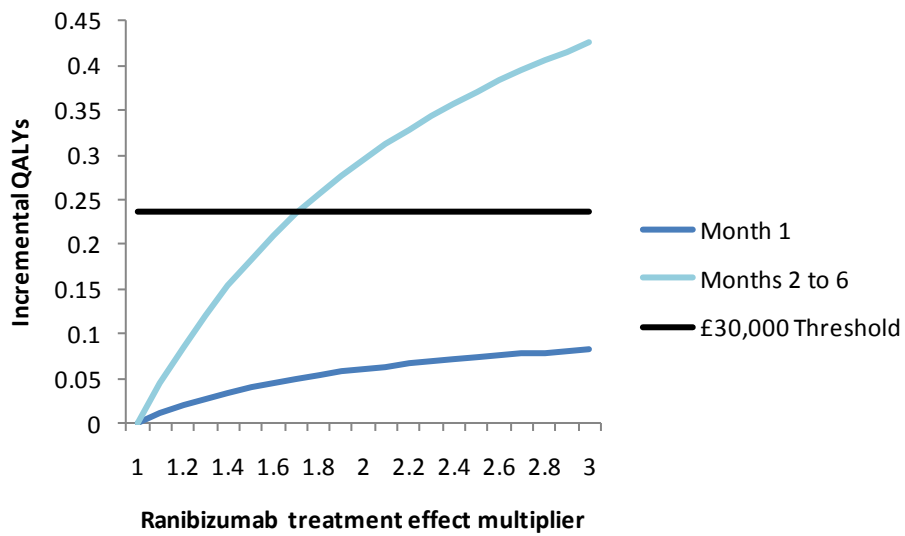
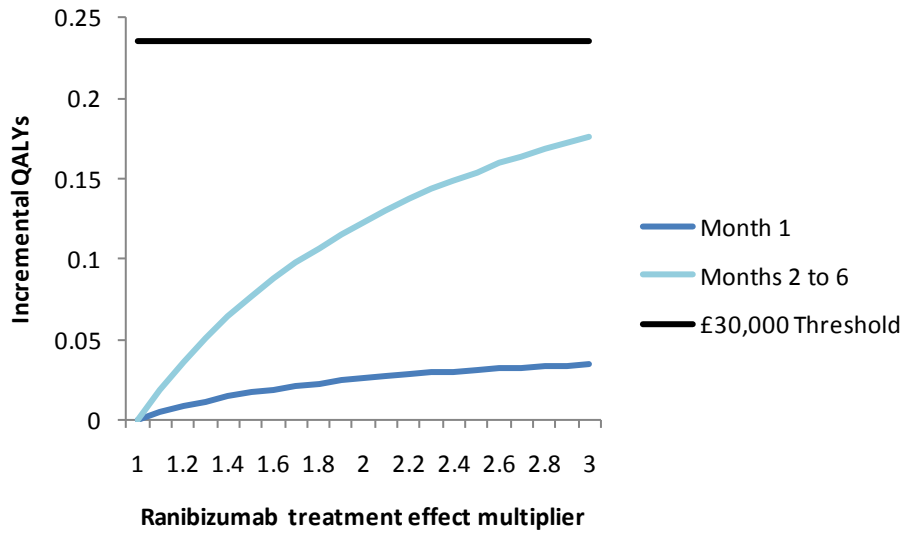


Figure 19. Threshold analysis of ERGs amended model for ranibizumab versus bevacizumab in MO secondary to CRVO



Analysis based on the manufacturer’s model suggests that ranibizumab would need to be 1.5 and 1.7 times more effective than bevacizumab, each month (between months 2 and 6) to obtain ICERs of £30,000 in MO secondary to BRVO and to CRVO, respectively. Considering the ERG’s amended model, ranibizumab would not obtain an ICER of £30,000 in MO secondary to BRVO or CRVO at monthly efficacy levels that are 3 times more than bevacizumab.

7 CONCLUSIONS

The manufacturer presents the case for the use of ranibizumab in macular oedema (MO) secondary to branch and central retinal vein occlusion (RVO) compared with the use of the recently approved dexamethasone intravitreal implant or current standard of care. The base case economic evaluation is conducted from a BSE perspective. The ERG considers this to be inappropriate in this indication, because RVO is a predominantly unilateral condition, with the majority of patients experiencing treatment in only their WSE. The ERG extensively investigated the assumptions and sources used in relation to the eye affected and utility gained from treatment. The ICERs generated from these investigations are always higher than the manufacturer's base case ICER, and, based on the information presented in the MS, the ERG selected what it thought to be the most reasonable representation of the expected gain of treatment in the RVO population. In addition, the ERG identified other limitations in the approach taken by the manufacturer, resulting in further recommended modifications.

Ranibizumab versus best supportive care in MO secondary to CRVO

Patient level data from the CRUISE trial are used to inform a comparison between ranibizumab and best supportive care. The ERG considers the CRUISE trial to be a well designed and conducted trial that is appropriate for use in this comparison. The base case ICER generated by the manufacturer was £8,643. Application of the ERG's adjustment for the expectation that treatment will predominantly be administered to the WSE increased the ICER to £49,323. Further modifications reduced the ICER to £43,760.

Ranibizumab versus grid laser photocoagulation (standard care) in MO secondary to BRVO

The manufacturer bases the case for ranibizumab compared with grid laser photocoagulation (GLP), which is standard care in this population, in MO secondary to BRVO entirely on the BRAVO⁽¹⁵⁾ trial. The ERG notes that in isolation BRAVO is unsuitable to inform this comparison. Additional evidence on the efficacy of GLP in this indication is available from the BVOS study.⁽¹⁴⁾ However, the model structure prohibits the inclusion of these data.

The ERG proposed using the BRAVO trial to inform a comparison between immediate and delayed therapy with ranibizumab, alongside "rescue" GLP. Application of this analysis to the manufacturer's model results in an ICER of £6,500 for immediate versus 6 month delayed treatment. However, once the modifications recommended by the ERG are incorporated into this analysis the ICER increases significantly to £31,410.

Ranibizumab versus dexamethasone intravitreal implant in RVO

The manufacturer incorporates dexamethasone intravitreal implant into the economic analysis in an exploratory way. The ERG notes that there is a potential bias towards ranibizumab in the manufacturer's approach. However, the presence of conflicting bias makes it difficult to say with certainty which treatment is favoured in the manufacturer's approach. The ERG considers that the use of an adjusted indirect comparison results would be more appropriate than the manufacturer's current approach. However, the nature of the model structure prevents incorporation of the results from the indirect comparison.

The base case ICERs obtained from the manufacturer's analysis are £5,486 and £7,174 for MO secondary to BRVO and CRVO, respectively. After adjustment of the perspective to consider the worse-seeing eye (WSE), the ICERs increase to £34,598 and £42,147 in MO secondary to BRVO and CRVO, respectively. Further modification yields ICERs of £31,122 and £37,433 for MO secondary to BRVO and CRVO, respectively.

7.1 *Implications for research*

The ERG considers that there is a need for further research into the safety and clinical benefit of ranibizumab compared with all treatments currently used in clinical practice. The ERG notes that a focus on the long-term sustainability of ranibizumab treatment would inform the optimal treatment pathway for patients with MO secondary to RVO. In addition, the ERG notes that there is currently a paucity of data on the effects of ranibizumab treatment in patients with MO secondary to ischaemic RVO and the impact of visual impairment in the WSE. There is a need for utility data associated with visual impairment in the WSE.

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Appendix 1. Key characteristics of the BRAVO, CRUISE and ROCC RCTs

Table A1.1. Key characteristics of BRAVO⁽¹⁵⁾

Study: Design and patients	Intervention/comparator	Key inclusion criteria	Key exclusion criteria	Outcomes
<p>BRAVO^(15;16) 397 people Phase III, double blind RCT Three armed RCT assessing ranibizumab 0.5 mg (n = 131 people), ranibizumab 0.3 mg (n = 134 people) and sham injection (n = 132 people)</p> <p>Multicentre RCT: 93 sites in the USA</p> <p>Patients with MO secondary to branch retinal vein occlusion</p> <p>People were randomised 1:1:1 (ranibizumab 0.5 mg: ranibizumab 0.3 mg: sham injection)</p> <p>For each patient, one eye was</p>	<p>Monthly intracocular ranibizumab (0.3 mg or 0.5 mg) for 6 months</p> <p>Before injection with ranibizumab, topical anaesthetic drops were applied. A lid speculum was inserted, and, after subconjunctival injection of 2% lidocaine and cleaning of the injection site with 5% povidone iodine, a 30-gauge needle was inserted through the pars plana, and 0.05 mL of ranibizumab injected.</p> <p>Comparator: sham injection</p> <p>Patients in the sham group received similar treatment to those in the ranibizumab groups until the point of injection. Sham injection comprised placing the needleless hub of a syringe against the injection site and depressing the plunger to imitate injection.</p> <p>Starting at 3 months,</p>	<p>Criteria apply to study eye:</p> <ul style="list-style-type: none"> • Age ≥18 years of age with foveal centre-involved ME secondary to BRVO diagnosed within 12 months before study initiation • BCVA 20/40 to 20/400 Snellen equivalent using the ETDRS charts • Mean central subfield thickness ≥250 micrometres from 2 OCT measurements (central 1 mm diameter circle with a Stratus OCT3) on 2 measurements, one at screening confirmed by University of Wisconsin Fundus Photograph Reading Center, the other on day 0 confirmed by the investigating physician 	<p>Criteria apply to study eye:</p> <ul style="list-style-type: none"> • Prior episode of RVO • Brisk afferent pupillary defect (i.e., obvious and unequivocal) • >10-letter improvement in BCVA between screening and day 0 • History of radial optic neurotomy or sheathotomy. • Intraocular corticosteroid use in study eye within 3 months before day 0 • History or presence of wet or dry AMD • Panretinal scatter photocoagulation or sector laser photocoagulation within 3 months before day 0 or anticipated within 4 months after day 0 • Laser photocoagulation for ME within 4 months before day 0 (for patients who had previously received grid laser photocoagulation, the area of leakage at day 0 must have extended into the fovea [i.e., prior laser treatment was inadequate], and there could be no evidence of laser damage to the fovea) • Evidence upon examination of any diabetic retinopathy • CVA or MI within 3 months before day 0 • Prior anti-VEGF treatment in study or fellow eye within 3 months before day 0 or systemic anti-VEGF or pro-VEGF treatment within 6 	<p><u>Primary outcome</u> Mean change from baseline BCVA in the study eye at month 6</p> <p><u>Secondary outcomes</u></p> <ul style="list-style-type: none"> • Mean change from baseline BCVA letter score over time to month 6 • Percentage of patients who gained ≥15 letters from baseline BCVA at month 6 • Percentage of patients who lost <15 letters from baseline BCVA at month 6 • Percentage of patients with CFT ≤250 micrometres at month 6 • Mean change from baseline CFT over time to month 6. • Incidence and severity of ocular and non-ocular adverse events and serious adverse events) <p><u>Exploratory outcomes</u></p> <ul style="list-style-type: none"> • Percentage of patients with Snellen equivalent BCVA ≥20/40 at month 6

<p>chosen as the study eye. When both eyes were eligible, the eye with the worse BCVA at screening was treated.</p> <p><u>Stratification factors</u></p> <ul style="list-style-type: none"> • baseline BCVA letter score • study centre 	<p>people in all three arms became eligible for rescue laser treatment.</p> <p>Fluorescein angiography obtained within 30 days before laser grid application was used to guide treatment.</p> <p>Patients were eligible for laser treatment if haemorrhages had cleared sufficiently to allow safe application of laser and the following criteria were met:</p> <ul style="list-style-type: none"> • Snellen equivalent BCVA $\leq 20/40$ or mean central subfield thickness ≥ 250 micrometres • and, compared with the visit 3 months before the current visit, patient had a gain of < 5 letters in BCVA or a decrease of < 50 micrometres in mean central subfield thickness <p>If rescue laser was not given at month 3, the same criteria were applied at month 4, and again at month 5, if rescue laser was not given at month 4</p>		<p>months before day 0.</p>	<ul style="list-style-type: none"> • Percentage of patients with Snellen equivalent BCVA $\leq 20/200$ at month 6 • Mean change from baseline EFT over time to month 6, • Mean change from baseline NEI VFQ-25 composite score over time to month 6
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Table A1.2. Key characteristics of CRUISE⁽¹⁶⁾

Study: Design and patients	Intervention/comparator	Key inclusion criteria	Key exclusion criteria	Outcomes
<p>CRUISE⁽¹⁶⁾ 392 people Phase III, double blind RCT Three armed RCT assessing ranibizumab 0.5 mg (n = 130 people), ranibizumab 0.3 mg (n = 132 people) and sham injection (n = 130 people)</p> <p>Multicentre RCT: 95 sites in the USA</p> <p>Patients with MO secondary to central retinal vein occlusion</p> <p>People were randomised 1:1:1 (ranibizumab 0.5 mg; ranibizumab 0.3 mg; sham injection)</p> <p>For each patient, one eye was chosen as the study eye. When both eyes were eligible, the eye with the worse</p>	<p>Monthly intravitreal ranibizumab (0.3 mg or 0.5 mg) for 6 months</p> <p>Before injection with ranibizumab, topical anaesthetic drops were applied. A lid speculum was inserted, and, after subconjunctival injection of 2% lidocaine and cleaning of the injection site with 5% povidone iodine, a 30-gauge needle was inserted through the pars plana, and 0.05 mL of ranibizumab injected.</p> <p>Comparator: sham injection</p> <p>Patients in the sham group received similar treatment to those in the ranibizumab groups until the point of injection. Sham injection comprised placing the needleless hub of a syringe against the injection site and depressing the plunger to imitate injection.</p>	<p>Criteria apply to study eye:</p> <ul style="list-style-type: none"> • Age ≥18 years of age with foveal centre-involved ME secondary to CRVO diagnosed within 12 months before study initiation • BCVA 20/40 to 20/320 Snellen equivalent using the ETDRS charts • Mean central subfield thickness ≥250 micrometres from 2 OCT measurements (central 1 mm diameter circle with a Stratus OCT3) on 2 measurements, one at screening confirmed by University of Wisconsin Fundus Photograph Reading Center, the other on day 0 confirmed by the investigating physician 	<p>Criteria apply to study eye:</p> <ul style="list-style-type: none"> • Prior episode of RVO • Brisk afferent pupillary defect (i.e., obvious and unequivocal) • >10-letter improvement in BCVA between screening and day 0 • History of radial optic neurotomy or sheathotomy. • Intraocular corticosteroid use in study eye within 3 months before day 0 • History or presence of wet or dry AMD • Panretinal scatter photocoagulation or sector laser photocoagulation within 3 months before day 0 or anticipated within 4 months after day 0 • Laser photocoagulation for ME within 4 months before day 0 (for patients who had previously received grid laser photocoagulation, the area of leakage at day 0 must have extended into the fovea [i.e., prior laser treatment was inadequate], and there could be no evidence of laser damage to the fovea) • Evidence upon examination of any diabetic retinopathy • CVA or MI within 3 months before day 0 • Prior anti-VEGF treatment in study or fellow eye within 3 months before day 0 or systemic anti-VEGF or pro-VEGF treatment within 6 months before day 0. 	<p><u>Primary outcome</u> Mean change from baseline BCVA in the study eye at month 6</p> <p><u>Secondary outcomes</u></p> <ul style="list-style-type: none"> • Mean change from baseline BCVA letter score over time to month 6 • Percentage of patients who gained ≥15 letters from baseline BCVA at month 6 • Percentage of patients who lost <15 letters from baseline BCVA at month 6 • Percentage of patients with CFT ≤250 micrometres at month 6 • Mean change from baseline CFT over time to month 6 • Incidence and severity of ocular and non-ocular adverse events and serious adverse events) <p><u>Exploratory outcomes</u></p> <ul style="list-style-type: none"> • Percentage of patients with Snellen equivalent BCVA ≥20/40 at month 6 • Percentage of patients with Snellen equivalent BCVA ≤20/200 at month 6 • Mean change from baseline EFT over time to

BCVA at screening was treated.				month 6, <ul style="list-style-type: none"> • Mean change from baseline NEI VFQ-25 composite score over time to month 6
<u>Stratification factors</u> <ul style="list-style-type: none"> • baseline BCVA letter score • study centre 				

Table A1.3. Key characteristics of ROCC RCT⁽⁴²⁾

Study: Design and patients	Intervention/comparator	Key inclusion criteria	Key exclusion criteria	Outcomes
ROCC ⁽⁴²⁾ 32 people Multicenter, randomized, double-masked, sham-controlled, monitored RCT Multicentre RCT: 4 sites in Norway Patients with MO secondary to central retinal vein occlusion in 1 eye and who were previously untreated for the condition People were randomised 1:1 (method of randomisation not reported)	Monthly intravitreal ranibizumab (0.5 mg/0.05 mL) for the first 3 months. For the remainder of the 6-month study, treatment was administered at the discretion of the physician if macular oedema with cysts in the central macular area persisted Comparator: sham injection	<ul style="list-style-type: none"> • Patients with MO secondary to central retinal vein occlusion in 1 eye and who were previously untreated for the condition • Symptom duration ≤6 months • Age ≥50 years • BCVA score (using the Early Treatment Diabetic Retinopathy Study [ETDRS] chart) between ≤73 and ≥6 letters. Macular oedema was confirmed by the presence of intraretinal cysts in the central macular area by optical coherence tomography (OCT)	<ul style="list-style-type: none"> • Any concomitant ocular disease that could compromise the assessments in the study eye or induce complications such as active extraocular or intraocular infection or inflammation • Prior treatment of macular disease • History of uncontrolled glaucoma, filtration surgery, or corneal transplantation • Cataract surgery 3 months prior to baseline • Aphakia • Cataract or diabetic retinopathy in rapid progression • Vitreous haemorrhage or previous rhegmatogenous retinal detachment. • Patients were excluded if they had received other investigational drugs or current treatment for active systemic infection, or had received medication known to be toxic to the eye, or if there were contraindications for the use of an investigational drug • Patients were also excluded if they had a history of hypersensitivity or allergy to fluorescein, or it was not possible to obtain fundus photographs or fluorescein angiograms of sufficient quality to be 	The efficacy analysis was done on the per-protocol patient population <u>Primary outcome</u> <ul style="list-style-type: none"> • Mean change from baseline BCVA at 3 and 6 months • Change in macular thickness from baseline to months 3 and 6 <u>Secondary outcomes</u> <ul style="list-style-type: none"> • Number of injections • Incidence of adverse events

			analyzed • Women were excluded if they were or could be pregnant	
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Appendix 2. Quality assessments of BRAVO, CRUISE and ROCC

Table A2.1. BRAVO⁽¹⁵⁾

Question	Description taken from MS	Manufacturer's assessment	ERG assessment
Was randomisation carried out appropriately?	Subjects were randomised centrally using an interactive voice response system (IVRS) to prevent bias in treatment assignment. A dynamic randomisation method was used to obtain an approximately 1:1:1 ratio between the treatment arms, which is designed to achieve overall balance, balance within each category defined by visual acuity score and balance within each study centre between the three treatment arms.	Yes	Yes
Was the concealment of treatment allocation adequate?	In order to maintain treatment masking, patients assigned to Sham had a needleless hub of a syringe placed against the injection site and the plunger of the syringe was depressed to mimic an injection. Documented procedures were put in place to avoid inadvertent unmasking of study team members, and only the IVRS provider and an external and independent statistical coordinating centre (SCC) responsible for verifying subject randomisation and monthly study drug kit assignments, who are not otherwise involved in the study, will have access to the unmasking codes. Masking was maintained until after completion of the study (after all subjects have either completed the visit at month 12 or discontinued early from the study).	Yes	Yes
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	The three treatment groups were well balanced in terms of baseline demographics. At baseline, the three treatment groups were similar in terms of (study eye): ocular characteristics, fundus photography characteristics, total area of retinal haemorrhage in the centre subfield, mean total area of fluorescein leakage and mean total macular volume. Although the mean central subfield thickness was similar between	Yes	ERG noted slight difference in baseline central foveal thickness (CFT) between sham group (488.0 micrometres) and ranibizumab 0.5 mg group (551.7 micrometres). ERG also noted minor difference in proportion of people with MO of duration of >9–≤12 months from diagnosis to screening (16 [12.1%] in the sham

Question	Description taken from MS	Manufacturer's assessment	ERG assessment
	treatment groups at baseline, the mean central foveal thickness of the study eye was lower in the sham group (488.0 µm) compared with the 0.3 mg and 0.5 mg ranibizumab groups (522.1 µm and 551.7 µm, respectively).		group vs 7 [5.3%] in the ranibizumab 0.5 mg group)
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	<p>Subjects, study site personnel (with the exception of site personnel performing or assisting with the injection procedure), the designated evaluating physician (a qualified ophthalmologist), central reading centre personnel, and the Sponsor and its agents (with the exception of drug accountability monitors) were masked to treatment assignment. The investigator performing the injection (and assistant, if needed) were unmasked to treatment assignment (ranibizumab vs sham injection) but were masked to ranibizumab dose level. The injecting physicians were not involved in any other aspect of the study in any way and did not divulge the treatment assignment to anyone. Evaluating physicians were responsible for evaluating ocular assessments and all other aspects of the study. Visits for study drug injections were scheduled when both physicians were present. Visual acuity examiners were masked to treatment assignment and performed only visual acuity assessments and no other study assessments.</p> <p>Additionally, independent reviews of fundus photography, fluorescein angiography, and OCT were performed at a central reading centre (University of Wisconsin Fundus Photograph Reading Center) to provide an objective, masked assessment of these evaluations.</p>	Yes	Yes
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	<p>The study had good subject retention, and unexpected imbalances in drop-outs were not reported in the study</p> <p>A total of 376 (94.7%) subjects completed the study through Month 6</p> <ul style="list-style-type: none"> • Sham, 123 (93.2%) • 0.3 mg ranibizumab, 128 (95.5%) • 0.5 mg ranibizumab, 125 	No	No


Question	Description taken from MS	Manufacturer's assessment	ERG assessment
	(95.4%) A total of 356 subjects (89.7%) completed the study through Month 12. <ul style="list-style-type: none"> • Sham, 114 (86.4%) • 0.3 mg ranibizumab, 119 (88.8%) • 0.5 mg ranibizumab, 123 (93.9%) 		
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Outcomes were presented in the CSR; only those relevant to the decision problem are presented within this submission	No	
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Unless otherwise noted, the intent-to-treat approach was used for efficacy analyses and included all patients as randomised. Missing values for efficacy outcomes were imputed using the last observation carried-forward method.	Yes	ERG considers that last observation carried forward may not be most appropriate method for assessment of missing data

Table A2.2. CRUISE⁽¹⁶⁾

Question	Description taken from MS	Manufacturer's assessment	ERG assessment
Was randomisation carried out appropriately?	Subjects were randomised centrally using an interactive voice response system (IVRS) to prevent bias in treatment assignment. A dynamic randomisation method was used to obtain an approximately 1:1:1 ratio between the treatment arms, which is designed to achieve overall balance, balance within each category defined by visual acuity score and balance within each study centre between the three treatment arms.	Yes	Yes
Was the concealment of treatment allocation adequate?	In order to maintain treatment masking, patients assigned to Sham had a needleless hub of a syringe placed against the injection site and the plunger of the syringe was depressed to mimic an injection. Documented procedures were put in place to avoid inadvertent unmasking of study team members, and only the IVRS provider and an external and independent statistical coordinating centre (SCC) responsible for verifying subject randomisation and monthly study drug kit assignments, who are not otherwise involved in the study, will have access to the unmasking codes. Masking was maintained until after completion of the study (after all subjects have either completed the visit at month 12 or discontinued early from the study).	Yes	Yes
Were the groups similar at the	The three treatment groups were well balanced in terms of baseline demographics.	Yes	ERG noted minor

Question	Description taken from MS	Manufacturer's assessment	ERG assessment
outset of the study in terms of prognostic factors, for example, severity of disease?	At baseline, the three treatment groups were similar in terms of (study eye): ocular characteristics, fundus photography characteristics, total area of retinal haemorrhage in the centre subfield, mean total area of fluorescein leakage, mean central subfield thickness and mean total macular volume.		difference in proportion of people with MO of >3-≤6 months from diagnosis to screening (27 [20.8%] in the sham group vs 17 [13.1%] in the ranibizumab 0.5 mg group) and for >6-≤9 months from diagnosis to screening (4 [3.1%] in the sham group vs 10 [7.7%] in the ranibizumab 0.5 mg group)
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	<p>Subjects, study site personnel (with the exception of site personnel performing or assisting with the injection procedure), the designated evaluating physician (a qualified ophthalmologist), central reading centre personnel, and the Sponsor and its agents (with the exception of drug accountability monitors) were masked to treatment assignment.</p> <p>The investigator performing the injection (and assistant, if needed) were unmasked to treatment assignment (ranibizumab vs sham injection) but were masked to ranibizumab dose level. The injecting physicians were not involved in any other aspect of the study in any way and did not divulge the treatment assignment to anyone.</p> <p>Evaluating physicians were responsible for evaluating ocular assessments and all other aspects of the study. Visits for study drug injections were scheduled when both physicians were present. Visual acuity examiners were masked to treatment assignment and performed only visual acuity assessments and no other study assessments.</p> <p>Additionally, independent reviews of fundus photography, fluorescein angiography, and OCT were performed at a central reading centre (University of Wisconsin Fundus Photograph Reading Center) to provide an objective, masked assessment of these evaluations.</p>	Yes	Yes
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or	<p>The study had good subject retention, and unexpected imbalances in drop-outs were not reported in the study</p> <p>A total of 363 (92.6%) subjects completed the study through Month 6</p>	No	No


Question	Description taken from MS	Manufacturer's assessment	ERG assessment
adjusted for?	<ul style="list-style-type: none"> Sham, 115 (88.5%) 0.3 mg ranibizumab, 129 (97.7%) 0.5 mg ranibizumab, 119 (91.5%) <p>A total of 349 (89.0%) subjects completed the study through Month 12.</p> <ul style="list-style-type: none"> Sham, 109 (83.8%) 0.3 mg ranibizumab, 126 (95.5%) 0.5 mg ranibizumab, 114 (87.7%) 		
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Outcomes were presented in the CSR; only those relevant to the decision problem are presented within this submission	No	
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	<p>Unless otherwise noted, the intent-to-treat approach was used for efficacy analyses and included all patients as randomised.</p> <p>Missing values for efficacy outcomes were imputed using the last observation carried-forward method.</p>	Yes	ERG considers that last observation carried forward may not be most appropriate method for assessment missing data

Table A2.3. ROCC⁽⁴²⁾

Question	Description taken from MS	Manufacturer's assessment	ERG assessment
Was randomisation carried out appropriately?	Study reports that patients were randomised 1:1 to one of the two groups, but the method of randomisation was not reported	Not clear	Not clear
Was the concealment of treatment allocation adequate?	Method of allocation concealment was not reported.	Not clear	Not clear
Were the groups similar at the outset of the study in terms of prognostic factors?	The study does not provide detailed breakdown of the groups' baseline characteristics.	Not clear	<p>Not clear</p> <p>ERG noted that mean baseline BCVA scores and central macular thickness scores for both groups were reported. Mean baseline BCVAs were similar in the sham (41 ± 22 ETDRS letters) and ranibizumab groups (45 ± 23 ETDRS letters). Mean central macular thickness was higher in the ranibizumab group (661 ± 161 micrometres) than in the sham group (587 ± 154 ETDRS</p>

			micrometres).
Were the care providers, participants and outcome assessors blind to treatment allocation?	The patients were blinded to treatments. The investigating physician and nurse were masked toward the injecting physician and nurse and vice versa.	Yes	Yes
Were there any unexpected imbalances in drop-outs between groups?	There were no unexpected imbalances, but patients did drop-out of the groups: 1 patient in the ranibizumab groups withdrew, and 2 withdrew from the sham injection group.	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	–	No	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	The efficacy analysis was undertaken on the per-protocol patient population.	No	No

Appendix 3. Adverse effects from BRAVO, CRUISE and HORIZON

Table A3.1. Frequency of adverse events at 6-months in BRAVO

NCT00486018 BRAVO ⁽¹⁵⁾	Frequency of adverse events at 6-months, n (%) (Relative risk [95% CI], risk difference)		
	Sham (n = 131)	0.3mg ranibizumab (n = 134)	0.5mg ranibizumab (n=130)
Key Study Eye Ocular Adverse Events			
Any Intraocular Inflammation Event	4 (3.1)	2 (1.5)	0
Iridocyclitis	0	1 (0.7)	0
Iritis	4 (3.1)	1 (0.7)	0
Vitritis	0	0	0
Endophthalmitis	0	0	1 (0.8) ^a
Lens Damage	0	0	0
Cataract	4 (3.1)	1 (0.7)	4 (3.1)
Iris Neovascularisation	3 (2.3)	0	0
Neovascular glaucoma	0	0	0
Rhegmatogenous retinal detachment	0	1 (0.7) ^{a,b}	0
Retinal Tear	0	1 (0.7) ^{a,b}	0
Vitreous haemorrhage	6 (4.6)	6 (4.5)	2 (1.5)
Non-ocular serious adverse events potentially related to VEGF inhibition^g			
Haemorrhagic stroke	1 (0.8)	0	1 (0.8) ^c
Ischaemic stroke	0	0	0
Acute myocardial infarction	0	0	1 (0.8)
Unstable angina	0	0	1 (0.8)
Hypertension	0	2 (1.5)	0
Non-ocular haemorrhage, other	0	2 (1.5) ^d	1 (0.8) ^e
Intestinal perforation	0	0	1 (0.8)
Proteinuria	0	0	0
Antiplatelet Trialists' Collaboration arterial thromboembolic events (Serious adverse events)			
Vascular death	0	0	1 (0.8) ^f
Nonfatal myocardial infarction	0	0	1 (0.8)
Nonfatal haemorrhagic stroke	1 (0.8)	0	0
Nonfatal ischaemic stroke	0	0	0
^a Event was reported as serious. ^b The same patient had rhegmatogenous retinal detachment and retinal tear which were both classified as serious. ^c There was one patient death in the 0.5 mg ranibizumab group from haemorrhagic cerebral stroke. ^d In the 0.3mg ranibizumab group there was one intra-abdominal haematoma and one rectal haemorrhage. ^e The non-ocular haemorrhage in the 0.5 mg ranibizumab group was dye to post procedural (colonoscopy) haemorrhage.			

[†] The incident of vascular death in the 0.5 mg ranibizumab group was also reported as haemorrhagic stroke potentially related to VEGF inhibition

^g All non-ocular adverse events that were potentially related to VEGF inhibition were classified as serious

Table A3.2. Frequency of adverse events at 12 months in BRAVO

NCT00486018 BRAVO ⁽⁴⁴⁾	Frequency of adverse events at one year, n (%)			
	Sham ^a (n = 131)	Sham/0.5mg ^b (n=115)	0.3mg ranibizumab (n = 134)	0.5mg ranibizumab (n=130)
Key Study Eye Ocular Adverse Events				
Any intraocular inflammation event (iritis, vitritis)	4 (3.1)	1 (0.9)	3 (2.2)	0
Endophthalmitis	0	0	0	1 (0.8) ^c
Cataract	4 (3.1)	3 (2.6)	6 (4.5)	8 (6.2)
Iris Neovascularisation	3 (2.3)	0	1 (0.7)	1 (0.8)
Neovascular glaucoma	0	0	0	0
Rhegmatogenous retinal detachment	0	0	1 (0.7) ^{c,d}	0
Retinal Tear	0	0	1 (0.7) ^{c,d}	0
Vitreous haemorrhage	6 (4.6)	1 (0.9)	7 (5.2)	2 (1.5)
Non-ocular serious adverse events potentially related to VEGF inhibition^g				
Haemorrhagic stroke	-	1 (0.8) ^e	0	1 (0.8)
Ischaemic stroke	-	0	1 (0.7)	0
Transient ischaemic attack	-	0	0	0
Acute myocardial infarction	-	1 (0.9)	0	1 (0.8)
Angina pectoris	-	0	0	1 (0.8) ^f
Retinal artery embolism/occlusion	-	0	0	0
Hypertension	-	1 (0.9)	3 (2.2)	1 (0.8)
Non-ocular haemorrhage	-	0	2 (1.5)	1 (0.8)
Intestinal perforation	-	0	0	1 (0.8)
Proteinuria	-	0	0	0
Antiplatelet Trialists' Collaboration arterial thromboembolic events (Serious adverse events)				
Vascular death	-	0	0	0
Nonfatal myocardial infarction	-	1 (0.9)	0	1 (0.8)
Nonfatal haemorrhagic stroke	-	1 (0.8) ^e	0	1 (0.8)
Nonfatal ischaemic stroke	-	0	1 (0.7)	0
^a Outcomes during 6-month treatment period for safety evaluable sham-group patients (i.e. received at least one sham injection during the treatment period) ^b Outcomes during 6-month observation period for safety evaluable sham/0.5mg group patients (i.e. received at least one dose 0.5mg ranibizumab PRN during the observation period) ^c Event was reported as serious ^d The same patient had rhegmatogenous retinal detachment and retinal tear which were both classified as serious ^e Event occurred during 6-month treatment period (sham n=131) ^f Event was reported as unstable angina ^g All non-ocular adverse events that were potentially related to VEGF inhibition were classified as serious				

Table A3.3. Frequency of adverse events at 6 months in CRUISE

NCT00485836 CRUISE ⁽¹⁶⁾	Frequency of adverse events at 6-months, n (%) (Relative risk [95% CI], risk difference)		
	Sham (n=129)	0.3mg ranibizumab (n=132)	0.5mg ranibizumab (n=129)
Ocular Adverse Events			
Iridocyclitis	0	0	0
Iritis	3 (2.3)	2 (1.5)	2 (1.6) ^c
Vitritis	2 (1.6)	1 (0.8)	1 (0.8) ^c
Endophthalmitis	0	0	0
Lens Damage	0	0	0
Cataract	0	2 (1.5)	2 (1.6)
Iris Neovascularisation	9 (7.0)	2 (1.5)	1 (0.8) ^a
Neovascular glaucoma	2 (1.6)	0	0
Rhegmatogenous retinal detachment	0	0	0
Retinal Tear	0	0	0
Vitreous haemorrhage	9 (7.0) ^b	5 (3.8) (0.54 [0.19-1.58], 0.032)	7 (5.4) (0.78 [0.30-2.03], 0.016)
Non-ocular serious adverse events potentially related to VEGF inhibition^e			
Haemorrhagic stroke	0	0	0
Ischaemic stroke	0	0	0
Transient ischaemic attack	0	0	1 (0.8) ^d
Myocardial infarction	1 (0.8)	1 (0.8)	1 (0.8)
Angina pectoris	0	0	1 (0.8) ^d
Hypertension	1 (0.8)	0	0
Non-ocular haemorrhage, other	0	0	0
Proteinuria	0	0	0
Antiplatelet Trialists' Collaboration arterial thromboembolic events			
Vascular death	0	0	0
Nonfatal myocardial infarction	1 (0.8)	1 (0.8)	1 (0.8)
Nonfatal haemorrhagic stroke	0	0	0
Nonfatal ischaemic stroke	0	0	0
^a Event was reported as serious ^b One vitreous haemorrhage was reported as serious in the sham group ^c The same patient in the 0.5 mg ranibizumab group had both iritis and vitritis ^d The same patient in the 0.5 mg ranibizumab group had both transient ischaemic attack and angina pectoris ^e All non-ocular adverse events that were potentially related to VEGF inhibition were classified as serious			

Table A3.4. Frequency of adverse events at 12 months in CRUISE

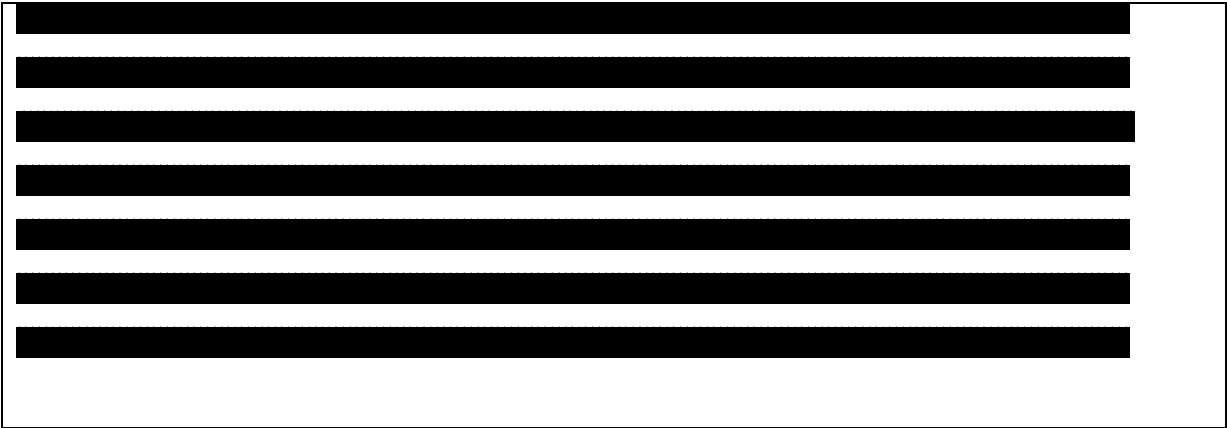
NCT00485836 CRUISE ⁽⁴⁴⁾	Frequency of adverse events at one year, n (%)			
	Sham ^a (n=129)	Sham/0.5mg ^b (n=110)	0.3mg ranibizumab (n=132)	0.5mg ranibizumab (n=129)
Ocular Adverse Events				
Any intraocular inflammation event (iritis, vitritis)	5 (3.9)	2 (1.8)	3 (2.3)	2 (1.6)
Endophthalmitis	0	0	0	0
Cataract	0	2 (1.8) ^c	5 (3.8)	9 (7.0)
Iris Neovascularisation	9 (7.0)	2 (1.8)	2 (1.5)	5 (3.9) ^c
Neovascular glaucoma	2 (1.6)	0	0	1 (0.8)
Rhegmatogenous retinal detachment	0	0	0	0
Retinal Tear	0	2 (1.8) ^c	0	2 (1.6)
Vitreous haemorrhage	9 (7.0) ^c	2 (1.8) ^c	7 (5.3)	7 (5.4)
Non-ocular serious adverse events potentially related to VEGF inhibition				
Haemorrhagic stroke	-	0	0	0
Ischaemic stroke	-	0	0	1 (0.8)
Transient ischaemic attack	-	0	1 (0.8)	1 (0.8) ^d
Acute myocardial infarction	-	1 (0.8) ^e	1 (0.8)	1 (0.8)
Angina pectoris	-	0	0	1 (0.8) ^d
Retinal artery embolism/occlusion	-	0	1 (0.8)	0
Hypertension	-	1 (0.8) ^e	0	0
Non-ocular haemorrhage	-	0	0	0
Intestinal perforation	-	0	0	0
Proteinuria	-	0	0	0
Antiplatelet Trialists' Collaboration arterial thromboembolic events				
Vascular death	-	0	0	0
Death of unknown cause	-	0	0	1 (0.8)
Nonfatal myocardial infarction	-	1 (0.8) ^e	1 (0.8)	1 (0.8)
Nonfatal haemorrhagic stroke	-	0	0	0
Nonfatal ischaemic stroke	-	0	0	1 (0.8)
^a Outcomes during the 6-month treatment period for safety evaluable sham-group patients (i.e. received at least one sham injection during the treatment period) ^b Outcomes during the 6-month observation period for safety evaluable sham/0.5mg group patients (i.e. received at least one dose 0.5mg ranibizumab PRN during the observation period) ^c Iris neovascularisation was reported as serious in one patient in the 0.5 mg ranibizumab group ^d The same patient in the 0.5 mg ranibizumab group had both transient ischaemic attack and angina pectoris ^e Occurred during the 6-month treatment period (sham n=129)				

Table A3.5. Frequency of adverse events in HORIZON one year extension study (BRVO patients from BRAVO)

NCT00379795 HORIZON	Frequency of adverse events in one year follow-up of BRAVO, n (%)		
	Sham/0.5mg (n = 93)	0.3mg ranibizumab (n = 103)	0.5mg ranibizumab (n = 104)
Ocular Adverse Events			
Any adverse event	2 (2.2%)	4 (3.9%)	6 (5.8%)
Amaurosis fugax	0	1 (1.0%)	0
IOP increased	0	1 (1.0%)	1 (1.0%)
Macular oedema	0	0	2 (1.9%)
Macular ischaemia	0	1 (1.0%)	0
Ischaemic optic neuropathy	0	0	1 (1.0%)
Retinal vein occlusion	0	1 (1.0%)	1 (1.0%)
Visual acuity reduced	1 (1.1%)	0	1 (1.0%)
Vitreous haemorrhage	1 (1.1%)	1 (1.0%)	0
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Non-ocular Serious Adverse Events Potentially related to VEGF inhibition			
Any adverse event	1 (1.1%)	5 (4.9%)	6 (5.8%)
Hypertension	0	1 (1.0%)	1 (1.0%)
Acute coronary syndrome	0	0	0
Acute myocardial infarction	0	0	0
Amaurosis fugax	0	1 (1.0%)	0
Angina pectoris	1 (1.1%)	0	0
Cerebral haemorrhage	0	0	0
Cerebrovascular accident	0	0	1 (1.0%)
Intestinal ischaemia	0	0	0
Myocardial infarction	0	1 (1.0%)	1 (1.0%)
Transient ischaemic attack	0	3 (2.9%)	0
Non-ocular haemorrhage	0	0	3 (2.9%) ^a
Other potentially associated events	0	0	1 (1.0%)
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Table A3.6. Frequency of adverse events in HORIZON one year extension study (CRVO patients from CRUISE)

NCT00379795 HORIZON	Frequency of adverse events in one year follow-up of CRUISE, n (%)		
	Sham/0.5mg (n=96)	0.3mg ranibizumab (n=107)	0.5mg ranibizumab (n=99)
Ocular Adverse Events			
Any adverse event	5 (5.2%)	10 (9.3%)	3 (3.0%)
Cataract	0	1 (0.9%)	0
Cystoid macular oedema	0	1 (0.9%)	0
Endophthalmitis	0	2 (1.9%)	0
IOP increased	0	1 (0.9%)	0
Macular oedema	1 (1.0%)	2 (1.9%)	2 (2.0%)
Ischaemic optic neuropathy	0	1 (0.9%)	0
Visual acuity reduced	3 (3.1%)	2 (1.9%)	1 (1.0%)
Visual acuity reduced transiently	0	1 (0.9%)	0
Vitreous haemorrhage	1 (1.0%)	0	0
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Non-ocular serious adverse events potentially related to VEGF inhibition			
Any adverse event	3 (3.1%)	2 (1.9%)	6 (6.1%)
Hypertension	0	0	0
Acute coronary syndrome	0	0	1 (1.0%)
Acute myocardial infarction	0	1 (0.9%)	0
Amaurosis fugax	0	0	0
Angina pectoris	0	0	0
Cerebral haemorrhage	1 (1.0%)	0	0
Cerebrovascular accident	0	0	1 (1.0%)
Intestinal ischaemia	1 (1.0%)	0	0
Ischaemic stroke	0	0	1 (1.0%)
Transient ischaemic attack	0	1 (0.9%)	0
Non-ocular haemorrhage	2 (2.1%) ^b	0	2 (2.0%) ^c
Other potentially associated events	0	0	1 (1.0%)
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Appendix 4. Details of the manufacturer’s approach to the inclusion of dexamethasone

The following method was used to estimate relative risks for dexamethasone intravitreal implant that could be used in the economic model. This methodology was used separately for BRVO and CRVO.

The manufacturer’s submission to NICE reported the mean change from baseline for both dexamethasone intravitreal implant (x1) and sham (x2) as well as the lower (ll) and upper (ul) limit of the 95% normal approximation confidence interval for the difference between mean changes from baseline of dexamethasone intravitreal implant versus sham (x1-x2) at Day 30 (MS; pg 59, Table 25 [BRVO] and Table 26 [CRVO]). Assuming that the standard deviation for dexamethasone intravitreal implant is equal to standard deviation for sham (s1=s2=s), the common standard deviation s can be derived as

$$s = (ul-x1+x2)/1.96*\sqrt{(1/n1+1/n2)}$$

where n1 and n2 are number of patients in the dexamethasone intravitreal implant and sham groups, respectively. If it is assumed that the change from baseline X1 (X2) comes from the normal distribution model with mean = x1 (x2) and standard deviation s for dexamethasone intravitreal implant (sham): $X1 (X2) \sim N(x1(x2), s)$, probabilities to:

gain ≥4 lines (gain ≥20 letters)
gain ≥2 and <4 lines (gain ≥10 and <20 letters)
no change (lose <2 and gain <2 lines) (lose <10 and gain <10 letters)
lose ≥2 lines and <4 (lose ≥10 and <20 letters)
lose ≥4 lines (lose ≥20 lines)

can be estimated for dexamethasone intravitreal implant as the following areas under curve:

Prob (X1 (X2) ≥20)		p11
Prob (10 ≥X1 (X2) <20)		p12
1-sum of other probabilities in the vector	=	100-p11-p12-p13-p14
Prob (-20 <X1 (X2) ≤-10)		p13
Prob (X1(X2) ≤-20)		p14

and for sham as the following areas under curve

Prob (X1 (X2) ≥20)		p21
Prob (10 ≥ X1 (X2) <20)		p22
1-sum of other probabilities in the vector	=	100-p21-p22-p23-p24
Prob (-20 <X1 (X2) ≤-10)		p23
Prob (X1(X2) ≤-20)		p24

Risk ratios $r_1=p_{11}/p_{21}$, ... up to, $r_4=p_{14}/p_{24}$ can then be calculated and multiplied by p_{11} , ... p_{41} , where:

p_{11} is the probability of (gain ≥ 4 lines [20 letters]) for control group)

...

p_{41} is the probability of (lose ≥ 4 lines (20 letters) for control group)

To obtain an ‘indirect estimate’ of dexamethasone intravitreal implant effect over the control group from BRAVO or CRUISE:

The risk ratios for dexamethasone intravitreal implant imputed into the model are then:

	BRVO	CRVO
r1	1.49	1.52
r2	1.19	1.27
r3	0.67	0.81
r4	0.5	0.67

These relative risks are applied to the month 1 progression rates of the standard care (control) arm in the model to estimate crude progression rates for dexamethasone intravitreal implant compared with ranibizumab.

In month 2, a relative risk of 1 was applied to derive dexamethasone intravitreal implant progression rates to avoid double counting as described previously.

As no published data for dexamethasone intravitreal implant were identified for 7 months or beyond, the 7–12 month data for ranibizumab was applied to approximate dexamethasone intravitreal implant progression. Thus, the model assumes identical effectiveness for ranibizumab and dexamethasone intravitreal implant from 7 months.