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

ERRATUM

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BMJ Technology Assessment Group

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

The table below lists the page to be replaced in the original document and the nature of the change:

Page No.	Change
13	Section 1.6: final paragraph reworded
23	Section 2.2: text relating to incidence and prevalence amended
42	Section 4.3.1: in Table 5, column heading labelled "Sham" amended to "Sham/0.5 mg"
44	Section 4.3.1: sentence commencing "These data are in accordance" replaced
46	Section 4.3.1: in Table 7, column heading labelled "Sham" amended to "Sham/0.5 mg"
48	Section 4.3.2: in Table 8, column heading labelled "Sham" amended to "Sham/0.5 mg"
92	Section 5.3.8: text relating to GLP direct costs amended
93	Section 5.3.8: text relating to costs of blindness amended
105	Section 5.4.1: in Table 52, text relating to Brazier utility recommendation 'for ocular conditions' deleted
108	Section 5.4.4: text relating to the manufacturer's clinical experts amended
113	Section 5.4.6: in Table 57, column heading labelled "Sham" amended to "Sham/0.5 mg"
116	Section 5.4.6: text relating to IPD amended
122	Section 5.4.6: Scenario J and scenario K ICERs corrected
133	Section 7: text relating to conflicting bias deleted Section 7.1: sentence outlining future research on efficacy and adverse effects of ranibizumab amended

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, in BRAVO and CRUISE, ranibizumab was administered each month during the treatment phase (0–6 months), even if the patient achieved clinical stability with good BCVA before the 6 month time point (51% in BRAVO ranibizumab 0.5 mg group and 45% in CRUISE ranibizumab 0.5 mg group). Although there are longer term data on the number of injections of ranibizumab given on a PRN basis from the observational phases of BRAVO and CRUISE and the HORIZON extension study, the effects of cessation of ranibizumab injections on visual acuity based on the recommended regimen are unknown.

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.

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 visual impairment due to 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%

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]. 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/0.5 mg (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 (*post-hoc* analysis)
Percentage at month 1	8.3%	32.8%	p <0.005 (*post-hoc* analysis)
Percentage at month 2	16.7%	39.7%	p <0.005 (*post-hoc* analysis)
Percentage at month 3	17.4%	50.4%	p <0.005 (*post-hoc* 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%)	–

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 suggest that there could be benefit in delaying treatment to allow for spontaneous improvement.

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 ≥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 ≥20/40 and CFT <250 microns at month 3 [redacted].

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 (%)	[redacted] (8.3)	[redacted] (16.7)	[redacted] (17.4)	[redacted] (32.8)	[redacted] (39.7)	[redacted] (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:

[redacted]

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/0.5 mg	Rani 0.5 mg
Last observation prior to GLP treatment for those patients receiving GLP treatment at month 3 [redacted]		
Number of patients being assessed[a]	[redacted]	[redacted]
Mean visual acuity	[redacted]	[redacted]
Mean change in BCVA from baseline	[redacted]	[redacted]
Outcomes measures at month 6 for those patients who received GLP treatment at month 3		
Number of patients being assessed	[redacted]	[redacted]
Mean visual acuity	[redacted]	[redacted]
Mean change in BCVA from baseline	[redacted]	[redacted]
Outcomes measures at month 12 for those patients who received GLP treatment at month 3		
Number of patients being assessed	[redacted]	[redacted]
Mean visual acuity	[redacted]	[redacted]
Mean change in BCVA from baseline	[redacted]	[redacted]
[redacted]		

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

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/0.5 mg (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%) [redacted]	62 (47.7%) [redacted]	p <0.0001[b]
Proportion at month 12, n (%)	43 (33.1%) [redacted]	66 (50.8%) [redacted]	–
Proportion of patients who gained ≥10 ETDRS letters			
Month 6, n (%)	[redacted]	[redacted]	[redacted]
			[redacted]
Mean [redacted] change from baseline NEI VFQ-25 Composite Score			
Month 6[d]	2.8 [redacted] 95% CI: 0.8 to 4.7 127 patients in analysis	6.2 [redacted] 95% CI: 4.3 to 8.0 128 patients in analysis	p <0.05 for rani vs sham[c]

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, the manufacturer assumes that 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 (57.6%). 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 annually 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 the costs of low vision aids and low vision rehabilitation were only applied 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 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

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 *et al*.[40], a source that was recommended in TA155[58]

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 may be 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".

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

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 21.4% [redacted] of patients in the ranibizumab group. Conversely, the effect of GLP may be underestimated as only 57.6% [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

	Probabilities		
Transition	**Ranibizumab**	**Sham/0.5 mg**	**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

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	[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: CRVO, central retinal vein occlusion; MO, macular oedema; PRN, *pro re nata*; 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, the absence of an explanatory key for the IPD submitted by the manufacturer, along with the late arrival of this data, meant the ERG was unable to formulate the month 7 to 12 transition probabilities for the sham arm required to permit this analysis.

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	£46,760
K	5.2	7.1	Brown	0.014[a]	Combination of BSE and WSE	Applied to only BSE	£68,827
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 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. 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 other treatments currently used in clinical practice for treatment of visual impairment due to MO secondary to RVO. 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.