NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Premeeting briefing

Ranibizumab for the treatment of macular oedema secondary to retinal vein occlusion (RVO)

This briefing presents the key issues arising from the manufacturer's submission, Evidence Review Group (ERG) report and statements made by consultees and their nominated clinical specialists and patient experts. Please note that this briefing is a summary of the information available and should be read with the full supporting documents.

The manufacturer was asked to provide:

- visual acuity outcomes at months 1, 2 and 3 for all patients randomised to the sham injection and ranibizumab 0.5 mg groups in the BRAVO trial
- visual acuity outcomes at months 6 and 12 for patients receiving laser treatment within the 6-month treatment period in the BRAVO trial
- comparisons between: ranibizumab and dexamethasone in the treatment of branch retinal vein occlusion (BRVO) and central retinal vein occlusion (CRVO); ranibizumab and bevacizumab in the treatment of BRVO and CRVO; and ranibizumab and grid laser photocoagulation in the treatment of BRVO
- a scenario analysis in which the model uses the pre-specified trial outcome of a gain or loss in visual acuity of greater than 15 letters, rather than 10 or more letters
- patient-level data for the validation of the transition probabilities presented in the model
- further justification for the choice of utilities and an updated model that includes age-adjusted utilities

- clarification of the administration cost of laser therapy.

Licensed indication

Ranibizumab (Lucentis, Novartis Pharmaceuticals UK) has a marketing authorisation for the treatment of 'visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO)'.

Key issues for consideration

- The manufacturer omitted direct or indirect comparisons of ranibizumab with bevacizumab and dexamethasone in macular oedema secondary to branch retinal vein occlusion and central retinal vein occlusion.
- In the base-case analysis, the model assumes all patients are treated in the better-seeing eye, whereas 91.7% and 90.0% of patients in the BRAVO and CRUISE trials respectively were treated in their worse-seeing eye.
- Concomitant grid laser photocoagulation was permitted in both the sham injection and ranibizumab groups in the BRAVO trial from 3 months, and again from 9 months during the observation phase (6–12 months). The effects of grid laser photocoagulation can last up to 3 years after administration.
- The use of concomitant grid laser photocoagulation potentially invalidates the comparison of ranibizumab with either sham injection or grid laser photocoagulation for BRVO.
- The manufacturer uses pooled transition probabilities in the model for ranibizumab versus grid laser photocoagulation for BRVO in order to account for the effect of concomitant laser from 3 months. The ERG applied unpooled transition probabilities to the model which increased the manufacturer's base-case ICER to £52,004.
- The ERG used the manufacturer's relative risks for the ranibizumab and dexamethasone comparison (0.55 for BRVO and 0.3 for CRVO) in their

additional analyses. If the ERG's preferred relative risks were applied, derived from their indirect comparison, (0.79 for BRVO and 0.4 for CRVO), the ERG's base-case ICERs would be increased further.

- Health states were defined in the model as changes of 10 letters (2 lines) rather than using the pre-specified trial outcome of a gain/loss of 15 letters or more.
- Uncertainty surrounding the required duration of ranibizumab treatment.
- The population in the scope includes all people with ischaemic and non-ischaemic retinal vein occlusion (RVO). Because people with brisk afferent pupillary defect (an indicator of retinal ischaemia) were excluded from the BRAVO and CRUISE trials, people with RVO and ischaemia of the retina are unlikely to have been included in the these studies.
- Long-term (24 months) follow-up data are available for patients completing the CRUISE or BRAVO trials through a single-arm extension study (HORIZON). [redacted] No comparative long-term data are available.

1 Decision problem

1.1 Decision problem approach in the manufacturer's submission

Population	People with visual impairment because of macular oedema secondary to retinal vein occlusion (RVO)
Intervention	Ranibizumab
Comparators	Central retinal vein occlusion (CRVO): i. Best supportive care (ischaemic and non-ischaemic CRVO) ii. Dexamethasone implant Branch retinal vein occlusion (BRVO): i. Dexamethasone implant ii. Grid pattern photocoagulation
Outcomes	Visual acuity (the affected eye), adverse effects of treatment, health-related quality of life
Economic evaluation	Cost–utility analysis using a lifetime time horizon in the primary analysis, and taking an NHS and Personal Social Services perspective

1.2 Evidence Review Group comments

1.2.1 Population

The populations in the BRAVO and CRUISE trials were limited to people with macular oedema secondary to non-ischaemic BRVO and CRVO, respectively, which are distinct subgroups of the population defined in the NICE scope and the eligible UK population. Approximately 20% of people with CRVO are reported to have retinal ischaemia.

1.2.2 Intervention

The treatment regimen is monthly intravitreal injections of ranibizumab continued until maximum visual acuity is achieved (when the person's visual acuity is stable for three consecutive monthly assessments while on ranibizumab treatment). If no improvement in visual acuity is observed over the course of the first three injections, cessation of treatment is recommended. People who achieve visual stability should be monitored monthly for visual acuity, and treatment with ranibizumab resumed when monitoring indicates loss of visual acuity because of macular oedema secondary to RVO. Monthly injections of ranibizumab 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.

1.2.3 Comparators

Ischaemic RVO

The retinal vein occlusion guidelines from the Royal College of Ophthalmologists indicate that best supportive care is the most appropriate treatment for people with visual impairment because of macular oedema secondary to ischaemic BRVO. Grid laser photocoagulation is more appropriate than best supportive care for people with macular oedema secondary to BRVO who have severe visual impairment or whose symptoms have been present for over a year; however very few people with these characteristics were included in the BRAVO trial.

Non-ischaemic RVO

The ERG noted that the manufacturer omitted comparisons with bevacizumab or dexamethasone intravitreal implant in macular oedema secondary to non-ischaemic BRVO or CRVO. The ERG considered that such comparisons were appropriate for this indication, and suggested that they could have been attempted. The following table summarises the ERG's comments on the

comparators for ischaemic and non-ischaemic BRVO and CRVO in the manufacturer's submission.

Type of macular oedema	Comparator in manufacturer's submission	ERG comments
Ischaemic CRVO	Best supportive care	Appropriate
Non-ischaemic CRVO	Best supportive care	Indirect comparisons of ranibizumab with dexamethasone and bevacizumab could have been attempted
Ischaemic BRVO	Best supportive care	Appropriate
Non-ischaemic BRVO	Grid laser photocoagulation	Grid laser photocoagulation is appropriate Indirect comparisons of ranibizumab with dexamethasone and bevacizumab could have been attempted

1.2.4 Outcomes

The ERG noted that the manufacturer presented data on improvement in visual acuity in only the treated eye, rather than for the whole person (bilateral visual acuity). The latter was the outcome measure specified in the final NICE scope. The manufacturer highlighted that whole person best corrected visual

acuity data were not available from the BRAVO and CRUISE trials. The ERG noted that the manufacturer included additional measures of visual acuity in the study eye. These included:

- the mean change from baseline best corrected visual acuity letter score over time to month 6
- the percentage of patients who gained 15 or more letters from baseline best corrected visual acuity at month 6
- the percentage of patients who lost under 15 letters from baseline best corrected visual acuity at month 6
- the proportion of people who gained 10 or more letters from baseline best corrected visual acuity at month 6. (This outcome was used to form the basis of the manufacturer's economic analysis)
- the mean change from baseline in the National Eye Institute Visual Functioning Questionnaire (NEI VFQ-25) near activities subscale over time up to 6 months and at 12 months
- the mean change from baseline in the NEI VFQ-25 distance activities subscale over time up to 6 months and at 12 months
- the incidence and severity of ocular and non-ocular adverse events and serious adverse events.

1.2.5 Economic evaluation

The ERG considered that the 15-year time horizon in the manufacturer's economic analysis was in line with that stipulated in the final scope issued by NICE.

1.2.6 Subgroups

The ERG noted that, of the subgroups defined in the NICE scope, the manufacturer was unable to carry out a subgroup analysis based on the presence or absence of retinal ischaemia, because people with retinal ischaemia were not included in either the BRAVO or CRUISE trials. The manufacturer was able to carry out analysis for baseline best corrected visual

acuity, baseline central foveal thickness, and duration of macular oedema from diagnosis to screening. It presented data for these subgroups on the primary outcome of change in mean best corrected visual acuity from baseline and the secondary outcome of the proportion of patients with an improvement in visual acuity of 15 or more letters. See tables 26 and 27 [BRAVO trial], and tables 28 and 29 [CRUISE trial] of the ERG report.

1.3 Statements from professional/patient groups and nominated experts

Submissions by patient organisations and patient experts highlighted the impact of RVO on health-related quality of life. Effects included loss of sight, increased reliance on support from family members and work colleagues and particular difficulties associated with the considerable risk of developing problems in the other eye.

Clinical specialists commented that RVO is presently managed differently depending on whether the vascular occlusion involves CRVO or BRVO. They also noted that the majority of ophthalmologists do not treat the macular oedema in people with retinal ischaemia. Clinical evidence of retinal ischaemia was an exclusion criterion in the BRAVO and CRUISE trials, which were of ranibizumab therapy in BRVO and CRVO respectively. The Royal College of Ophthalmologists' interim guideline on management of RVO (December 2010) does not advocate treatment of macular oedema in the presence of significant retinal ischaemia. Clinical specialists highlighted that the recent licensing of the dexamethasone intravitreal implant is supported by the Royal College of Ophthalmologists' interim guideline for both non-ischaemic BRVO and CRVO, but uptake throughout the NHS has been slow. They noted that this was probably because of geographical variations in funding prior to the NICE final appraisal, and inexperience of using the implant device. The clinical specialists noted that bevacizumab has been used increasingly to treat both BRVO and CRVO, although practice varies

depending on local decision making. In addition, the clinical specialists noted that there was significant variation in dosage and dosing schedules and a lack of randomised controlled trial evidence of efficacy, safety or long-term data.

Patient organisations and patient experts commented that the potential benefits of ranibizumab in the treatment of macular oedema secondary to RVO included enabling the person to continue working and increasing their independence in terms of day-to-day activities carried out at home and at work. Some patients commented that the procedure of injecting ranibizumab was unpleasant but that the potential improvements outweighed the unpleasantness associated with the treatment.

2 Clinical-effectiveness evidence

2.1 Clinical effectiveness in the manufacturer's submission

The main sources of evidence cited in the manufacturer's submission were the BRAVO and CRUISE randomised controlled trials (RCTs) that evaluated the efficacy of ranibizumab in macular oedema secondary to branched retinal vein occlusion and to central retinal vein occlusion. Patients who completed the BRAVO and CRUISE 12-month trials could enter an open-label extension study (HORIZON).

2.1.1 BRAVO and CRUISE trials

The BRAVO and CRUISE trials were both three-armed RCTs carried out at multiple centres in the USA (93 sites for BRAVO and 95 sites for CRUISE). Patients with BRVO in BRAVO and patients with CRVO in CRUISE were randomised 1:1:1 to sham injection, monthly intraocular ranibizumab 0.3 mg or monthly intraocular ranibizumab 0.5 mg. Inclusion criteria for both BRAVO and CRUISE included macular oedema that had been diagnosed within 12 months of study initiation (further details of inclusion and exclusion criteria are presented in the manufacturer's submission (table B6, page 69). Patients

entered a 6-month treatment phase during which monthly injections were given, beginning on day 0. Rescue treatment with grid laser photocoagulation was permitted in BRAVO (but not CRUISE) for all eligible patients in both sham injection and ranibizumab groups from month 3 (see manufacturer's submission page 59 for eligibility details). In both BRAVO and CRUISE the treatment phase was followed by a 6-month observation phase during which all subgroups could receive ranibizumab as needed. Patients in the observation phase of BRAVO (but not CRUISE) could receive rescue treatment with grid laser photocoagulation from 3 months (that is, at month 9 of the study). The final treatment in both BRAVO and CRUISE was given at month 11 with a final study visit at month 12.

The primary outcome reported in both the BRAVO and CRUISE trials was the mean change from baseline in best corrected visual acuity score in the study eye at 6 months. Best corrected visual acuity was measured based on the Early Treatment of Diabetic Retinopathy Study (ETDRS) eye chart, assessed at a distance of 4 metres. Secondary outcomes for both BRAVO and CRUISE included the following:

- the mean change from baseline in the study eye up to 6 and 12 months
- the proportion of patients gaining visual acuity of 15 letters or more or losing less than 15 letters from baseline at 6 and 12 months
- the mean change in composite NEI VFQ-25 near activities and distance activities subscale over time, from baseline up to 6 months and at 12 months.

Results

Only results for ranibizumab 0.5 mg are reported because this is the dose for which European Medicines Agency approval is anticipated for the treatment of macular oedema secondary to RVO.

The number of patients randomised to BRAVO and CRUISE was 397 and 392 respectively. In both studies the average patient age was 65 years in the sham groups and 67 years in the ranibizumab groups. In BRAVO, 91.7% in the sham group and 95.4% in the ranibizumab group were treated in their worse seeing eye. In CRUISE, 90.0% in the sham group and 92.3% in the ranibizumab group were treated in their worse seeing eye. Baseline characteristics for patients for both studies are presented in the manufacturer's submission (Table B7, pg 71 for BRAVO and Table B8, pg 73 for CRUISE).

Details of treatment received throughout BRAVO, CRUISE and HORIZON are presented on page 91 of the manufacturer's submission (table B16). The mean number of ranibizumab injections in the treatment phase was 5.7 (BRAVO) and 5.6 (CRUISE). The mean number of ranibizumab injections in the observation phase was 2.7 (BRAVO) and 3.3 (CRUISE). More than 80% of patients from the sham injection group in both BRAVO and CRUISE received ranibizumab PRN during the observation phase. During the first 6 months of the BRAVO study, laser was used in 57.6% of patients in the sham injection group and in 21.4% of the patients in the ranibizumab group. Over the 12 month study period in BRAVO, [redacted] of patients in the sham/ranibizumab group and [redacted] of patients in the ranibizumab group received rescue laser treatment.

Efficacy results from the BRAVO trial (presented on pages 94 to 118 of manufacturer's submission)

At the 6-month time point in the BRAVO trial, patients in the 0.5 mg ranibizumab groups had gained a mean of 18.3 letters (95% confidence interval [CI] 16.0 to 20.6) from baseline best corrected visual acuity score, compared with a gain of 7.3 letters (95% CI 5.1 to 9.5) in the group receiving sham injection ($p < 0.0001$ for ranibizumab compared with sham injection). At month 12, the 0.5 mg ranibizumab group reported a mean gain in best corrected visual acuity score from baseline of 18.3 letters (95% CI 15.8 to

20.9) compared with the sham/0.5 mg group that had gained 12.1 letters (95% CI 9.6 to 14.6) by month 12. The manufacturer stated that the data from the BRAVO trial indicated that the effect of ranibizumab 0.5 mg was seen early on in treatment as shown by a statistically significant difference in visual acuity ($p < 0.0001$ compared with sham injection) being detected at day 7 after treatment. The manufacturer reported a mean improvement in visual acuity of between 15 and 20 letters (between 3 and 4 lines) after 6 months of treatment with ranibizumab, compared with 7 letters (1.5 lines) in the sham injection group. The observed improvement at month 6 from baseline in the NEI VFQ-25 composite score was statistically significantly greater in patients receiving ranibizumab 0.5 mg (10.4 points, 95% CI 8.3 to 12.4) than in patients receiving sham injection (5.4 points, 95% CI 3.6 to 7.3; $p < 0.005$ for ranibizumab compared with sham injection). The manufacturer reported that overall, the results from the BRAVO trial demonstrated a clinically meaningful and statistically significant effect of ranibizumab on visual acuity and patient-reported outcomes based on the NEI VFQ-25 at 6 months. For the 6-month observation period of the BRAVO trial, in which all patients could receive ranibizumab as needed, the 0.5 mg ranibizumab group reported a mean gain in best corrected visual acuity score from baseline of 18.3 letters (95% CI 15.8 to 20.9) compared with 12.1 letters (95% CI 9.6 to 14.6) in the sham/0.5 mg ranibizumab group. A summary of the results is presented in table 1.

Table 1 Summary of BRAVO efficacy data (table 5 of ERG report)

Timeframe	Sham/0.5 mg (n = 132)	Ranibizumab 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]	[redacted] (61.1%) [redacted]	p < 0.00001[a]
Proportion at month 12, n (%)	[redacted] (43.9%) [redacted]	[redacted] (60.3%) [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[c]	5.4 [redacted] 95% CI: 3.6 to 7.3	10.4 [redacted] 95% CI: 8.3 to 12.4	p < 0.005 for ranibizumab vs sham[b]
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]

	[redacted]	[redacted]	

[a] [redacted]

Abbreviations used in table: BCVA, best corrected visual acuity; CI, confidence interval; ETDRS, Early Treatment Diabetic Retinopathy Study; NEI VFQ-25, National Eye Institute Visual Functioning Questionnaire-25; [redacted]; Rani, ranibizumab; [redacted]

The manufacturer carried out a post hoc analysis stratified by rescue laser photocoagulation to investigate the effects of adding this treatment to ranibizumab. The results are presented on page 378 of the manufacturer's submission. The manufacturer concluded that concomitant use of laser photocoagulation in the ranibizumab group did not inflate the efficacy results for ranibizumab.

Efficacy results from the CRUISE trial (presented on pages 94 to 118 of the manufacturer's submission)

For the CRUISE trial, the manufacturer presented data at 6 and 12 months for several visual acuity outcomes for macular oedema secondary to CRVO, some of which were exploratory outcomes. The manufacturer reported improvements in visual acuity at month 6 in patients receiving 0.5 mg ranibizumab, with patients achieving a mean gain in best corrected visual acuity score from baseline of 14.9 letters (95% CI 12.6 to 17.2) compared with 0.8 letters (95% CI −2 to 3.6; $p < 0.0001$). The manufacturer also reported that a significantly greater proportion of patients in the ranibizumab 0.5 mg treatment group gained at least 15 letters from baseline best corrected visual acuity score compared with patients receiving sham injection. In addition, patients receiving ranibizumab 0.5 mg demonstrated significantly greater improvements in vision-related function as measured by the NEI VFQ-25 than patients receiving sham injection. An improvement from baseline in the mean NEI VFQ-25 composite score was observed at month 1

in patients receiving ranibizumab. At the 6-month time point, the mean change from baseline visual acuity of the fellow eye was reported to be [redacted] in both the sham injection and 0.5 mg ranibizumab groups. The manufacturer stated that this demonstrates that it is reasonable to assume that all improvements in physical functioning were as a result of improvements in visual acuity of the study eye.

In the CRUISE trial, the manufacturer reported that the significant improvements in visual acuity and vision-related function in the ranibizumab treatment group observed at month 6 were generally maintained, on average, through to month 12 with treatment as needed (13.9 letters [95% CI 11.5 to 16.4] for ranibizumab 0.5 mg compared with 7.3 letters [95% CI 4.5 to 10.0] for sham/0.5 mg ranibizumab).

Table 2 Summary of efficacy data from CRUISE (table 8 of ERG report)

Timeframe	Sham/0.5 mg (n = 130)	Ranibizumab 0.5 mg (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 (%)	(33.1%)	(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]
Mean change from baseline NEI VFQ-25 Composite Score			
Month 12[d]	5.0	6.6	

[a] Difference in means (vs sham) 14.1; 95% CI: 10.5 to 17.7.

Abbreviations used in table: BCVA, best corrected visual acuity; CI, confidence interval; ETDRS, Early Treatment Diabetic Retinopathy Study; NEI VFQ-25, National Eye Institute Visual Functioning Questionnaire-25; ; Rani, ranibizumab; .

Subgroup analysis in the BRAVO and CRUISE trials

The manufacturer performed analysis for baseline best corrected visual acuity, baseline central foveal thickness and duration of macular oedema from diagnosis to screening for the subgroups listed in the NICE scope. It presented data for these subgroups on the primary outcome of the change in mean best corrected visual acuity from baseline, and the secondary outcome of the proportion of patients with a visual acuity improvement of 15 letters or more (see tables B22 and B23 [BRAVO] and tables B24 and B25 [CRUISE] of the manufacturer's submission). The manufacturer acknowledged that

some of the subgroups were small (size ranged from 9 to 83 patients in subgroups within one arm). The results of the subgroup analyses were similar to the overall results in the BRAVO and CRUISE trials, with patients receiving ranibizumab having greater improvements at month 6 compared with sham injection. The manufacturer was unable to carry out a subgroup analysis based on presence or absence of retinal ischaemia.

HORIZON extension study

For patients who entered the open label extension (HORIZON) study, ranibizumab 0.5mg was given at intervals of at least 30 days. 67% of patients from BRAVO and 60% of patients from CRUISE completed month 12 of HORIZON. The primary outcome for the HORIZON extension study was mean change from HORIZON baseline in BCVA score in the study up to 24 months. [redacted] and mean change from baseline in central foveal thickness over time up to 12 months. The manufacturer presented results from the first 12 months of the HORIZON extension study. From the BRAVO trial baseline, patients with BRVO receiving sham/0.5 mg and 0.5 mg ranibizumab achieved mean changes in best corrected visual acuity of +15.6 letters and +17.5 letters, respectively. From the CRUISE trial baseline, CRVO patients receiving sham and 0.5 mg ranibizumab achieved mean changes in best corrected visual acuity of +7.6 and +12.0 letters respectively (table B21 of the manufacturer's submission).

Adverse events

The manufacturer presented data on adverse effects at 6 and 12 months' follow-up from the BRAVO (tables B31 and B32 of the manufacturer's submission) and CRUISE trials (tables 33 and 34 of the manufacturer's submission) and from a further 12 months' follow-up from the HORIZON extension study (tables 35 and 36 of the manufacturer's submission. The manufacturer stated that ranibizumab had been found to be safe and well-

tolerated in patients with macular oedema secondary to RVO in the BRAVO and CRUISE trials. In BRAVO, there were 7 adverse events (5.4%) in the ranibizumab 0.5 mg group compared with 17 (13%) in the sham injection group, excluding occurrences of raised intraocular pressure. In CRUISE, there were 13 adverse events (10.1%) in the ranibizumab 0.5 mg group compared with 25 (19.4%) in the sham injection group, excluding occurrences of raised intraocular pressure [redacted] Results from HORIZON suggest a low rate of serious adverse events at month 24. The incidence of study eye serious adverse events and serious adverse events potentially related to systemic vascular endothelial growth factor (VEGF) inhibition across treatment arms was 2 to 9% and 1 to 6%, respectively.

A comparison of the systemic safety profile of ranibizumab with that of bevacizumab was discussed in the manufacturer's submission. The manufacturer stated that, in patients with age-related macular degeneration, ranibizumab was associated with an improved safety profile over bevacizumab. The manufacturer provided data from three large retrospective studies in support of this statement. However, these studies compared bevacizumab and ranibizumab for the treatment of age-related macular degeneration rather than for RVO. The manufacturer acknowledged that age-related macular degeneration manifests later in life than RVO, and so the mean age of patients in the BRAVO and CRUISE trials was lower than those reported in the age-related macular degeneration studies.

Health-related quality of life

The BRAVO and CRUISE trials collected vision-related quality-of-life data using the NEI VFQ-25 questionnaire. The manufacturer stated 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 statistically significant ($p < 0.005$ and $p < 0.05$ for BRAVO and CRUISE respectively) difference in NEI VFQ-25 score at month 6 between treatment with ranibizumab and the sham arm (see tables B17 and B18 of the manufacturer's submission). The manufacturer conducted a systematic review to identify utility values reported in the literature for populations with visual impairment because of RVO, with priority given to populations with macular oedema secondary to BRVO or CRVO. The manufacturer stated that consideration would have been given to patients with diabetic macular oedema or age-related macular degeneration if utility values for RVO could not be identified (page 208 of manufacturer's submission). Seven studies were identified. Brown et al. (1999) 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. is a US study assessing preferences for different levels of visual acuity in a population of patients with vision loss from various causes; 7% of whom had RVO (table B52 of the manufacturer's submission).

2.1.2 Meta-analysis and Indirect comparison

In addition to the CRUISE RCT, the manufacturer identified a second smaller RCT (ROCC) that assessed the effect of ranibizumab in the treatment of macular oedema secondary to CRVO. The results of the meta-analysis indicated that there was strong evidence ($p < 0.00001$) that, in patients with macular oedema secondary to non-ischaemic CRVO, ranibizumab was associated with improvement in best corrected visual acuity compared with sham injection (as measured by ETDRS score) at month 6 (see section 10.3, appendix 16, of the manufacturer's submission).

A systematic review was undertaken to identify RCTs involving potential comparators for ranibizumab in the treatment of macular oedema secondary to RVO. The manufacturer's submission states that bevacizumab is not considered to be an appropriate comparator because its use in the NHS is not

routine and not considered best practice (page 121 of manufacturer's submission). The manufacturer considered the feasibility for indirect comparisons of ranibizumab with bevacizumab, dexamethasone intravitreal implant, laser photocoagulation and intravitreal triamcinolone. The manufacturer discussed the feasibility of conducting an indirect comparison of ranibizumab with dexamethasone intravitreal implant or bevacizumab in CRVO and of ranibizumab with dexamethasone intravitreal implant, bevacizumab or grid laser photocoagulation in BRVO.

The manufacturer stated that because of the differences between ranibizumab and dexamethasone intravitreal implant trial populations, an indirect comparison between these agents was not undertaken for CRVO or BRVO. Because of a lack of appropriate reliable data, the manufacturer commented that an indirect comparison between ranibizumab and bevacizumab was not possible. In addition, the manufacturer stated that because of fundamental differences in trial design, ranibizumab could not be compared indirectly to laser photocoagulation therapy (see section 5.7 of the manufacturer's submission).

2.2 Evidence Review Group comments

The ERG considered the search strategy used by the manufacturer to be comprehensive.

The ERG noted that the effect of ranibizumab in ischaemic BRVO and CRVO populations had not been assessed because people with brisk afferent pupillary defect were excluded from the trials.

The ERG considered that the concomitant use of laser photocoagulation starting from month 3 confounds the results of the BRAVO study and that definite conclusions cannot be drawn as to the effects of ranibizumab compared with sham injection or compared with laser photocoagulation alone (page 47 of ERG report). Furthermore, clinical advice to the ERG suggested

that concomitant use of ranibizumab and laser photocoagulation does not represent how ranibizumab would be used in clinical practice.

The ERG considered that the most relevant data for determining the comparative effectiveness of ranibizumab in treating macular oedema secondary to retinal vein occlusion are the pre-PRN data (that is, at month 6). However this may not be long enough to determine the long-term effects of ranibizumab.

The ERG noted that data from the single-arm extension study (HORIZON) indicated a deterioration in best corrected visual acuity at month 24 in people with macular oedema secondary to CRVO, which could suggest that the as needed dosing regimen is insufficient in this population, and a more frequent treatment regime would be required to maintain the initial observed benefit.

In terms of adverse events, the ERG noted 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 macular oedema secondary to RVO are needed before a definitive conclusion can be drawn on this issue.

The ERG noted that the results of the subgroup analyses mirror the overall results in the BRAVO and CRUISE trials, with ranibizumab-treatment being associated with greater improvements in visual acuity at month 6, compared with sham injection. The ERG also noted that the results did not seem to suggest that duration of macular oedema secondary to RVO, or baseline visual acuity or central foveal thickness were prognostic factors in the effectiveness of ranibizumab for the treatment of macular oedema secondary to BRVO or CRVO.

One key limitation in the evidence highlighted by the ERG was a lack of comparisons in either BRVO or CRVO for ranibizumab compared with dexamethasone intravitreal implant or bevacizumab, both of which were listed

as comparators of interest in the final scope. The ERG commented that the manufacturer should have performed an adjusted indirect comparison to produce a valid estimate of the efficacy of ranibizumab compared with bevacizumab, dexamethasone intravitreal implant, and grid laser photocoagulation. Based on the evidence presented in the manufacturer's submission, the ERG performed exploratory analyses for CRVO and BRVO.

Additional work conducted by the ERG

Based on the information presented in the manufacturer's submission, the ERG performed an adjusted indirect comparison of ranibizumab with dexamethasone intravitreal implant in CRVO, using the direct comparisons with sham injection in the CRUISE trial and the twin dexamethasone intravitreal implant trials (GENEVA) respectively, as the common comparator. The ERG presented analyses that suggested a trend favouring ranibizumab over dexamethasone in macular oedema secondary to both BRVO and CRVO. Based on exploratory analyses of the proportion of people whose visual acuity improved by 15 or more ETDRS letters, the ERG found a relative risk (RR) of 0.53 (95% CI 0.26 to 1.07) in patients with macular oedema secondary to CRVO for achieving this outcome at 6 months for ranibizumab compared with dexamethasone intravitreal implant, where a RR of less than 1.0 favours ranibizumab (see table 18, page 66 of the ERG report). In patients with macular oedema secondary to BRVO, the RR of achieving a visual 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 (table 22, page 71 of the ERG report). However, the ERG commented that the results should be interpreted with caution as the likely bias identified in the trials used was in favour of ranibizumab and so the results may overestimate the efficacy of ranibizumab.

From the trials reported in the manufacturer's submission, the ERG was able to construct a linear network of trials using BRAVO (ranibizumab compared with sham), Moradian 2011 (bevacizumab compared with sham), and Russo

2009 (bevacizumab compared with grid laser photocoagulation). The ERG commented that while the 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 in visual acuity with ranibizumab over bevacizumab and 8 letters improvement with ranibizumab over grid laser photocoagulation at month 3. The results of the mixed treatment comparison are presented in table 3.

The ERG noted that ranibizumab and bevacizumab may have similar efficacy in the treatment of macular oedema 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 −10.1 to 4.3). The direction of bias for this comparison is thought to be towards ranibizumab and is associated with a 3-letter improvement in visual activity for ranibizumab compared with bevacizumab at month 3. The ERG was of the opinion that this translates to a difference in efficacy between ranibizumab and bevacizumab that is not clinically meaningful. The ERG noted that there is insufficient evidence to suggest a difference in the safety profile of ranibizumab and bevacizumab in the treatment of RVO and considers that it is reasonable to assume equivalent safety profiles for ranibizumab and bevacizumab.

Regarding the comparison of ranibizumab versus grid laser photocoagulation, the exploratory mixed treatment comparison favoured ranibizumab, with a mean difference in visual acuity at 3 months of −8.0 letters (95% credible interval −17.0 to 1.2). However, the ERG commented that the benefit of grid laser photocoagulation is not in the short-term but in the long-term and can occur for up to 3 years.

Table 3 Mean difference in change in EDTRS letters from baseline, for bevacizumab, GLP, and sham using ranibizumab as the reference treatment in BRVO (see table 25, page 73 of ERG report)

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
(Negative numbers favour ranibizumab, positive numbers favour the comparator). Abbreviations used in table: BRVO, branch retinal vein occlusion; ETDRS, Early Treatment Diabetic Retinopathy Study; GLP, grid laser photocoagulation.			

2.3 Statements from professional/patient groups and nominated experts

Clinical specialists noted that the trial design of both BRAVO and CRUISE reflected well the typical person presenting with RVO in the UK. They noted that the BRAVO and CRUISE trials used monthly follow-up and injections as required, which is consistent with the way ranibizumab is used currently. The use of laser after 3 months for people with BRVO, and not at all for CRVO, fits with current practice. Clinical specialists commented that the primary outcome used in the trials (mean change in visual acuity from baseline) is a useful and tangible outcome measure and that quality of life and visual function (NEI VFQ-25 questionnaire) were measured. Clinical specialists stated that the BRAVO and CRUISE trials used monthly follow-up and injections as required, which is the way that ranibizumab is used currently. The use of laser after 3 months for patients with BRVO, and not at all for CRVO, fits with current practice. They commented that the BRAVO and CRUISE trials demonstrated significant benefits at 6 months for ranibizumab, and at 12 months these benefits were maintained.

Clinical specialists noted that the safety profile presented for ranibizumab was very favourable and consistent with ranibizumab use in age-related macular degeneration with minimal significant local or systemic concerns. They commented that raised intraocular pressure is not a concern with ranibizumab injections, and there is more long-term experience with ranibizumab through its use in wet age-related macular degeneration since 2008. However, the

clinical specialists commented that the long-term outcomes for vision and complications after treatment with ranibizumab were still unknown.

3 Cost effectiveness

3.1 Cost effectiveness in the manufacturer's submission

The manufacturer's *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 visual impairment because of macular oedema secondary to RVO, with a starting age of approximately 66 years, over a 15-year time horizon. Eight best corrected visual acuity health states and death are included in the model structure (figure B16 [page 188] of the manufacturer's submission). Each best corrected visual acuity health state has an associated utility and mortality risk, depending on whether the better-seeing eye or worse-seeing eye is treated. In the base-case analysis, it is assumed that all patients are treated in their better-seeing eye. People 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 adverse events have an associated cost and disutility applied, and people considered to be blind accumulate the additional costs of blindness. Blindness is defined as a visual acuity equal to or less than 35 letters in the better-seeing eye.

The main comparators for ranibizumab in the economic evaluation are grid laser photocoagulation (standard care) and best supportive care for macular oedema secondary to BRVO and CRVO, respectively. In addition, an exploratory indirect comparison with dexamethasone intravitreal implant was conducted in both BRVO and CRVO, but no comparison with bevacizumab was submitted.

Subgroup analyses were undertaken for baseline best corrected visual acuity score above and below 54 letters, and for time since diagnosis (less than 3 months, 3 to less than 6 months, 6 months or greater).

3.1.1 Treatment effectiveness

Treatment-effectiveness estimates for ranibizumab, grid laser photocoagulation (standard care) and best supportive care were based on individual patient level data from the BRAVO and CRUISE trials for macular oedema secondary to BRVO and CRVO, respectively. Probabilities were calculated for the following transitions:

- gaining at least 4 lines in visual acuity (improving by two health states)
- gaining between 2 and 4 lines (improving by one health state)
- no change (staying in their current health state)
- losing between 2 and 4 lines (worsening by one health state)
- losing at least 4 lines (worsening by two health states).

Transition probabilities were determined monthly and subsequently used to calculate overall monthly transition probabilities for the months 0 to 1, months 2 to 6, and months 7 to 12. For 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, because of the absence of any comparator data after month 6. For 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 grid laser photocoagulation in the comparator arm and considers this a conservative approach (page 194 of manufacturer's submission).

Table 4 Transition probabilities for ranibizumab and standard care from BRAVO (BRVO) and CRUISE (CRVO) trials (derived from table 32 in ERG report)

Transition	BRVO – ranibizumab	BRVO – standard care	CRVO – ranibizumab	CRVO – standard care
Month 1				
Gain at least 4 lines	[redacted]	[redacted]	[redacted]	[redacted]
Gain between 2 and 4 lines	[redacted]	[redacted]	[redacted]	[redacted]
No change	[redacted]	[redacted]	[redacted]	[redacted]
Lose between 2 and 4 lines	[redacted]	[redacted]	[redacted]	[redacted]
Lose at least 4 lines	[redacted]	[redacted]	[redacted]	[redacted]
Months 2 to 6				
Gain at least 4 lines	[redacted]	[redacted]	[redacted]	[redacted]
Gain between 2 and 4 lines	[redacted]	[redacted]	[redacted]	[redacted]
No change	[redacted]	[redacted]	[redacted]	[redacted]
Lose between 2 and 4 lines	[redacted]	[redacted]	[redacted]	[redacted]
Lose at least 4 lines	[redacted]	[redacted]	[redacted]	[redacted]
Months 7 to 12[a]				
Gain at least 4 lines	[redacted]	[redacted]	[redacted]	[redacted]
Gain between 2 and 4 lines	[redacted]	[redacted]	[redacted]	[redacted]
No change	[redacted]	[redacted]	[redacted]	[redacted]
Lose between 2 and 4 lines	[redacted]	[redacted]	[redacted]	[redacted]
Lose at least 4 lines	[redacted]	[redacted]	[redacted]	[redacted]

BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion

[a] Assumption: data were pooled across both treatment arms for months 7 to 12 to generate transition probabilities for BRVO and the month 2 to 6 transition probabilities were reapplied for months 7 to 12 for CRVO

Dexamethasone intravitreal implant is incorporated into the model by the application of relative risks derived from an exploratory indirect comparison, using data from Allergan's submission to NICE for dexamethasone intravitreal implant in macular oedema secondary to RVO. Risk ratios were identified for dexamethasone from the literature (Haller et al. 2010) and assigned to the

probabilities observed in the control groups of the BRAVO and CRUISE trials. Table 5 below 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 5 Relative risks for dexamethasone intravitreal implant versus sham at month 1 (reproduced from table B46 of the MS)

Transition	BRVO	CRVO
Gain at least 4 lines	[redacted]	[redacted]
Gain between 2 and 4 lines	[redacted]	[redacted]
No change[a]	[redacted]	[redacted]
Lose between 2 and 4 lines	[redacted]	[redacted]
Lose at least 4 lines	[redacted]	[redacted]

[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

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 that 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 that is applied to all modelled arms beginning at year 3.

3.1.2 Utilities

The manufacturer's model applies different utility values to each best corrected visual acuity health state, depending on whether the better-seeing eye or worse-seeing eye is treated. Although the BRAVO and CRUISE trials collected vision-related quality of life data (using NEI VFQ-25) this is not a preference-based measure and does not include a direct estimation of utility weights. Seven studies reporting utility values were identified through a

systematic review, and from these, a study by Brown et al. (1999) was chosen as the source for utilities in the model. The manufacturer's rationale was that this was the only study that reported utility values by visual acuity states. Brown et al. is a US study assessing preferences for different levels of visual acuity in a population of patients with vision loss from various causes (7% had RVO).

Brown et al. presented separate utility values for visual acuity in the better-seeing eye and worse-seeing eye. However, the manufacturer only used the utility values for visual acuity in the better-seeing eye and assumed a flat curve of 0.85 for utility associated with visual acuity in the worse-seeing eye (that is, representing no improvement in utility from treating the worse-seeing eye). The rationale for this was that there were inconsistencies between the worse-seeing eye utilities reported by Brown et al. and the significant impact of visual impairment in the worse-seeing eye on vision-related quality of life reported elsewhere and observed in the BRAVO and CRUISE trials. Better-seeing eye 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 utilise these data (summarised in table 6). Utilities were not adjusted for age and the worse-seeing eye is not considered in the base case.

Table 6 Summary of the better-seeing eye (BSE) utility values used in the economic analysis

Visual acuity (Brown et al.[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, better-seeing eye; TTO, time trade off.					

Adverse event disutility

Disutilities were applied to each patient experiencing an adverse event in the model. The disutilities of adverse events are shown in table 7.

Endophthalmitis and retinal tear were excluded because of their low incidence

in the BRAVO and CRUISE trials. Vitreous haemorrhage was also excluded, however the manufacturer states that this is a conservative assumption since the incidence was higher in the sham injection group than the ranibizumab group.

Table 7 Adverse events included in the model

Adverse event	Disutility	Source	Duration (months)	Source
Cataracts	–0.14	Brown et al. 2007	6.00	Assumption
IOP increased (treated with drug)	–0.01	Vaahtoranta-Lehtonen et al. 2007	0.03 (one day)	Assumption
IOP increased (treated with surgery)	–0.01	Vaahtoranta-Lehtonen et al. 2007	6.00	Assumption
Stroke	–0.26	Schwander et al. 2009	Lifetime	Assumption
Abbreviations in table: IOP, intraocular pressure.				

3.1.3 Costs and resource use

In the economic evaluation, the manufacturer identifies three key types of cost: intervention and comparator costs; health state costs; and adverse event costs. These are summarised in table 8.

Table 8 Costs and resource use

Technology costs	
Ranibizumab – technology cost	£742.17
Ranibizumab – administration cost	£192.00
Ranibizumab – follow-up visit cost	£151.00
Laser (BRVO) –technology cost	£0.00
Laser (BRVO) – administration cost	£110.59
Laser (BRVO) – follow-up visit cost	£151.00
Observation (CRVO) – technology cost	£0.00
Observation (CRVO) – administration cost	£0.00
Observation (CRVO) – follow-up visit cost	£151.00
Dexamethasone – technology cost	£870.00
Dexamethasone – administration cost	£295.25
Dexamethasone – follow-up visit cost	£151.00
Costs of blindness	
First year cost	£6,286.10
Subsequent annual costs	£6,067.93
*Technology costs of **treating** adverse events*	
Cataract	£800.00
IOP increased (treated with drug)	£31.67
IOP increased (treated with surgery)	£872.63

3.1.4 Results

The manufacturer submitted an approved patient access scheme (PAS) price of ranibizumab of [redacted] (£742.17 [redacted] in parallel with the main submission that provided base-case results for the incremental cost per quality-adjusted life year (QALY) gained for the following comparisons:

- ranibizumab compared with grid laser photocoagulation in macular oedema secondary to BRVO (table 9)
- ranibizumab compared with best supportive care in macular oedema secondary to CRVO (table 10).

The results of incremental analyses for BRVO and CRVO were also presented:

- ranibizumab, grid laser photocoagulation and dexamethasone intravitreal implant for macular oedema secondary to BRVO (table 11)
- ranibizumab, best supportive care and dexamethasone intravitreal implant (table 12) for patients with macular oedema secondary to CRVO.

Further details can be found on pages 259 and 260 of the manufacturer's submission.

Table 9 Base-case cost-effectiveness results of ranibizumab compared with grid laser photocoagulation (standard care): macular oedema secondary to BRVO with PAS

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
GLP	£11,990	12.561	7.705	–	–	–	–
Ranibizumab	£[redacted]	[redacted]	[redacted]	£[redacted]	[redacted]	[redacted]	£20,494
Abbreviations used in table: GLP, grid laser photocoagulation; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Table 10 Base case cost-effectiveness results of ranibizumab compared with best supportive care: macular oedema secondary to CRVO

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
BSC	£20,727	12.149	7.061	–	–	–	–
Ranibizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£8,643
Abbreviations used in table: CRVO, central retinal vein occlusion; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Table 11 Base-case incremental results: macular oedema secondary to BRVO

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) (QALYs)	ICER vs GLP (QALYs)
GLP	£11,990	12.56	7.705	–	–	–	–	–
Dex	£16,448	12.58	7.769	£4,458	0.02	0.065	£68,742	£68,742[a]
Rani	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£5,486	£20,494

[a] Extended dominance over dexamethasone intravitreal implant

Abbreviations used in table: BRVO, branched retinal vein occlusion; Dex, dexamethasone intravitreal implant; GLP, grid laser photocoagulation; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; Rani, ranibizumab.

Table 12 Base-case incremental results: macular oedema secondary to CRVO

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) (QALYs)	ICER (£) vs GLP (QALYs)
Best supportive care	£20,727	12.15	7.061	–	–	–	–	
Dex	£22,945	12.21	7.270	£2,218	0.06	0.209	£10,622	£10,622[a]
Rani	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£8,643

[a] Extended dominance over dexamethasone intravitreal implant

Abbreviations used in table: CRVO, central retinal vein occlusion; Dex, dexamethasone intravitreal implant; GLP, grid laser photocoagulation; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; Rani, ranibizumab

When an incremental analysis was carried out including all of the comparators, dexamethasone intravitreal implant was ruled out by extended dominance for patients with macular oedema secondary to either BRVO or CRVO.

Sensitivity analysis

The manufacturer carried out deterministic sensitivity analysis for CRVO and BRVO by varying:

- the frequency of ranibizumab treatment in the first year (3 or 12 injections)
- the frequency of ranibizumab treatment in the second year (3 or 6 injections)
- ranibizumab treatment in year 3 (1 injection)
- the administration and follow-up costs
- the frequency of visits for ranibizumab injection in years 2 and 3
- the discount rate used.

The ICERs for each analysis are presented in table 13. The manufacturer did not present sensitivity analyses for ranibizumab compared with dexamethasone in either BRVO or CRVO that included the PAS. Sensitivity analyses for ranibizumab compared with dexamethasone not including the PAS are presented in tables B87 and B88 of the manufacturer's submission.

Table 13 Deterministic sensitivity analysis for ranibizumab

	BRVO – rani vs laser (with PAS)	**CRVO – rani vs BSC (with PAS)**
Base case	**£20,494**	**£8,643**
Frequency of ranibizumab treatment in year 1, 3 injections	£8,527	£644
Frequency of ranibizumab treatment in year 1, 12 injections	£30,067	£12,643
Frequency of ranibizumab treatment in year 2, 3 injections	£21,633	£3,834
Frequency of ranibizumab treatment in year 2, 6 injections	£28,468	£11,428
Continued ranibizumab treatment in year 3, 1 injection	£23,284	£10,193
Administration costs, £96	£16,944	£6,242
Administration costs, £288	£24,044	£11,045
Follow up costs, £76	£19,941	£8,721
Follow up costs, £227	£21,054	£8,565
Frequency of ranibizumab visits in year 2, 4	£20,750	£8,586
Frequency of ranibizumab visits in year 2, 8	£22,798	£10,293
Frequency of ranibizumab visits in year 3+, 0	£11,551	£8,586
Frequency of ranibizumab visits in year 3+, 4	£29,437	£18,274
Discount rate costs and benefits, 0%	£15,049	£5,135
Discount rate costs and benefits, 6%	£24,556	£11,302
Discount rate costs 3.5% Discount rate benefits, 0%	£16,286	£6,810

Two scenario analyses were carried out regarding the proportion of worse-seeing eye involvement at baseline and 12 months:

- scenario 1 (trial based): 5.2% better-seeing eye at baseline, 7.1% best seeing eye at month 12

- scenario 2 (expected in clinical practice [assumption]): 10% better-seeing eye at baseline, 20% better-seeing eye at month 12.

The manufacturer varied the slope of the worse seeing eye utility curve, which was assumed to be flat. The utility curves are presented in figures 9 to 12 of the ERG report (pages 101 and 102). For scenario 1, the incremental cost-effectiveness ratios (ICERs) varied from £530,361 to £18,251 (BRVO) and from £301,603 to £12,038 (CRVO). For scenario 2, the ICERs varied from £154,610 to £18,462 (BRVO) and from £92,047 to £11,745 (CRVO).

Probabilistic sensitivity analysis

The manufacturer presented the probability of ranibizumab being cost effective in the manufacturer's submission (without PAS) and in the PAS submission (with PAS). This is presented in table 14 below.

Table 14 Probability of cost effectiveness (with PAS)

	Probability of being cost effective		
	Threshold = £0	**Threshold = £ 20,000**	**Threshold = £ 30,000**
BRVO: ranibizumab vs laser	1.6%	45.5%	57.2%
CRVO: ranibizumab vs best supportive care	10.3%	74.5%	83.3%

3.2 Evidence Review Group comments

Population

The ERG noted that most patients with retinal ischaemia were excluded from the BRAVO and CRUISE trials, as a result of the exclusion criteria of brisk afferent papillary defect, which as the manufacturer states, equates to severe retinal ischaemia. The ERG considered that the results of any analyses could only be applied to people without retinal ischaemia.

Treatment effectiveness estimates

The ERG commented that the manufacturer should have considered using the primary endpoint of 15 letters visual acuity in place of 10 letters, which the

manufacturer could not provide as part of the ERG's clarification request. There were no comparative data for GLP (BRVO) or BSC (CRVO) beyond 6 months because patients entered an observation phase from 6 months where ranibizumab could be given to all patients, on an as needed basis.

In addition, the ERG noted that it is not possible to separate the effect of grid laser photocoagulation from ranibizumab in the BRAVO trial because it is given concomitantly after 3 months in both arms. The ERG noted that there was insufficient evidence to conclude that grid laser photocoagulation had no effect in the ranibizumab arm. The ERG noted that the treatment period of the BRAVO trial was insufficient to capture any benefits of grid laser photocoagulation on patient outcomes, which may last longer than 3 years.

The ERG noted that 21.4% of patients in the ranibizumab group received grid laser photocoagulation compared with 57.6% in the sham arm, which would result in an overall bias towards ranibizumab. The manufacturer attempts to account for the effect of grid laser photocoagulation by pooling transition probabilities calculated during the observation phase of the trial (months 7 to 12). The ERG commented that pooling of transition probabilities would have an inflationary effect on the efficacy of ranibizumab because the benefit seen in patients in the sham treatment arm who received ranibizumab therapy would be added to the continued effect of ranibizumab therapy in those patients initially randomised to receive ranibizumab. The ERG therefore requested the unpooled transition probabilities from the BRAVO patient level data for months 7 to 12 (table 15). The ERG conducted sensitivity analyses using these unpooled transition probabilities and noted that the ICER obtained for ranibizumab compared with grid laser photocoagulation (for BRVO) increased to £52,004 for months 7 to 12, and ranibizumab was dominated in the analyses at months 13 to 24 and months 7 to 12 and 13 to 24.

Table 15 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 noted that the unpooled transition probabilities revealed a decline in the effect of ranibizumab when patients switched to the observation phase where all groups received ranibizumab as needed (after 6 months; presented in table 58 of the ERG report). This suggested that continuous treatment may be required for longer than 6 months.

Comparisons with dexamethasone and bevacizumab

The ERG noted that the manufacturer incorporated dexamethasone intravitreal implant into the economic analysis in an exploratory way. The ERG commented that there is a potential bias towards ranibizumab in the manufacturer's approach. The ERG considered that the use of 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. Also, after month 1 no additional benefit for dexamethasone is assumed, therefore analysis is strongly biased towards ranibizumab. The ERG conducted an indirect comparison of ranibizumab with dexamethasone intravitreal implant, which provided relative risks of an improvement in visual acuity of 10 letters (two lines) or more for patients with macular oedema secondiary to BRVO and CRVO. The relative risks increase from 0.55 to 0.79 for ranibizumab compared with dexamethasone in BRVO. For CRVO, the corresponding figures were 0.30 to 0.40. The ERG commented that the relative risks calculated from the manufacturer's model were more favourable to

ranibizumab in both BRVO and CRVO. The ERG commented that, as the ERG's indirect comparison was known to be biased towards ranibizumab, the manufacturer's approach to modelling dexamethasone was largely biased towards ranibizumab.

The ERG commented that an exploratory analysis using an indirect comparison of ranibizumab with bevacizumab can be done as part of a mixed treatment comparison (see 'Additional work undertaken by the ERG' below for the ERG's cost-minimisation analysis of ranibizumab compared with bevacizumab).

Assumption regarding proportion of patients treated in their better-seeing eye

The ERG noted that in the base-case analysis the model assumes all patients are treated in the better-seeing eye, despite the fact that 91.7% and 90% of patients in the BRAVO and CRUISE trials, respectively, were treated in their worse-seeing eye. The ERG considered that it is not reasonable to assume equivalent gains in utility and reductions in costs as seen in treating a patient in their worse-seeing eye. The ERG considered the manufacturer's use of a better-seeing eye model to be inappropriate in macular oedema secondary to RVO because RVO is a predominantly unilateral condition, and therefore most patients will receive treatment in only their worse-seeing eye.

Utility values

The ERG noted that the utility values for visual acuity in the better-seeing eye were taken from Brown et al. (1999) rather than the study by Brazier et al. (2009) previously recommended in 'Ranibizumab and pegaptanib for the treatment of age-related macular degeneration' (NICE technology appraisal guidance 155). The ERG commented that the study by Brazier et al. should be used as the source for utility associated with visual acuity in the better-seeing eye in this assessment, since the opinion of clinical specialists from both the manufacturer and the ERG concurred that the utility associated with

visual acuity may be applicable across vision disorders (page 226 of manufacturer's submission).

The ERG noted that the manufacturer's standardisation approach to age adjustment would fail to account for the difference between the UK and US patient populations. A standard multiplicative approach to age adjustment would be more applicable. The ERG commented that the age adjustment of the utilities presented by Brazier et al. was not necessary as age is adjusted for in the analysis.

Mortality

The ERG noted that the evidence of no significant risk of increased mortality attributable to RVO presented by the manufacturer was inconclusive (discussed on page 118 of the ERG report). The ERG also noted that the mortality risk associated with 'some' visual impairment reported in Christofferson et al. (2007) should be applied to patients experiencing visual impairment in their worse-seeing eye, 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'.

3.2.1 Additional work undertaken by the ERG

The ERG undertook four exploratory analyses that examined:

- the effect of assumptions around treating the better-seeing or worse-seeing eye and incorporating Brazier utilities
- using the above scenario and adjusting for mortality and visual impairment in the worse-seeing eye
- immediate compared with delayed treatment in BRVO
- cost-minimisation analysis of bevacizumab.

Scenario analysis around better-/worse-seeing eye incorporating amendment to utility assumptions

In this analysis (scenario L of table 67 on page 122 of the ERG report) the ERG varied the percentage of people with better-seeing eye at baseline to 10% (100% in the manufacturer's base case) and used the Brazier et al. utilities. The ICER using this scenario from this analysis was £49,323 per QALY gained.

Model modifications

The ERG amended the manufacturer's model to include:

- an increased risk of mortality associated with RVO
- age-adjusted utilities.

These amendments were also applied to the ERG's scenario as described above. The amendments were made for the comparisons of ranibizumab with BSC for CRVO and for ranibizumab with dexamethasone for both BRVO and CRVO. Table 16 illustrates that these modifications increased the manufacturer's base-case ICERs for all comparisons and conversely, decreased the ERGs base-case ICERs for all comparisons.

Table 16 ERG's base-case ICERs

Comparison	Manufacturer's base case	Manufacturer's base case with ERG model modifications	ERG scenario	ERG scenario with model modifications
Ran vs BSC – CRVO	£8,643	£11,111	£49,323	£43,760
Ran vs Dex – CRVO	£7,174	£9,143	£42,147	£37,443
Ran vs Dex – BRVO	£5,486	£6,978	£34,598	£31,122

The ICERs generated for ranibizumab compared with dexamethasone from the BRAVO trial are derived using the pooled transition probabilities meaning

that there is uncertainty around the £34,598 and £31,122 per QALY gained estimates. Using the unpooled transition probabilities would increase these ICERs further. In addition, the comparisons of ranibizumab with dexamethasone for both BRVO and CRVO used relative risks derived from the manufacturer's model (0.55 for BRVO and 0.30 for CRVO) rather than those derived from the ERG's indirect comparison (0.79 and 0.40, respectively) (see table 17).. The ERG commented that this would bias the results in favour of ranibizumab and if the ERG's suggested relative risks were applied, the ICERs would increase further.

Immediate versus delayed treatment

The ERG notes that a model based solely on evidence from the BRAVO trial may best be used to inform decisions regarding the effect of the delay of treatment with ranibizumab on treatment outcome. In this analysis that used the manufacturer's base-case model, the ICER for administering immediate as opposed to delayed treatment was £6,500 per QALY gained.

However, once the modifications recommended by the ERG (worse-seeing eye model perspective: adjustments for age, and increased risk of mortality associated with RVO and visual impairment in the worse-seeing eye) were incorporated into this analysis, the ICER increased to £31,410.

Table 17. 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.				

Cost-minimisation analysis of bevacizumab

The cost-minimisation analysis conducted by the ERG (section 6.2 of the ERG report) uses the price of £50 per month, consistent with that used in the NICE technology appraisal of dexmethasone for RVO. This resulted in the dominance of bevacizumab over ranibizumab, with the incremental costs of ranibizumab treatment of [redacted] and [redacted] for patients with macular oedema secondary to BRVO and CRVO respectively. The ERG commented, however, that the difference between ranibizumab and bevacizumab is not, in their opinion, clinically meaningful.

3.2.2 Equality and diversity

No equalities issues were raised during the scoping or re-scoping process

4 Authors

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Appendix A: Sources of evidence considered in the preparation of the premeeting briefing

A The Evidence Review Group (ERG) report for this appraisal was prepared by BMJ -Technology Assessment Group (BMJ-TAG):

- Edwards S, Lois N, Barton S et al. Ranibizumab for the treatment of macular oedema caused by retinal vein occlusion (RVO), July 2011.

B Submissions or statements were received from the following organisations:

I Manufacturer/sponsor:

- Novartis Pharmaceuticals

II Professional/specialist, patient/carer and other groups:

- NHS Wirral Primary Care Trust
- Royal College of Nursing
- Royal College of Ophthalmologists
- Royal National Institute of Blind People (RNIB)