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

ERG's response to Novartis' comments on ACD

BMJ Technology Assessment Group

Evidence Review Group (ERG) comments on Novartis' responses to the Appraisal Committee Document (ACD) for ranibizumab for the treatment of macular oedema caused by retinal vein occlusion (RVO)

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ERG comments are numbered in accordance with Novartis' responses to the ACD as outlined in the document forwarded to NICE dated 15th December 2011.

In summary, the ERG considers the key points to be:

1. The effectiveness of ranibizumab in patients with ischaemic disease remains unknown;
2. The bias in the indirect comparison of ranibizumab and dexamethasone is difficult to quantify, and may be minimal, but is likely to favour ranibizumab;
3. The effect of using ranibizumab *pro re nata* (PRN) data as a proxy for the longer term efficacy of grid laser photocoagulation (GLP) or dexamethasone is unclear;
4. The assumption of a 0.3 maximum utility gain in the worse-seeing eye (WSE) is not evidence based.

Throughout this report dexamethasone intravitreal implant is referred to as dexamethasone.

1. Utility values

a) The use of Brazier utilities

The ERG maintains the view that the utility values estimated by Brazier *et al*.(Czoski-Murray et al. 793-99) are the most suitable for use in the economic model developed by the manufacturer as these values represent a public valuation of health-related quality of life as per the NICE reference case.(National Institute for Health and Clinical Excellence)

The ERG agrees with the manufacturer that an improvement in best corrected visual acuity (BCVA) of 10 or more letters (measured on the ETDRS [Early Treatment Diabetic Retinopathy Study] scale) is considered clinically meaningful. [redacted]

The limitations of the ERG's approach to the application of the Brazier utilities are highlighted in the ERG's initial report.(BMJ-TAG) The manufacturer's approach addresses the issue of model calibration and is consistent with the approach taken by the assessment group for TA155.(SHTAC)

b) Utility gain of treating the worse-seeing eye

The paucity of data for the utility decrement associated with visual impairment in the WSE has been acknowledged by the committee and the ERG. The manufacturer's original approach was to adopt a better-seeing eye (BSE) modelling perspective and to assume no utility gain from the treatment of visual impairment in the WSE. In Novartis' response to the ACD, the manufacturer accepts the committee's preference for a WSE perspective in the base case and presents an analysis using the proportions of BSE/WSE patients treated in BRAVO[(Campochiaro et al. 1102-12)] and CRUISE.[(Brown et al. 1124-33)] As part of this analysis, the manufacturer has amended the maximum utility gain of treating the WSE from 0.1 (as assumed by the ERG) to 0.3.

The rationale for using a maximum utility gain of 0.3 for treatment of the WSE comes from an extrapolation of evidence presented by Brown *et al*.[(Brown et al. 643-47)] Brown *et al*.[(Brown et al. 643-47)] estimated a 0.1 utility difference between patients with good bilateral vision and patients with good unilateral vision (good vision defined as 20/20–20/25). Patients with good unilateral vision had BCVA in the WSE that ranged from 'no light perception' to 20/40. The manufacturer assumed that the 0.1 utility decrement estimated by Brown *et al*.[(Brown et al. 643-47)] reflected the difference between no visual impairment in the WSE and a BCVA of 20/40 (health state 66–75 letters) in the WSE. Based on this assumption, the manufacturer extrapolated the 0.1 utility loss to apply to further vision loss in the WSE, resulting in an overall utility decrement of 0.3 from no visual impairment in the WSE to blindness in the WSE (equivalent to a 0.043 slope of the WSE utility curve).

As part of their analysis Brown *et al*.[(Brown et al. 643-47)] stratified patients with good unilateral vision according to the visual acuity of the WSE. The results of this analysis are presented in Table 1 below; there was no obvious correlation between mean utility values and vision in the WSE, and the difference between group means was not significant (p=0.86).

Table 1. Mean utility values in patients with unilateral good vision, stratified by visual acuity in the WSE (Brown *et al*.[(Brown et al. 643-47)])

Vision in the WSE	n	Mean utility value	Standard deviation	95% CI
20/40–20/50	24	0.87	0.16	0.81–0.93
20/70–20/100	12	0.90	0.16	0.81–0.99
20/200–20/400	14	0.94	0.13	0.81–1.00
Counting fingers-light perception	25	0.88	0.18	0.81–0.95
No light perception	6	0.81	0.16	0.65–0.97
Abbreviations used in this table: CI, confidence interval; WSE, worse-seeing eye.				

The ERG considers that the evidence presented by Brown *et al*.[(Brown et al. 643-47)] suggests that the utility decrement of 0.1 applies to the loss of good vision in one eye, whatever the extent of that loss may be. The ERG has seen no evidence to support the manufacturer's suggestion that the utility loss of 0.1

applies only to visual impairment in the WSE up to a BCVA of 20/40. Moreover, the ERG has seen no evidence that the reduction in utility will be maintained as vision deteriorates. In fact, the evidence presented by Brown *et al*.[Brown et al. 643-47] suggests that further deterioration in visual acuity in the WSE (assuming good vision in the BSE) does not affect utility. Although, as stated by Brown *et al*.[Brown et al. 643-47], "additional data will be necessary to address this question".

2. Inconsistencies between the Committee's appraisal of dexamethasone and its appraisal of ranibizumab for the treatment of RVO

a) Excess mortality associated with RVO

As part of the appraisal process, the ERG considered the evidence submitted by the manufacturer on the risk of cardiovascular mortality associated with RVO. The ERG acknowledged that the evidence was inconclusive. However, based on clinical advice and a review of the submitted evidence, the ERG determined that the relative of risk of death reported by Tsaloumas *et al*.[Tsaloumas et al. 821-27] most appropriately reflected any additional risk of cardiovascular death in RVO patients. The manufacturer has submitted further evidence in the form of an NHS evidence review,[NHS] which concludes that the evidence of additional mortality risk associated with RVO is contradictory. The ERG makes no comment on whether the precedent set in TA229 regarding RVO mortality should also apply in this appraisal.

b) Time horizon

The ERG make no comment on time horizon as it is for the Appraisal Committee to decide whether the precedent set in TA229 should apply in this appraisal.

3. Best supportive care as a relevant comparator for CRVO

The ERG has no comment; the ERG considers that this is a decision for the Appraisal Committee. The final scope issued by NICE for this Single Technology Appraisal (STA) listed best supportive care as a relevant comparator in ischaemic RVO only.[National Institute for Health and Clinical Excellence]

4. Extent of bias towards ranibizumab in comparison to dexamethasone

In Novartis' response, the manufacturer suggests that the comparison of ranibizumab with dexamethasone could be biased against ranibizumab. The ERG acknowledges that there is uncertainty surrounding the extent of bias in the exploratory indirect comparisons of ranibizumab versus dexamethasone but that the extent of this bias is difficult to quantify. The ERG agrees that the effects of the bias could be minimal but maintains that, for most of the factors identified (listed below) as potentially introducing bias, the direction of the bias favours ranibizumab.

In the ERG's report, based on the manufacturer's submission and additional data, the ERG highlighted three factors that it postulated could introduce a degree of bias favouring ranibizumab in the indirect comparison versus dexamethasone:

- Duration of macular oedema (MO). The ERG highlighted that, based on baseline characteristics, the mean duration of MO secondary to BRVO and to CRVO was shorter in BRAVO[(Campochiaro et al. 1102-12)] and CRUISE[(Brown et al. 1124-33)] than in the GENEVA[(Haller et al. 1134-46)] trials (~3 months in BRAVO/CRUISE vs ~5 months in GENEVA);

- Increased baseline retinal thickness (by ~130 micrometres) in GENEVA[(Haller et al. 1134-46)] trials compared with CRUISE[(Brown et al. 1124-33)];

- Development of neovascularisation in patients in the sham group in GENEVA[(Haller et al. 1134-46)] suggested that at least some patients in GENEVA had ischemic disease. Correspondingly, in BRAVO[(Campochiaro et al. 1102-12)] and CRUISE,[(Brown et al. 1124-33)] patients were screened for brisk afferent pupillary defect (APD) and, if found, excluded. The presence of ischaemic patients in the GENEVA trials might have led to an underestimation of the treatment effect of dexamethasone in perfused patients.

The manufacturer has raised concerns about the ERG's comments around duration of MO and development of neovascularisation in patients in GENEVA; the issue of rates of neovascularisation is discussed in Section 4e.

As Novartis indicates in the response to the ACD, the stage from which timing of duration of MO was measured differed between BRAVO[(Campochiaro et al. 1102-12)]/CRUISE[(Brown et al. 1124-33)] and the GENEVA[(Haller et al. 1134-46)] trials. In BRAVO/CRUISE, the duration of MO was calculated at the screening visit, which, in the response, the manufacturer states was at least 30 days prior to the baseline visit, whereas, in the GENEVA trials, the duration of MO was calculated at the baseline visit. Thus, the manufacturer argues that the mean duration of MO in BRAVO/CRUISE was assessed at least 30 days earlier than in the GENEVA trials. The manufacturer indicates that this difference should be considered when comparing ranibizumab versus dexamethasone. However, it is not clear from the manufacturer's response how large an effect the manufacturer considers this difference would have on any analysis. In addition, the full publications of BRAVO[(Campochiaro et al. 1102-12)] and CRUISE[(Brown et al. 1124-33)] indicate that the screening period took place from day –28 to day –1, which the ERG interprets to mean that the interval between screening and baseline visit could be a maximum of 28 days, rather than a minimum of 30 days. To adjust data from BRAVO/CRUISE to the baseline visit to impose comparability with data from GENEVA, the ERG considers that it would be necessary to add, at most, 28 days to the individual patient's recorded duration of MO and subsequently

recategorise patients based on duration of MO. At this time, the ERG does not have access to data from BRAVO and CRUISE to facilitate this analysis. It could be that most people in BRAVO and CRUISE in the category of duration of MO of 3 months or less might remain in this category. Moreover, the manufacturer states in their original submission that duration of MO was longer in GENEVA than in either BRAVO or CRUISE, and, on this basis, the ERG considers that the indirect comparison likely favours ranibizumab.

The manufacturer also comments that, in CRUISE, [redacted] (Brown et al. 1124-33)" Subgroup analyses reported in CRUISE and the manufacturer's original submission for the key predefined outcomes assessed suggest conflicting results in terms of response based on duration of condition in CRVO. In patients with MO secondary to CRVO, the ERG considers data at 6 months to be the most appropriate indicator of effectiveness of ranibizumab because post 6 months all patients became eligible for ranibizumab PRN. At 6 months, the difference between the ranibizumab 0.5 mg and sham group in mean change in BCVA from baseline was greater for the subgroup of patients with diagnosis of CRVO of more than 3 months (15.3 ETDRS letters; Table 2) compared with those with duration of condition of 3 months or less (13.2 ETDRS letters). However, the difference between treatment and sham group in proportion of patients with an improvement of 15 or more ETDRS letters at 6 months (Table 2) was smaller in patients with diagnosis of CRVO of more than 3 months (28.9%) compared with those with a diagnosis of 3 or less months (32.6%). The ERG considers that the association between duration of condition and treatment response, based on the outcomes measured and reported in CRUISE, is unclear. It should be noted that statistical testing for an interaction between subgroups based on duration of RVO was not performed and so there is no conclusive evidence on a difference in treatment effect between the subgroups in CRVO.

Table 2. Summary of subgroup analyses based on duration of CRVO

Time from CRVO diagnosis to screening (months)	Number of patients in each arm sham /ranibizumab 0.5 mg	Sham	Ranibizumab 0.5 mg	
Mean change from baseline BCVA in ETDRS letters at month 6				
		Mean ([redacted]) [95% CI for mean]	Mean [redacted] [95% CI for mean]	[redacted]

<3	80/74	1.1 [–2.9 to 5.1]	14.3 [11.1 to 17.5]	[redacted]
≥3	50/56	0.4 [–3.4 to 4.1]	15.7 [12.4 to 18.9]	[redacted]
Proportion of patients who gained ≥15 ETDRS letters at month 6				
		n (%) [95% CI for %]	**n (%) [95% CI for %]**	[redacted]
<3	80/74	18.8%	51.4%	[redacted]
≥3	50/56	14.0%	42.9%	[redacted]

[a] [redacted]

[b] [redacted]

The last-observation-carried-forward method was used to impute missing data.

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

In the economic analysis, the manufacturer claims that the assumption of equivalent efficacy for ranibizumab and dexamethasone from month 7 to 24 is likely to contribute to the bias against ranibizumab. The ERG understands that the manufacturer has used pooled data from BRAVO to inform patient transitions in the ranibizumab and dexamethasone model arms from month 7 onwards. One implication of using pooled data is to inflate the efficacy of ranibizumab with the incorporation of patients new to ranibizumab therapy (this is discussed further in Section 6). However, it is unclear whether using pooled data to approximate dexamethasone efficacy would overestimate or underestimate the efficacy of dexamethasone. In the revised model, the manufacturer uses the 7 to 12 month data of the ranibizumab arm of BRAVO to inform all transitions from month 7 to 24. This assumes equivalent efficacy between dexamethasone and ranibizumab PRN. The ERG notes that the efficacy of ranibizumab declines when patients receive PRN rather than monthly treatment (this is discussed further in Section 6).

a) Indirect comparison of ranibizumab and dexamethasone: use of data at 3 months

The ERG considers that the rescue use of GLP from 3 months in BRAVO confounds results in both the sham and ranibizumab 0.5 mg groups from that time point, and thus data at 3 months are the most relevant to the decision problem presented. The ERG agrees with the manufacturer with regards to the decline in efficacy of dexamethasone, but notes that Figure 6 of the Haller publication[(Haller et al. 1134-46)] suggests that decline commences from 2 months post implantation rather than beyond 3 months post implantation, as indicated by the manufacturer. Thus, the ERG's exploratory analysis in MO secondary to BRVO based on results at 3 months accounts for a degree of decline in efficacy of dexamethasone.

It should be noted that Figure 6 in the paper published by Haller and colleagues[(Haller et al. 1134-46)] represents combined data on MO secondary to BRVO and CRVO. The data used by the ERG for

change in BCVA at 3 months were taken from the manufacturer's submission to the STA process for dexamethasone for MO secondary to RVO and are based on subgroup analyses of the different types of RVO.(Allergan) However, data reported in the manufacturer's submission for dexamethasone support the observation of a decline in efficacy of dexamethasone from 2 months post implantation; the decline in efficacy seems to be greater in MO secondary to CRVO. Data from BRAVO(Campochiaro et al. 1102-12) and CRUISE(Brown et al. 1124-33) suggest that most of the benefit with ranibizumab occurs within the first 3 months of treatment. Taken together with the observation that there is a decline in efficacy of dexamethasone commencing from 2 months in MO secondary to BRVO, in the ERG's opinion, assessing data at 3 months is unlikely to bias against ranibizumab.

The manufacturer's model structure precluded the application of the ERG's indirect comparison results. Therefore, the efficacy estimates of ranibizumab and dexamethasone used to inform the cost effectiveness analysis presented in the ERG report are the same as those used by the manufacturer.

b) Dexamethasone treatment frequency

In TA229,(NICE) the committee agreed that re-treatment with dexamethasone is likely to occur at 4 months rather than 6 months in clinical practice.(NICE) Based on this, the manufacturer argues that higher costs of acquisition and administration associated with re-treatment after 4 months should be applied to the dexamethasone model arm. The ERG notes that, in consideration of the cost-effectiveness evidence associated with dexamethasone, the committee accepted a re-treatment frequency that was a mid-point between the two extremes: re-treatment based on clinical opinion (4 months) and that used in the GENEVA trials (6 months).(NICE) Consequently, the ERG considers that a re-treatment frequency of 5 months would be equivalent to the re-treatment frequency accepted by the Appraisal Committee in TA229. Moreover, the ERG notes that a higher re-treatment frequency would also result in a more stable efficacy for dexamethasone, a factor not accounted for in the manufacturer's revised model.

c) Adverse events associated with dexamethasone

The manufacturer has updated the model originally submitted with regard to adverse events (AEs), as follows:

- Iris neovascularisation has been included as an AE for ranibizumab and dexamethasone;
- The rates of cataract for dexamethasone have been updated based on the 12 month outcomes of the GENEVA studies;(Haller et al. 2453-60)
- AEs have been included in year 2 (all AEs).

The manufacturer has not discussed the assumptions surrounding the implementation of iris neovascularisation. However, the submitted model indicates that a cost of £576 is applied per event; the application of this cost has minimal impact on the incremental cost-effectiveness ratio (ICER). The AE rates for ranibizumab and dexamethasone used in the original and updated models are displayed in Table 3.

Table 3. Previous and updated adverse event rates used in the manufacturer's model

Adverse event	Original model				Updated model			
	Ranibizumab		Dexamethasone		Ranibizumab		Dexamethasone	
	Year 1	Year 2	Year 1	Year 2	Year 1	Year 2	Year 1	Year 2
Cataracts	6.60%	0.00%	14.80%	0.00%	6.60%	5.42%	21.40%	21.40%
IOP increased (treated with drug)	10.00%	0.00%	50.40%	0.00%	10.00%	5.42%	50.40%	50.40%
IOP increased (treated with surgery)	0.00%	0.00%	1.40%	0.00%	0.00%	0.49%	1.40%	1.40%
Stroke	0.05%	0.00%	0.05%	0.00%	0.05%	0.05%	0.05%	0.05%
Iris neovascularisation	0.00%	0.00%	0.00%	0.00%	0.40%	0.98%	0.90%	0.90%
Abbreviations used in table: IOP, intraocular pressure.								

For ranibizumab, the rate of iris neovascularisation in year 1 was derived from the 6 month rates reported in BRAVO[(Campochiaro et al. 1102-12)] and CRUISE.[(Brown et al. 1124-33)] It is not clear how the rate of iris neovascularisation was calculated for year 2. All other year 2 AE rates are taken from HORIZON.[(Campochiaro et al.)] For dexamethasone, the rate of iris neovascularisation is the 6 month rate reported in the GENEVA trials.[(Allergan)] All other year 1 and year 2 AE rates are taken from the recently published 12 month outcomes of GENEVA.[(Haller et al. 2453-60)]

The manufacturer highlights the limited data available for the safety of dexamethasone, a concern shared by the appraisal committee in TA229.[(NICE)] The ERG agrees that a higher re-treatment schedule for dexamethasone than that used in GENEVA[(Haller et al. 2453-60)] is likely to have an impact on the number and severity of AEs. Consequently, the AE profile used in the manufacturer's updated model is likely to favour dexamethasone.

d) Ranibizumab year 2 treatment frequency

The ERG notes that no information is available for patients that did not enter HORIZON following BRAVO or CRUISE and therefore considers that any assumptions regarding their treatment requirements cannot be substantiated.

e) Ischaemic disease and neovascularisation

The ERG acknowledges that the rates of neovascularisation reported at 6 months in the sham groups for BRAVO[(Campochiaro et al. 1102-12)] and CRUISE[(Brown et al. 1124-33)] (Table 7 of Novartis' response) suggest that people with a degree of ischaemic disease were included in the trials. However, in the manufacturer's submission to the STA process, the manufacturer comments that 0 patients in BRAVO and 2 patients in CRUISE had ischaemic disease at baseline based on the definition used in the CVOS study.[(The Central Vein Occlusion Study 1087-95)] The ERG notes that none of BRAVO,[(Campochiaro et al. 1102-12)]

CRUISE[Brown et al. 1124-33] or GENEVA[Haller et al. 1134-46] defined ischaemia or reported proportion of patients with ischaemia at baseline in the original publications.

The ERG stated that the authors of the GENEVA trials proposed that, based on presence of neovascularisation, at least some people with ischaemic disease had been included and that this would underestimate the treatment effect of dexamethasone. As the manufacturer highlights, the higher rates of neovascularisation reported from BRAVO and CRUISE suggest that this factor could introduce bias towards dexamethasone, rather than ranibizumab, in an indirect comparison. However, as highlighted in an earlier point, the ERG deems the degree of bias in any of its exploratory analyses to be difficult to quantify.

The ERG considers it important to note that patients with MO secondary to CRVO and ischaemia are more likely to develop iris neovascularisation and are unlikely to go on to develop retinal neovascularisation, [redacted]. Differences between conditions in likelihood of site of development of neovascularisation should be considered when interpreting the results on neovascularisation from the GENEVA trials as the rates reported are for patients with MO secondary to RVO, and are not reported separately for BRVO and CRVO. In addition, on re-assessing the data, the ERG considers other potentially confounding factors to be the low number of events in each trial, and the large difference in the number of patients assessed; GENEVA assessed neovascularisation in 423 patients in the sham group compared with 132 patients in the sham group in BRAVO and 130 patients in the sham group in CRUISE.

In highlighting the rate of neovascularisation in the GENEVA trials, the ERG was attempting to highlight a potential area of confounding with respect to comparison of treatments in non-ischaemic RVO, rather than draw conclusions on the comparative effectiveness of ranibizumab and dexamethasone in ischaemic patients. The ERG does not consider that conclusions can be drawn on how the differences in rates of neovascularisation will influence the relative effectiveness of the two treatments, but concedes that its initial assessment of the direction of bias attributable to neovascularisation could have been incorrect.

The issue of the definition of ischaemia is discussed in more detail in point 9.

5. Comparisons to dexamethasone in BRVO patients with macular haemorrhage

The ERG considers that there is insufficient information in the Novartis response to fully evaluate the appropriateness of comparing data from the full population of BRAVO with that of the whole BRVO population of GENEVA to inform evaluation of treatments in the subgroup of patients with macular haemorrhage. The ERG believes that this is the first presentation of the data from BRAVO on patients with macular haemorrhage.

In the manufacturer's original submission, the manufacturer notes that "a subgroup of BRVO patients with macular haemorrhage who are unsuitable for laser was not analysed. Exploratory analysis is ongoing in order to identify this group of patients according to an easily operationalisable and consistent definition." At this time, the ERG has been unable to locate a definition for macular haemorrhage within the manufacturer's submission; the Novartis response defines macular haemorrhage as "definite macular haemorrhage", but no further details are provided. Given that the identification of patients with macular haemorrhage was an exploratory analysis, the ERG considers that any results generated from the analysis should be interpreted with caution.

The ERG has been unable to ascertain a definition for macular haemorrhage or an account of what extent of macular haemorrhage precluded use of laser in the GENEVA trials, or in the manufacturer's submission to NICE as part of the STA process.(Allergan) Considering GENEVA, an additional factor that should be considered is that the enrolled population comprised people with MO secondary to RVO, and, as such, patients with BRVO and macular haemorrhage are a subgroup of a subgroup. Thus, analysis of those with macular haemorrhage is based on small patient numbers compared with the full trial population and should also be interpreted with caution.

Although the manufacturer asserts that the full population can be used as a proxy for the subgroup of patients with macular haemorrhage, the ERG considers that the manufacturers of ranibizumab and dexamethasone might be using different criteria for assessing extent of macular haemorrhage, and thus it could be inappropriate to compare data on treatment effects in this subgroup as the populations might not be directly comparable.

6. Pooled versus un-pooled transition probabilities for months 7 to 24 in BRVO patients

The original model submitted by the manufacturer used pooled data from BRAVO(Campochiaro et al. 1102-12) to determine the transitions of all BRVO patients from month 7 to 24. The ERG has previously observed that the use of pooled data would inflate the efficacy of ranibizumab by adding the benefits obtained by newly initiated patients. However, the ERG also noted that the effect (overestimation or underestimation) of using pooled data to approximate the efficacy of GLP is unknown. Consequently, the ERG did not endeavour to present a revised base case for the comparison of ranibizumab and GLP, due to the confounded nature of the data from BRAVO(Campochiaro et al. 1102-12) and the absence of long-term efficacy data for GLP.

The manufacturer now presents a revised model that uses only data from the ranibizumab arm of BRAVO(Campochiaro et al. 1102-12) to inform the transitions of all BRVO patients from month 7 to 24. This assumes that after 6 months of treatment, patients treated with GLP or dexamethasone will experience the same benefit as patients treated with ranibizumab who are moving on to PRN treatment. The manufacturer claims this as a conservative assumption. However, it is not clear whether this

assumption is conservative and the ERG notes that there is a decline in efficacy between monthly ranibizumab and ranibizumab PRN (Table 4).

Table 4. BRVO patient transition probabilities monthly ranibizumab versus ranibizumab PRN

Transitions	Monthly ranibizumab (months 2 to 6)	Ranibizumab PRN (months 7 to 12)
Gain >4 lines	3.0%	1.5%
Gain between 2 and 4 lines	22.6%	17.1%
No change	60.5%	64.6%
Lose between 2 and 4 lines	12.3%	14.2%
Lose >4 lines	1.7%	2.6%
Abbreviations used in table: PRN, *pro re nata*.		

In support of the assumption that equivalent efficacy between patients treated with GLP and patients moving on to ranibizumab PRN is conservative, the manufacturer cites data from SCORE.[Scott et al. 1115-28] The SCORE trial was designed to compare standard care versus intravitreal triamcinolone, with standard care defined as GLP in eyes without dense macular haemorrhage and deferral of GLP until haemorrhage cleared in eyes with dense macular haemorrhage. Of 137 patients randomised to standard care, 39 patients (28% of standard care group) had dense macular haemorrhage and were therefore ineligible for immediate GLP. Of the 39 patients for whom GLP was deferred, 20 patients (14.6%) did not receive GLP in the first 12 months; 2 patients in the group without macular haemorrhage at randomisation did not receive GLP. Results for patients treated with GLP are not reported separately. Thus, the ERG considers that results from SCORE could potentially underestimate the effects of GLP in patients eligible for immediate GLP. SCORE reported a mean change from baseline visual acuity of 2.6 letters from month 8 to month 12 (change from baseline visual acuity: an increase from 1.6 letters at month 8 to 4.2 letters at month 12), compared with an increase of 4.8 letters (a rise from 7.3 letters at 6 months to 12.1 letters at 12 months) in the sham/ranibizumab 0.5 mg group of BRAVO. In addition, as the ERG has highlighted earlier, the ERG considers data post 3 months in BRAVO in both arms to be confounded; the concomitant use of rescue GLP in the sham and ranibizumab groups after 3 months means that ranibizumab is not compared directly with either sham injection or GLP. The ERG is aware of an on-going trial (RABAMES[Ranibizumab for Branch Retinal Vein Occlusion Associated Macular Edema Study (RABAMES)]) that is assessing the effects of ranibizumab alone, GLP alone, and ranibizumab plus GLP, which could go some way to clarifying this issue.

In addition to the concern over the appropriateness of assuming equal efficacy between ranibizumab and GLP, the ERG notes that the manufacturer has continued to assume the same natural deterioration rate for GLP and ranibizumab following treatment cessation at year 2.

The use of HORIZON data to estimate transition probabilities

In addition to the above amendments in the transition probabilities, the manufacturer submitted a scenario model that allegedly included transition probabilities for year 2 that were based on patient level data from HORIZON.[(Campochiaro et al.)] However, the model received still used the pooled transition probabilities of the original model and therefore the ERG were unable to validate any analyses based on data from HORIZON.

7. The inclusion of bevacizumab as a comparator in this STA is inappropriate

The ERG considers that the inclusion of bevacizumab as a comparator in this STA reflects current clinical practice within the NHS, and is aligned with the NICE 'Guide to the Methods of Technology Appraisal',[(National Institute for Health and Clinical Excellence)] which states: "The Appraisal Committee does not normally make recommendations regarding the use of a drug outside the terms of its marketing authorisation, as published in the manufacturer's summary of product characteristics. It can, however, consider unlicensed comparator technologies if these are used regularly in the NHS." The ERG considers inclusion of bevacizumab to reflect clinical practice rather than to make recommendations on unlicensed therapies.

8. Limitations of the ERG's approach to the comparison versus bevacizumab have not been fully explored

a/b) Quality of studies included and methodology of the indirect comparison

The ERG did not have the capacity to perform a systematic review of the literature to inform the exploratory work undertaken and relied on the information presented within the manufacturer's submission. In the ERG report, the ERG highlighted key differences between trials included in the adjusted indirect comparisons, that is, BRAVO,[(Campochiaro et al. 1102-12)] Moradian[(Moradian et al. 193-200)] and Russo.[(Russo et al. 511-15)] The manufacturer describes the limitations of the Russo[(Russo et al. 511-15)] study in detail, and the ERG agrees with the manufacturer's assessment of the quality of this trial.

The manufacturer highlights that the ERG made a typographical error in the data reported for Russo (Table 15 of Novartis' response). The manufacturer has identified that the standard deviations were reported to be 18 and 12 for bevacizumab and GLP, respectively. The ERG noted what it considered a discrepancy in the reporting of the standard deviations in the original publication of the Russo trial.[(Russo et al. 511-15)] Change in BCVA at 1 month was reported as 0.69 ± 0.13 with GLP vs 0.56 ± 16 with bevacizumab. The ERG assumed, given the size of the change in BCVA from baseline, that some of the standard deviations as reported were incorrect and required the addition of a decimal point. The ERG acknowledges that this is an assumption but due to time constraints the ERG was unable to contact the original authors to verify that this assumption is correct. The manufacturer also has concerns around the ERG's implementation of the standard deviations for BCVA at 3 months as

variance around the change in BCVA from baseline at 3 months. The ERG assumed that the variance around BCVA would be a reasonable approximation for variance around the change in BCVA from baseline. The ERG acknowledges that this is a strong assumption and has now calculated the variance around change in BCVA at 3 months. The ERG notes that there is little difference between the standard deviation for BCVA and that for change in BCVA from baseline at 3 months (SD for BCVA at 3 months as corrected from Russo[Russo et al. 511-15]: 0.12 for GLP vs 0.18 for bevacizumab; SD for change in BCVA from baseline at 3 months as calculated by ERG; 0.125 for GLP vs 0.170 for bevacizumab). Thus, the ERG considers the effect sizes and credible intervals generated from its exploratory indirect comparison to be accurate.

c/d) Interpretation of the indirect comparison

As highlighted earlier, the ERG has commented that its analyses were exploratory and based on information presented within the manufacturer's submission. At the time of writing the ERG report, the published CATT[Martin et al. 1897-908] study represented the most appropriate indicator on the comparative effectiveness of ranibizumab and bevacizumab, albeit in a different ocular condition (wet age-related macular degeneration [AMD]) and outcomes reported at 12 months rather than 3 months. The ERG highlighted the non-inferiority margin used in CATT[Martin et al. 1897-908] as a reference point for the effect difference generated from the ERG's exploratory analysis. The ERG commented that "ranibizumab and bevacizumab may have similar efficacy in BRVO, as indicated by the results of the mixed treatment comparison, where the mean difference at month 3 was –2.9 letters (95% credible interval [CrI]: –10.1 to 4.3)" but did not comment on non-inferiority or equivalence. The ERG agrees with the manufacturer that the results of the exploratory analysis do not demonstrate non-inferiority or equivalency of bevacizumab compared with ranibizumab in the treatment of MO secondary to RVO. Results from the IVAN trial,[A randomised controlled trial of alternative treatments to inhibit VEGF in age-related choroidal neovascularisation] which uses a non-inferiority margin of 3–4 letters, are awaited.

As with all exploratory analyses, the ERG appreciates that there is uncertainty surrounding the level of bias in the analyses. The issue of ischaemia is discussed in more detail in point 9.

e) Safety considerations

In the response to ACD comment, the manufacturer cites a retrospective analysis by Curtis and colleagues[Curtis et al. 1273-79] as a reference for safety signals associated with bevacizumab. Curtis *et al*.[Curtis et al. 1273-79] assessed the risks of mortality, myocardial infarction, bleeding, and stroke associated with ranibizumab, bevacizumab, pegaptanib, and photodynamic therapy for the treatment of AMD (cohort of 146,942 patients). Curtis and colleagues[Curtis et al. 1273-79] carried out two secondary analyses based on two observations. The authors noted that: (i) by the end of the study period, almost all newly

treated patients received bevacizumab or ranibizumab as first-line therapy; and (ii) that their primary analysis could be subject to selection bias based on socioeconomic status (people with poorer socioeconomic status are more likely to have received bevacizumab and to have poorer health). One analysis limited the populations to new users of bevacizumab or ranibizumab between July and December 2006. Results of this analysis suggest that ranibizumab is associated with a significantly lower risk of stroke (Hazard Ratio [HR] 0.78; 95% CI: 0.64 to 0.96) and all-cause mortality (HR 0.86; 95% CI: 0.75 to 0.98). However, the second analysis further limited the study population to those who received either ranibizumab or bevacizumab in a medical practice that used a single drug exclusively, which was carried out in an attempt to mitigate the effects of confounding by socioeconomic status. This analysis found no significant difference between ranibizumab and bevacizumab in stroke (HR 0.87; 95% CI: 0.61 to 1.24) or all-cause mortality (HR 1.10; 95% CI: 0.85 to 1.41).

At the time of writing, CATT(Martin et al. 1897-908) is the only published trial directly comparing ranibizumab versus bevacizumab. Ocular AEs recorded as occurring in the study eyes within 12 months were endophthalmitis and pseudoendophthalmitis, both of which were rare. Endophthalmitis occurred in 0.7% (2/301) of patients receiving ranibizumab monthly and 1.4% (4/286) of patients receiving bevacizumab monthly; there were no occurrences in patients receiving ranibizumab or bevacizumab as needed. There was one case of pseudoendophthalmitis in the group receiving ranibizumab monthly. The ERG notes that there is a statistically significant difference between bevacizumab and ranibizumab in overall rate of serious systemic adverse effects (includes all-cause mortality, arteriothrombotic events, and venous thrombotic events) favouring ranibizumab (RR 1.29; 95% CI: 1.01 to 1.66). The authors of CATT note that hospitalisations accounted for a large proportion of the recorded serious adverse effects (298 hospitalisations from 370 individual serious systemic AEs [80.5%]). In addition, the authors highlight that "the excess numbers of these events were distributed over many different types of conditions, most of which were not identified in cancer trials involving patients who were receiving intravenous doses of bevacizumab that were 500 times those used in intravitreal injections."

Both CATT and the retrospective cohort analysis carried out by Curtis *et al*.(Curtis et al. 1273-79) were in patients with AMD, which manifests later in life than RVO, and patients assessed are older than those with RVO.

The ERG commented in its original report that more data on the adverse effect profile of ranibizumab compared with bevacizumab in the treatment of MO secondary to RVO are needed before a conclusion can be drawn on this issue.

f) Rationale for cost minimisation analysis (CMA)

The manufacturer has questioned the use of a CMA in the comparison of ranibizumab versus bevacizumab, stating that "the ERG's use of a cost minimisation analysis is fundamentally flawed when the efficacy and safety of bevacizumab and ranibizumab in RVO has not been established as equivalent." The CMA carried out by the ERG was based on the results of an exploratory indirect comparison and consequently is itself an exploratory analysis. The ERG considers that the emerging safety signals related to bevacizumab may be accounted for by external factors such as socioeconomic status (see Section 8e above for more details). Moreover, the ERG considers the assumption of equivalent safety profiles to be reasonable in an exploratory analysis. However, the ERG agrees with the manufacturer that further research into the safety of bevacizumab is required.

9. Ischaemic disease has not been adequately defined

Although the ERG appreciates the manufacturer's comment that the ERG did not define ischaemia in its report, for various reasons which it will outline here, the ERG maintains that no conclusions can be drawn on the effectiveness of ranibizumab in people with ischaemic RVO. The importance of differentiating between ischaemic and non-ischaemic disease is reflected in the final scope issued by NICE, which requested, if possible, subgroup analysis in those with ischaemic RVO, and highlighted by the RCO guidelines.(The Royal College of Ophthalmologists) In terms of visual acuity, prognosis is good in non-ischaemic CRVO and poor in ischaemic CRVO.(The Royal College of Ophthalmologists)

In the submission to the STA process, the manufacturer highlights that there is considerable variation in the criteria used to define the presence of ischaemia, citing references in support of this statement.(The Royal College of Ophthalmologists;Hayreh et al. 201-17) Definitions that are widely used at this time are those from the landmark BVOS(The Branch Vein Occlusion Study Group 271-82) and CVOS(The Central Vein Occlusion Study 1087-95) studies, which outline criteria for ischaemia in BRVO and CRVO, respectively. The ERG noted in its report that the criteria set out in BVOS and CVOS are for ischaemia in the peripheral retina. Ischaemia was not predefined in BRAVO(Campochiaro et al. 1102-12) or CRUISE(Brown et al. 1124-33) and was not measured at baseline visit.

The ERG agrees that the exclusion criterion in BRAVO and CRUISE of presence of APD would exclude those with severe retinal ischaemia and not those with minor ischaemic disease. The manufacturer highlights in the submission that applying the exclusion criterion of brisk APD meant that few patients fulfilled the definition of ischaemia, which precluded subgroup analysis in this population. Based on the criteria for ischaemia outlined in CVOS, the manufacturer reported that 0 patients and 2 patients with ischaemic RVO were identified in BRAVO and CRUISE, respectively.

Finally, as the manufacturer indicates in its submission, ischaemia of the macular is the only type of ischaemia relevant to this STA and none of the key trials used in the ERG's exploratory analyses reports data on number of patients with baseline macular ischaemia, including BRAVO and CRUISE.

It is important to note that, in RVO, the prognosis could differ if the macula is ischaemic than if it is not.

The ERG has based its comments on the uncertainty of the effects of ranibizumab in the treatment of patients with ischaemia on statements made by the manufacturer in its original submission. The ERG acknowledges that, based on rates of neovascularisation, patients with ischaemia have potentially been included in BRAVO and CRUISE, but this cannot be assumed and the ERG maintains that the effects of ranibizumab in the subgroup of patients with MO secondary to ischaemic RVO are unknown.

Assessment of the manufacturer's revised cost-effectiveness analyses

The Appraisal Committee raised several concerns regarding the economic evaluation originally submitted by the manufacturer, as follows:

4.14 The inappropriateness of the assumption that all patients would be treated in their BSE;

4.15 The absence of age adjustment in the utility values used;

4.16 The substantial impact on the ICER of the use of pooled transition probabilities in ranibizumab versus GLP in BRVO;

4.18 The absence of a mortality risk associated with RVO;

4.20 The potential bias in the comparison between ranibizumab and dexamethasone in CRVO;

4.21 The exclusion of bevacizumab, a comparator likely to display equal efficacy to ranibizumab in CRVO;

4.22 The unfeasibility of a comparison of ranibizumab and GLP due to the highly confounding nature of the data available for this comparison;

4.23 The potential bias and uncertainty in the comparison of ranibizumab with dexamethasone in BRVO;

4.24 The exclusion of bevacizumab, a comparator likely to display equal efficacy to ranibizumab in BRVO.

The manufacturer has responded to these issues as follows:

4.14 The economic model has been adjusted to assume that 90% of patients receive treatment in their WSE;

4.15 Utility values have been derived from a regression equation developed by Brazier *et al*.[Czoski-Murray et al. 793-99] which incorporates age as a covariate;

4.16 The use of pooled transition probabilities in the comparison of ranibizumab and GLP has been superseded by the use of data from the ranibizumab arm of BRAVO to inform all model transitions from month 7 onwards;

4.18 The manufacturer has suggested that this concern is not justified;

4.20 The manufacturer has suggested that this concern is not justified;

4.21 The manufacturer has suggested that this concern is not justified;

4.22 The manufacturer has suggested that this concern is not justified;

4.23 The manufacturer has suggested that this concern is not justified;

4.24 The manufacturer has suggested that this concern is not justified.

In addition to addressing the concerns of the Appraisal Committee, the manufacturer has also updated the economic model to include:

- An increased maximum utility gain (increased from 0.1 to 0.3) in the WSE;
- Updated AE rates associated with ranibizumab and dexamethasone;
- Increased frequency of dexamethasone re-treatment;
- A lifetime time horizon.

Furthermore, the manufacturer submitted an additional scenario model that allegedly incorporated transition probabilities calculated from patient level data available from HORIZON. However, the model received by the ERG still used the pooled transition probabilities of the original model and therefore the ERG was unable to validate any analyses based on this scenario model.

ERG validation of model revisions

A formal validation of the manufacturer's revised economic model was not possible given the time constraints of the commentary process. Consequently, validation has been limited to the replication of the manufacturer's original base case.

Additional cross checks have been carried out to verify the implementation of:

- the additional mortality risk associated with WSE visual impairment;
- Brazier utilities and additional treatment benefit in the WSE;
- unpooled transition probabilities;
- AEs in year 2.

The ERG was able to replicate the base case ICER for each revised analysis to within a couple of pounds, suggesting a well correlated model. In addition, the cross checks of the manufacturer's amendments generally corroborated with the manufacturer's description. The only exception to this was the addition of AEs, in which the manufacturer did not describe the assumptions surrounding the addition of iris neovascularisation as an AE. However, the impact of this addition was minimal.

Manufacturer's revisions

The manufacturer has submitted a revised base case for the following comparisons:

- Ranibizumab versus dexamethasone in BRVO;
- Ranibizumab versus BSC in CRVO;
- Ranibizumab versus dexamethasone in CRVO.

These revised analyses include the following amendments:

- The assumption that 90% of patients will be treated in their WSE;
- The use of Brazier utilities in the BSE;
- The assumption of a 0.3 maximum benefit to treatment of the WSE;
- The incorporation of an increased mortality risk from visual impairment in the WSE;
- The use of unpooled transition probabilities (BRVO analysis only);
- The update of AEs to include events in the second year of treatment;
- The frequency of re-treatment with dexamethasone (only applicable to comparisons with dexamethasone).
- A lifetime horizon.

The cumulative impact of these amendments compared to the manufacturer's original base case is displayed in Tables 5 to 7 for each submitted comparison.

Table 5. Ranibizumab versus dexamethasone in BRVO

Scenario	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Manufacturer's original base case	[redacted]	[redacted]	**£5,486**
Manufacturer's amendments addressing previous ACD concerns			
10% treated in BSE	[redacted]	[redacted]	66,175
The use of Brazier utilities	[redacted]	[redacted]	49,360
Assuming a maximum benefit from WSE treatment of 0.3	[redacted]	[redacted]	15,774
Not addressed: RVO associated mortality	?	?	?
WSE VI associated mortality	[redacted]	[redacted]	15,696
Not addressed: Frequency of ranibizumab injections	?	?	?
Use of unpooled transition probabilities	[redacted]	[redacted]	15,641
Not addressed: Duration of treatment effect	?	?	?
Not addressed: Potential bias in the comparison of dexamethasone and ranibizumab	?	?	?
Not addressed: Use of post-hoc 10 letter outcome as the basis for economic model	?	?	?
Additional amendments carried out by the manufacturer			
Update of AEs rates	[redacted]	[redacted]	13,300
Increased frequency of dexamethasone re-treatment	[redacted]	[redacted]	8,014
Lifetime time horizon	[redacted]	[redacted]	6,600
Manufacturer's revised base case	[redacted]	[redacted]	**6,600**

Table 6. Ranibizumab versus BSC in CRVO

Scenario	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Manufacturer's original base case	[redacted]	[redacted]	**£8,643**
Manufacturer's amendments addressing previous ACD concerns			
10% treated in BSE	[redacted]	[redacted]	107,226
The use of Brazier utilities	[redacted]	[redacted]	76,026
Assuming a maximum benefit from WSE treatment of 0.3	[redacted]	[redacted]	21,927

Not addressed: RVO associated mortality	?	?	?
WSE visual impairment associated mortality	[redacted]	[redacted]	21,771
Not addressed: Frequency of ranibizumab injections	?	?	?
Use of unpooled transition probabilities	N/A		
Not addressed: Duration of treatment effect	?	?	?
Not addressed: Potential bias in the comparison of dexamethasone and ranibizumab	?	?	?
Not addressed: Use of post-hoc 10 letter outcome as the basis for economic model	?	?	?
Additional amendments carried out by the manufacturer			
Update of AEs	[redacted]	[redacted]	22,105
The frequency of dexamethasone re-treatment	N/A		
Lifetime time horizon	[redacted]	[redacted]	18,817
Manufacturer's revised base case	[redacted]	[redacted]	**18,817**
Abbreviations used in table: AEs, adverse events; BSC, best supportive care; CRVO, central retinal vein occlusion; ICER, incremental cost effectiveness ratio; QALY, quality adjusted life year; WSE, worse-seeing eye.			

Table 7. Ranibizumab versus dexamethasone in CRVO

Scenario	**Incremental costs (£)**	**Incremental QALYs**	**ICER (£/QALY)**
Manufacturer's original base case	[redacted]	[redacted]	**£7,174**
Manufacturer's amendments addressing previous ACD concerns			
10% treated in BSE	[redacted]	[redacted]	84,959
The use of Brazier utilities	[redacted]	[redacted]	63,363
Assuming a maximum benefit from WSE treatment of 0.3	[redacted]	[redacted]	19,639
Not addressed: RVO associated mortality	?	?	?
WSE visual impairment associated mortality	[redacted]	[redacted]	19,509
Not addressed: Frequency of ranibizumab injections	?	?	?
Use of unpooled transition probabilities	N/A		

Not addressed: Duration of treatment effect	?	?	?
Not addressed: Potential bias in the comparison of dexamethasone and ranibizumab	?	?	?
Not addressed: Use of post-hoc 10 letter outcome as the basis for economic model	?	?	?
Additional amendments carried out by the manufacturer			
Update of AEs	[redacted]	[redacted]	17,503
The frequency of dexamethasone re-treatment	[redacted]	[redacted]	13,521
Lifetime time horizon	[redacted]	[redacted]	11,656
Manufacturer's revised base case	[redacted]	[redacted]	**11,656**
Abbreviations used: Abbreviations used in table: ACD, Appraisal Committee Document; AEs, adverse events; CRVO, central retinal vein occlusion; ICER, incremental cost effectiveness ratio; QALY, quality adjusted life year; WSE, worse-seeing eye.			

Clearly, the maximum utility benefit of treatment in the WSE is the main driver of the manufacturer's revised model. As discussed in Section 1b, the ERG maintains that there is a benefit to treatment of patients in their WSE and that currently available evidence indicates that this is likely to be no more than 0.1. The ERG considers the manufacturer's assumption of a maximum benefit of 0.3 to be unsubstantiated. The ICERs associated with the manufacturer's revised base case using maximum utility benefits of 0.1, 0.2 and 0.3 for a lifetime and 15-year time horizon are displayed in Table 8 and Table 9, respectively.

Table 8. The influence of maximum utility gain in the WSE on the ICERs of the manufacturer's revised comparisons, under a lifetime time horizon

Comparison	**Maximum utility gain in the WSE**		
	0.1	**0.2**	**0.3**
Ranibizumab versus dexamethasone in BRVO	11.396	8,436	6,600
Ranibizumab versus BSC in CRVO	35,678	24,905	18,817
Ranibizumab versus dexamethasone in CRVO	26,773	19,583	15,220
Abbreviations used: BRVO, branch retinal vein occlusion; BSC, best supportive care; CRVO, central retinal vein occlusion; ICER, incremental cost effectiveness ratio; WSE, worse-seeing eye.			

Table 9: The influence of maximum utility gain in the WSE on the ICERs of the manufacturer's revised comparisons, under a 15-year time horizon

Comparison	Maximum utility gain in the WSE		
	0.1	0.2	0.3
Ranibizumab versus dexamethasone in BRVO	13,784	10,229	8,014
Ranibizumab versus BSC in CRVO	42,346	29,365	22,105
Ranibizumab versus dexamethasone in CRVO	30,766	22,526	17,503
Abbreviations used: BRVO, branch retinal vein occlusion; BSC, best supportive care; CRVO, central retinal vein occlusion; ICER, incremental cost effectiveness ratio; WSE, worse-seeing eye.			

Regarding the additional revisions of the manufacturer's model, the ERG accepts the:

- adoption of a 90% WSE perspective;
- use of Brazier utilities;
- assumption of excess mortality associated with visual impairment in the WSE;
- updated adverse event rates.

However, the ERG maintains that there may be an increased risk of cardiovascular death associated with RVO, although the evidence for this is inconclusive. Furthermore, the ERG considers that the manufacturer's assumption of a greater re-treatment frequency for dexamethasone is inappropriate in the absence of a similar adjustment for efficacy and safety.

The use of ranibizumab PRN data to inform the longer term efficacy of dexamethasone results in a great deal of uncertainty in the comparison of ranibizumab with dexamethasone in BRVO and CRVO. The manufacturer of dexamethasone reported lifetime costs and QALYs gained with dexamethasone treatment in CRVO of £12,332 and 11.18, respectively.(Cummins et al.) Whereas, based on the revised model submitted by Novartis, treatment of CRVO patients with dexamethasone would result in lifetime costs and QALYs gained of £[redacted] and [redacted], respectively.

The ERG revised base case for each comparison is presented in Table 10, these were calculated by:

- removing the additional re-treatment costs applied to dexamethasone (where applicable);
- assuming a maximum utility gain of 0.1 for treatment of the WSE.

In addition, the results are also presented using an increased risk of cardiovascular mortality and the original time horizon of 15 years.

Table 10. The ERG's revised ICERs (£) for each comparison, based on the manufacturer's revised model

Scenario	**Ranibizumab versus dexamethasone in BRVO**		**Ranibizumab versus BSC in CRVO**		**Ranibizumab versus dexamethasone in CRVO**	
Time horizon	Lifetime	15 years	Lifetime	15 years	Lifetime	15 years
Manufacturer's revised ICERs	6,600	8,014	18,817	22,105	11,656	13,521
ERG revised ICERs (calculated by removing additional re-treatment costs for dexamethasone and assuming a maximum benefit of 0.1 in the WSE)	19,518	22,875	35,678	42,346	26,773	30,766
ERG revised ICERs (including RVO mortality)	21,753	24,328	40,602	45,909	29,750	32,760
Abbreviations used in table: BRVO, branch retinal vein occlusion; BSC, best supportive care; CRVO, central retinal vein occlusion; ERG, Evidence Review Group; ICER, incremental cost effectiveness ratio; WSE, worse-seeing eye.						

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