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Aflibercept for treating visual impairment caused by macular oedema secondary to central retinal vein occlusion – a single technology assessment

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List of Abbreviations

AC	Appraisal Committee
AE	Adverse Events
AMD	Age-related Macular Degeneration
BCVA	Best Corrected Visual Acuity
BRVO	Branch Retinal Vein Occlusion
BSE	Better-Seeing Eye
CRT	Central Retinal Thickness
CRUISE	Central Retinal Vein OcclUsIon Study: Evaluation of Efficacy and Safety
CRVO	Central Retinal Vein Occlusion
CVOS	Central Vein Occlusion Study
DA	Disc Area
DD	Disc Diameter
DIC	Deviance Information Criterion
DMO	Diabetic Macular Oedema
DSU	Decision Support Unit
EMA	European Medicine Agency
EQ-5D	EuroQol-5D
ERG	Evidence Review Group
ETDRS	Early Treatment Diabetic Retinopathy Study
FA	Fluorescein Angiography
FAS	Full Analysis Set
FDA	Food and Drug Administration
FEI	Fellow Eye Involvement
GENEVA	Global Evaluation of implaNtable dExamethasone in retinal Vein occlusion with macular edemA
GMC	General Medical Council
HRQoL	Health Related Quality of Life
HS	Health States
ICER	Incremental Cost-Effectiveness Ratio
IOP	Intraocular Pressure
ITT	Intention To Treat
IVAN	Inhibition of VEGF in Age-related choroidal Neovascularisation
LOCF	Last Observation Carried Forward

MO	Macular oedema
MS	Manufacturer Submission
NEI-VFQ-25	National Eye Institute visual functioning questionnaire 25
NHS	National Health Service
NMA	Network Meta-analysis
NVG	Neovascular Glaucoma
OCT	Optical Coherence Tomography
OR	Odds Ratio
PAS	Patient Assess Scheme
PRN	Pro re nata
PRP	Pan Retinal Photocoagulation
QALY	Quality Adjusted Life Years
QoL	Quality of Life
RCO	Royal College of Ophthalmologists
RCT	Randomised Controlled Trial
ROCC	randomised study comparing ranibizumab to sham in patients with macular edema secondary to central Retinal vein OCClusion
RPE	Retinal Pigment Epithelium
RR	Relative Risk
RVO	Retinal Vein Occlusion
SAE	Serious Adverse Event
SCORE	The Standard Care vs. COrticosteroid for REtinal Vein Occlusion
SD	Standard Deviation
SE	Standard Error
SPC	Summary Product Characteristic
STA	Single Technology Assessment
TEAE	Treatment Emergent Adverse Event
TPM	Transition Probability matrices
VA	Visual Acuity
VEGF	Vascular Endothelial Growth Factor
VI	Visual Impairment
VIEW	VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD
VL	Visual Loss
WSE	Worse-Seeing Eye
WTP	Willingness To Pay

1. SUMMARY

1.1 Introduction

In central retinal vein occlusion (CRVO), the main vein draining blood from the retina is blocked, usually by a blood clot. This results in back pressure leading to accumulation of fluid (oedema) and haemorrhages.

The macula is the central and most sensitive part of the retina, and is used for fine detail vision such as reading. Oedema of the macula causes visual impairment. In a minority of cases, there is spontaneous recovery without treatment, but in most cases the outlook is poor, especially in the ischaemic sub-type where several lines of vision may be lost. At onset, about 20% of cases are ischaemic, but up to another 25% (depending on definition) become ischaemic over time.
Central retinal vein occlusion (CRVO) is usually unilateral at onset but about 5% of patients develop it in the other eye. In about 30% of non-ischaemic CRVO, there is spontaneous resolution of macular oedema (MO).

Current treatment for macular oedema secondary to CRVO involves injecting either corticosteroids or anti-VEGF drugs into the eye. The steroids include dexamethasone, in the long-acting form Ozurdex, and triamcinolone. Dexamethasone was approved by NICE in TA 229. Triamcinolone is not licensed for use in the eye, but has been widely used. It is licensed for use in joints. The anti-VEGF drugs oppose the effect of vascular endothelial growth factor which increases vascular permeability and worsens oedema. Ranibizumab was approved for MO after CRVO in 2013. Bevacizumab is not licensed for eye use, but is for cancer, and has been widely used for eye conditions including age-related macular degeneration (AMD) and diabetic macular oedema (DMO).

Aflibercept has been licensed by EMA, firstly for the treatment of adults with neovascular wet AMD, and recently for the treatment of MO secondary to CRVO.
There are currently two drugs recommended by NICE for CRVO, ranibizumab and dexamethasone.

1.2 Decision problem

The manufacturer gives a concise, accurate account of the problem of CRVO, including:

- the presentation is usually acute and the most frequent symptom is an abrupt decrease of central vision.

- blockage of the vein causes back pressure, with some or all of intraretinal haemorrhages, retinal venous engorgement and tortuosity, optic disc swelling, cotton wool spots, and macular oedema.
- the macular oedema leads to loss of vision, and the visual acuity (VA) soon after onset is a strong predictor of prognosis. The more the accumulation of fluid, the more effect on the vision.
- there are two main sub-types, ischaemic and non-ischaemic, with the latter have a poorer prognosis. In some cases of non-ischaemic CRVO, spontaneous recovery occurs.
- there are approximately 12 new patients with MO secondary to CRVO per 100,000 of the population in England and Wales each year. This equates to 6,840 in a population of around 57 million.

The Bayer submission states that the standard of care is now ranibizumab, following NICE approval of that, and they state that ranibizumab treatment requires monthly monitoring, which has implications for workload in Ophthalmology. They argue that there is an unmet need for effective treatments without the burden of monthly monitoring. Bayer considered that dexamethasone should not be considered as a comparator, but assessed its cost-effectiveness for completeness. However they did not include bevacizumab, which was in the NICE scope, and has been widely used.

1.3 Summary of submitted clinical effectiveness evidence

The evidence on clinical effectiveness comes from two trials, COPERNICUS and GALILEO. Patients in the trials were adults (aged ≥18 years) with visual impairment due to MO caused by CRVO diagnosed not more than 9 months before study initiation. Mean central retinal thickness (CRT) in all study eyes was ≥ 250 um using optical coherence tomography (OCT) and patients had an Early Treatment Diabetic Retinopathy Study (ETDRS) best-corrected visual acuity (BCVA) of 73 to 24 letters (20/40 to 20/320) in the study eye.

In both trials, aflibercept (2 mg intravitreal injection) was compared against sham injection. The primary endpoint of both trials was the proportion of eyes with a gain of 15 or more ETDRS letters (≥3 lines) from baseline to week 24. The other outcomes included mean change in BCVA from baseline, CRT, ETDRS letter gain or loss, the proportions of patients progressing to ocular neovascularisation, vision-related quality of life (QoL) and safety parameters. Subgroup analyses were carried out by age, sex, ethnicity, geographic location, baseline BCVA, baseline perfusion status, and time since CRVO diagnosis.

GALILEO included 177 patients and COPERNICUS included 189 patients. Bayer say that both ischaemic (non-perfused) and non-ischaemic (perfused) CRVO were included. The manufacturer defined non-perfused as those with ≥ 10 disc areas (DA) of capillary non-perfusion of fluorescin angiography (FA) and perfused as those with < 10 DA of capillary non-perfusion of FA. Those with indeterminate perfusion were classed as non-perfused. According to this definition, 15.6% and 8.5% were ischaemic in COPERNICUS and GALILEO respectively.

In the COPERNICUS trial, aflibercept was given every 4 weeks for 24 weeks while the comparison group received a sham injection, a needleless syringe placed on the cornea. During weeks 24 to 52, patients in both groups received aflibercept if they met protocol-specified retreatment criteria. If they did not then, patients received a sham injection. All patients were assessed monthly using retreatment criteria from week 24 to week 52. After completing 52 weeks, patients continued up to 100 weeks, were monitored every 12 weeks, and received aflibercept as needed.

In the GALILEO trial, patients in the intervention arm received aflibercept every 4 weeks for 24 weeks while the comparison arm received a sham injection. From weeks 24 to week 52, patients remained in their original treatment group and received their allocated treatment as needed. From week 52 to week 76, both groups were followed up, and could receive aflibercept every 8 weeks.

In both trials, significantly more patients in the aflibercept group gained 15 or more ETDRS letters than in the sham groups (at 24 weeks, 60% vs. 22%, difference 38% in GALILEO and 56% vs. 12%, difference 44% in COPERNICUS). The results of subgroup analyses (based on age, sex, ethnicity, baseline BCVA, geographic location, baseline perfusion status, time since CRVO diagnosis) were consistent with the results of the overall population. The proportion of patients gaining 15 or more EDTRS letters at 24 weeks after treatment with aflibercept was greater in patients beginning treatment within 2 months of diagnosis compared to those with longer disease duration (69 versus 39%).

In both trials, patients in the aflibercept arm had a significant improvement in BCVA at 6 months, and this was maintained at 12 months and was significantly greater than the improvements in the sham groups (difference to sham 21.7 letters in COPERNICUS and 14.7 letters in GALILEO). The difference between the aflibercept and sham groups was 12.7 letters in the COPERNICUS trial after 52 weeks (all groups on aflibercept as needed) and 13.2 letters in the GALILEO trial (interventions maintained). In both trials, most patients (over 90% in both trials at week 24, [redacted]) did not lose any EDTRS letters. Between 1 and 5% lost up to 15 letters in the aflibercept groups up to week 52, compared to between 15 and 27% in the original sham groups.

NEI VFQ-25 total scores increased (i.e. improved) significantly more in the aflibercept group at 6 months in both trials. There was no significant change over time and no significant difference between intervention groups at any of the time points in EQ-5D scores.

The most common (in at least 3% of patients) adverse effects with aflibercept were conjunctival haemorrhage, eye pain, reduced VA and increased IOP.
Based on the findings from this appraisal and the appraisal of aflibercept for wet AMD, the safety profile of aflibercept appears similar to ranibizumab. As is usual with the anti-VEGFs, the main AEs come from the injection rather than the drug. However the EMA did express some concern about cerebrovascular events in the trials of aflibercept in AMD, while concluding that the safety profile of aflibercept appeared to be similar to that of ranibizumab,

In the absence of a head to head comparison of aflibercept against ranibizumab in CRVO, the manufacturer undertook a network meta-analysis (NMA) to assess the effects of the two treatments. Two studies (CRUISE and ROCC) investigated ranibizumab, two studies (COPERNICUS and GALILEO) aflibercept, and two studies dexamethasone (GENEVA 008 and GENEVA 009). Bevacizumab was not included in the NMA. The efficacy endpoints analysed were: proportion of patients gaining ≥15 letters of BCVA from baseline at 6 months; proportion of patients losing ≥15 letters of BCVA from baseline at 6 months; mean change in BCVA/number of letters read from baseline at 6 months

The NMA reported that aflibercept was significantly superior to dexamethasone in terms of proportion of patients gaining at least ≥15 letters from baseline to 24 weeks but non-significantly superior to ranibizumab. Ranibizumab was non-significantly superior to aflibercept in the proportion of patients losing at least ≥15 letters from baseline to 24 weeks. Patients receiving aflibercept gained significantly more letters at six months than those on dexamethasone. There was no significant difference between aflibercept and ranibizumab.

1.4 ERG's comments on clinical effectiveness

The Evidence Review Group (ERG) regard the aflibercept trials of being of good quality, and providing good evidence that aflibercept is effective in improving vision after CRVO, with an acceptable safety record. One weakness is that patients were not asked, at the end of the trials, whether they thought they had been allocated to aflibercept or sham.

As regards frequency of injections and monitoring, we note that dexamethasone implants may be given only every 4 months, and that monitoring will be less frequent than after aflibercept. However we agree with Bayer's assertion that ranibizumab will probably be used more than dexamethasone, in the National Health Service (NHS). The ERG also expects that bevacizumab use will decline now that ranibizumab has been approved by NICE and also taking into account the General Medical Council (GMC) disapproval of the use of unlicensed drugs when licensed ones are available, and the absence of any recommendation from NICE.

The ERG had concerns about the evidence for the value of aflibercept in ischaemic CRVO. In the trials, non-perfused was defined as more than 10 DA of capillary non-perfusion, which is not a strict definition of ischaemic CRVO. The ERG prefers the stricter definition suggested by Hayreh. Using that, the ERG thinks there were few patients with ischaemic CRVO in the trials. Details of mean or median of non-perfused areas had not been given.

The ERG had access to a NMA undertaken by an academic group (Ford et al submitted for publication). The results reported in the Bayer submission and those reported by the academic group were similar.

The ERG also had access to an independent systematic review (submitted for publication) of treatment of MO after CRVO and this confirmed that the Bayer submission included all relevant published trials of aflibercept, ranibizumab and dexamethasone.

1.5 Summary of cost effectiveness submitted evidence by the manufacturer

The manufacturer submitted a de novo cost utility model with a four week cycle length and a lifetime horizon. Health states are defined in terms of 15 ETDRS letter-wide bands, resulting in five health states for the treated eye and five health states for the fellow eye: 25 health states in total. The model assumes that the BCVA of the fellow eye is constant. The base case assumes one year of treatment.

The initial patient distribution is taken from the pooled COPERNICUS and GALILEO patient data. For each of the six cycles from baseline to week 24:

- The probabilities of the treated eye improving and worsening for aflibercept are drawn from the pooled COPERNICUS and GALILEO patient data.
- The probabilities of the treated eye improving for ranibizumab are calculated by applying the [redacted] relative risk (from the manufacturer's NMA) of improving by at least 15 letters at week

24 to the corresponding aflibercept probabilities of improving. The probabilities of worsening for ranibizumab are assumed to be the same as those of aflibercept.

- The probabilities for dexamethasone are calculated in the same manner as those for ranibizumab, only applying the [redacted] relative risk of improving by at least 15 letters at week 24.

For weeks 24 to 52 treatment continues, but given a lack of comparative clinical efficacy data it is assumed that the BCVA of the treated eye is constant. Thereafter a slow visual worsening is modelled using data drawn from the literature, with 0.0296% worsening by one health state each 4 week cycle.

Quality of life values for the base case are drawn from EQ-5D data collected during the GALILEO trial. This is augmented by a scenario analysis that applies QoL values drawn from Czoski-Murray et al (2009).

The number of administrations during for baseline to 24 weeks and for 24 weeks to 52 weeks are

- 5.75 and 2.55 to give a total of 8.30 for aflibercept, at a direct drug cost of £816.00 excluding the PAS and [redacted] including the PAS;
- 5.50 and 3.30 to give a total of 8.80 for ranibizumab, at a direct drug cost of £742.17 excluding the PAS; and,
- 1.85 and 2.15 to give a total of 4.00 for dexamethasone, at a direct drug cost of £870.00.

Unfortunately, the reduced PAS price for ranibizumab has not been communicated for this assessment and as a consequence the manufacturer applies ranibizumab PAS percentages from 10% to 50% in 5% increments.

Administrations also incur a cost of £257 for aflibercept and ranibizumab based upon 48% requiring day case administration, and £321 for dexamethasone due to a higher 75% proportion requiring day case administration.

A one-stop monitoring model is applied, where administration visits can double as monitoring visits. The number of dedicated monitoring visits for baseline to 24 weeks are 0.00 for aflibercept, 0.00 for ranibizumab and 0.92 for dexamethasone, and for 24 weeks to 52 weeks are 2.43 for aflibercept, 2.03 for ranibizumab and 1.08 for dexamethasone. These incur a cost of £197.

The base case does not include adverse events, but these are included within a scenario analysis.

A blindness mortality multiplier of 1.54, a first year cost of blindness of [redacted] and a subsequent annual cost of blindness of [redacted] are applied.

Manufacturer results: Aflibercept versus ranibizumab

The base case results for the comparison with ranibizumab excluding the aflibercept PAS are net costs of [redacted], net gains of 0.054 quality adjusted life years (QALYs) and a cost effectiveness estimate of [redacted] per QALY.

Scenario analyses that lengthen the treatment duration to 2 years and to 5 years are estimated to improve the cost effectiveness of aflibercept. Applying the Czoski-Murray quality of life values worsens it to [redacted] per QALY.

Including the aflibercept patient assess scheme (PAS) and varying the ranibizumab PAS from 10% to 50% of the published price in 5% increments results in aflibercept having a lower total [redacted] cost up to and including a ranibizumab PAS of 45%. If the ranibizumab PAS is 50% the net costs are estimated to be £315 resulting in a cost effectiveness estimate of £5,871 per QALY.

Manufacturer results: Aflibercept versus dexamethasone

The base case results for the comparison with dexamethasone excluding the aflibercept PAS are net costs of [redacted], net gains of 0.189 QALYs and a cost effectiveness estimate of [redacted] per QALY. Including the aflibercept PAS results in net costs of £612 and a cost effectiveness estimate of £3,236 per QALY.

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

1.6.1 Strengths

The submission is clearly written with a transparent model structure. The broad underlying model structure is reasonable, though there are concerns with the derivation of the week 24 patient distributions as outlined later in section 1.6.2.

Resource use for the first year of the modelling for the comparison of aflibercept with ranibizumab; i.e. for the base case, is well documented and sourced from the relevant trial data.

The 24 week model output for the comparison of aflibercept with ranibizumab shows a good correspondence with the network meta-analysis (NMA) results for the 24 week BCVA mean net gain in letters.

1.6.2 Weaknesses and areas of uncertainty

Clinical inputs

When data are missing, the clinical effectiveness estimates rely upon last observation carried forward (LOCF). The patient level data that populates the transition probability matrices (TPMs) within the economic model is based upon observed data. The data supplied in response to the economic clarification questions switches back to LOCF. The impact of using observed data within the modelling is unknown.

The manufacturer also refers to different data cuts of the observed data in their clarification response. In the light of this it is unclear quite what data underlies the observed data of the economic model and how well it is aligned with the data the underlies the clinical effectiveness estimates.

The model only incorporates the relative risk of gaining at least 15 letters at week 24, and not the relative risk of losing at least 15 letters at week 24.

- For the comparison with ranibizumab, the relative risk of losing at least 15 letters at week 24 is in favour of ranibizumab.
- For the comparison with dexamethasone, the relative risk of losing at least 15 letters at week 24 seems likely to be in favour of dexamethasone.

Quality of life values

The analysis of the EQ-5D data from the European subset of the GALILEO trial does not control for the BCVA of the better-seeing eye (BSE). Due to the structure of the data, this may tend to exaggerate the estimated impact of changes in the BCVA of the worse-seeing eye (WSE). But the EQ-5D data from all patients within the GALILEO trial, with some admittedly rather ad hoc adjustments by the ERG to attempt to control for the BCVA of the BSE, could be seen as suggesting a slightly better cost effectiveness for aflibercept than the manufacturer analysis. In the light of this, there are uncertainties about the EQ-5D data.

The clinical effectiveness section refers to the adjusted EQ-5D values. The ERG asked at clarification for more information about these adjustments, and also for adjusted values in order to be able to compare them with those used within the modelling. No description of the adjustments or adjusted values were provided.

The manufacturer survey of the literature identifies the Czoski-Murray reference and used this in a sensitivity analysis, but due to the date cut-off used, it does not identify the Brown (1999) reference which has also been used extensively in NICE STAs of treatments for eye conditions. The values from the literature typically worsen the cost effectiveness estimates, with the values of Brown resulting in the worst costs effectiveness estimates. The Czoski-Murray study mimicked the central visual loss in AMD, whereas CRVO can affect the whole retina, and affect peripheral vision.

The implementation of the quality of life values within the modelling is slightly peculiar.

- For the trial EQ-5D data of the base case, it is assumed that this is WSE QoL data. As a consequence, this is only applied when the treated eye is modelled as being the WSE. Should it cross over to be the BSE, no QoL changes are anticipated. But this applies to relatively few patients: around 3% at baseline rising to 10% at 24 weeks.
- For the Czoski-Murray values, it is assumed that this is BSE quality of life data. As a consequence, this is only applied when the treated eye is modelled as being the BSE. Should it cross over to be the WSE, no quality of life changes are anticipated.

This may be unduly conservative.

Resource use

The £257 cost per administration visit is derived from a weighted average of 2010-2011 HES outpatient and day case data. The ERG believes that all costing should be as outpatients. Revising these to 2011-2012 HES data, restricting the data to C89.3 with this being costed using NHS reference cost BZ23Z and including an additional cost for OCT based upon NHS reference cost RA23Z results in an administration cost of £181.

The assumption of 4.0 doses for dexamethasone in the first year is too high. The pooled GENEVA dosing for CRVO patients reported in the Allergan submission for the single technology assessment (STA) of dexamethasone for retinal vein occlusion (RVO) reports only 1.86 doses on average.

Note that based on trial data, there is little difference in the numbers of aflibercept and ranibizumab injections in the first year. In routine care, the number of aflibercept injections may be less.

Modelling approach

The model does not employ any stopping rules. Some patients will be non-responders and cease treatment before week 24, some stopping after three months. Some will respond, be stable before week 24 and so also stop treatment before week 24. The manufacturer has the data that would be required to implement this for the aflibercept arm, but implementing it for ranibizumab and for dexamethasone might be more complicated.

The model assumes a slow but steady decline, common to all treatments. In effect this appears to anticipate that the week 24 net gain from aflibercept will remain for the lifetime of the patient, despite only one year of treatment being received. This may be optimistic.

It appears that a more logical structure for the model would be to apply the week 24 relative risk of gaining letters and the week 24 relative risk of losing letters to the baseline to week 24 aflibercept TPM coupled with the baseline patient distribution in order to estimate the week 24 patient distribution.

The current approach of applying only the week 24 relative risk of gaining letters but compounding it six times over the first six months of the modelling does not seem correct. By chance, it results in week 24 patient distributions for ranibizumab compared to aflibercept for the central estimates of the deterministic model that are not too far out of line with those that would result from the more logical structure for the model. Both approaches result in a mean gain in BCVA from aflibercept over ranibizumab at week 24 that are quite closely aligned with that of the NMA.

But it is unclear what effect the compounding of the week 24 relative risk of gain has within the probabilistic modelling, and for this reason the probabilistic results need to be treated with caution.

The current modelling approach results in week 24 patient distributions for aflibercept compared to dexamethasone for the central estimates of the deterministic model that suggest a mean gain in BCVA from aflibercept over dexamethasone that is somewhat less than that of the NMA. It appears possible that the more logical model structure would result in estimates more closely aligned with the estimate of the mean gain in BCVA from aflibercept over dexamethasone of the NMA.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

ERG results: Aflibercept versus ranibizumab

The ERG revisions to the modelling, excluding both the aflibercept PAS and the ranibizumab PAS, result in a net cost estimate of [redacted], a net gain of 0.053 and a cost effectiveness estimate of [redacted] per QALY. The net costs of the original manufacturer estimates are slightly higher at [redacted], the net gain is similar at 0.054, with these resulting in a cost effectiveness estimate of [redacted] per QALY.

Within the ERG analyses that apply the aflibercept PAS, the ranibizumab PAS can be varied from 0% to 50% in 5% increments. The [redacted] costs for aflibercept remain [redacted] those of ranibizumab up to and including a ranibizumab PAS of 40%. The total costs in the aflibercept arm remain below those of ranibizumab up to and including a ranibizumab PAS of 45%. As a consequence, aflibercept is estimated to dominate ranibizumab up to and including a ranibizumab PAS of 45%. A ranibizumab PAS of 50% results in the total costs of the aflibercept arm being £203 more than those of the ranibizumab arm, and a cost effectiveness estimate of £3,820 per QALY.

The following sensitivity analyses all include the PAS.

Applying the relative risk of losing letters within the model framework, where these are compounded six times during the first six months, has a dramatic effect upon the modelled patient gain from aflibercept over ranibizumab. It all but eliminates it. But the compounding of relative risks when both the relative risk of gaining letters and the relative risk of losing letters are applied results in model outputs that are not aligned with the validation data.

Applying the upper confidence interval for the relative risk of gaining 15 or more letters at 6 months of [redacted] results in many of the cost effectiveness estimates falling into the southwest quadrant of the cost-effectiveness plane (lower cost but lower health gain), with patient gains of 0.047 QALYs from ranibizumab. If the PAS for ranibizumab is equal to or more than 25%, ranibizumab is estimated as being cost effective at the £30,000 per QALY threshold. If the PAS for ranibizumab is a little more than 30% ranibizumab is estimated as being cost effective at the £20,000 per QALY threshold. If the PAS for ranibizumab is 50% aflibercept ceases to be cost saving, and so is dominated by ranibizumab.

Equalising the dosing and monitoring frequencies between aflibercept and ranibizumab still results in aflibercept being estimated to be cost effective relative to ranibizumab, though it now ceases to be cost saving if the PAS for ranibizumab is 45% or more.

Varying the source of the QoL data changes the net QALY gain in the predictable directions, but the broad conclusions remain unchanged.

ERG results: Aflibercept versus dexamethasone

ERG revisions to the modelling of aflibercept compared to dexamethasone result in a net cost including the aflibercept PAS of £2,285, a net gain of 0.186 QALYs and a cost effectiveness estimate of £12,265 per QALY. The net costs are somewhat greater than the manufacturer estimate of £612, but the net QALYs are broadly in line with the manufacturer estimate of 0.189. The difference in the net costs estimate mainly arises from the number of administrations of dexamethasone during the first

year being revised from the 4.00 of the manufacturer base case to the 1.86 suggested by the pooled analysis of the GENEVA trials' CRVO subset of patients.

The sensitivity analyses for the comparison with dexamethasone are more variable than those of the comparison with ranibizumab, in part due to the revised cost effectiveness estimate being £12,265 per QALY.

Applying the lower confidence interval limit of [redacted] for the relative risk of gaining at least 15 letters at 24 weeks results in some improvement in the cost effectiveness estimate to £9,023 per QALY, but applying the upper confidence interval limit of [redacted] somewhat worsens the cost effectiveness estimate to £24,991 per QALY.

Of more concern may be lengthening the assumed duration of treatment, coupled with the dexamethasone dosing proposed by Allergan from a survey of experts it undertook for the STA of dexamethasone for RVO. These analyses also equalise the monitoring frequency for years 2 to 5 between aflibercept and dexamethasone. The 5 year treatment duration worsens the cost effectiveness estimate to £18,699 per QALY.

As in the comparison with ranibizumab, the choice of the source of utilities changes the net QALY gains in the predictable direction. Applying Brown (1999) with WSE effects worsens the cost effectiveness estimate to £16,833 per QALY. Combining this with a lengthening of the time horizon to 5 years worsens the cost effectiveness estimate to £25,621 per QALY.

While probably a worst case scenario analysis for this particular variable, the sensitivity analysis that equalises the administration cost between aflibercept and dexamethasone worsens the cost effectiveness estimate to £13,644 per QALY.

1.8 Conclusions

Aflibercept is clinically effective in most cases of macular oedema due to CRVO, but a question remains over its value in truly ischaemic CRVO because of lack of data. (The same applies to ranibizumab.)

There are no direct comparisons with other drugs in CRVO. Indirect comparison with ranibizumab suggests that overall, there is not much difference in clinical effectiveness. The number of aflibercept injections may be lower in routine care than in the trials and in the Bayer modelling.

Cost comparisons are not publicly transparent because both aflibercept and ranibizumab have confidential price reductions. Sensitivity analyses making different assumptions about prices, give results that can vary from aflibercept dominating ranibizumab, to having cost-effective ICERs compared to ranibizumab, and to ranibizumab dominating aflibercept.

2. BACKGROUND

Retinal vein thrombosis can affect the main vein of the retina, the central vein (central retinal vein occlusion or CRVO) or one of its branches (branch retinal vein occlusions or BRVO). CRVO is more serious as it usually leads to poorer vision, more severe complications, and in most cases, does not improve spontaneously. In both CRVO and BRVO, blood accumulates in the blood vessels as a result of the blockage, with the subsequent increased back pressure causing fluid (oedema) and haemorrhages in the retina. The accumulation of fluid at the macula (macular oedema, MO) leads to a reduction in visual acuity (VA). The blockage is usually by thrombosis but in some young individuals with inflammatory diseases such as SLE it may be due to phlebitis.

It usually presents as sudden painless loss of vision in the affected eye. It usually affects only one eye. However unlike some other conditions causing MO, CRVO affects the whole retina, and so affects peripheral vision too, which can lead to problems with navigation and day to day living if the other eye is impaired.

The leakage of fluid is accompanied by an increase in vascular endothelial growth factor (VEGF) which increases the permeability of the blood vessels (increasing the diffusion of fluid through the wall of the blood vessel) and worsens the situation.

The Central Vein Obstruction Study (CVOS) Group reported (1997)[1] that VA at presentation is a strong predictor of outcome.

The population based Beaver Dam Eye Study measured visual loss in 4068 persons living in Beaver Dam, Wisconsin, aged 43 to 86 years of age. On the basis of vision in the better eye, 8.3% of the population at risk developed impaired vision (20/40 or worse) and 0.8% developed severe visual impairment (20/200 or worse) over a 15-year period, with 12% of impaired vision being due to BRVO and CRVO.[2]

The Royal College of Ophthalmologists (RCO) guidelines[3] reported that prognosis depends on initial VA after onset. Those with good vision (20/40 or better) have the best chance of retaining good vision. Only 20% of eyes with initial VA 20/50 to 20/200 improve spontaneously to 20/50, and 80% of those with baseline VA worse than 20/200 do not improve.

Retinal vein obstruction (RVO) is the second most common cause of vascular visual loss, surpassed only by diabetic retinopathy (DR).

The natural history of CRVO

CRVO is divided into two groups: ischaemic and non-ischaemic (or perfused). However there is debate about the definition of ischaemic CRVO. It means that blood flow into the retina is reduced. CRVO is often defined as ischaemic when areas equivalent to at least 10 times the area of the optical disc (disc areas, DA) have no capillary perfusion. Some, however, have argued that stricter criteria should be used to define ischaemic CRVO. As Hayreh has pointed out, most people with ischaemic areas of only 10 disk diameters (DD) do not develop the complications of ischaemia such as neovascularisation and neovascular glaucoma. The CRVO study showed that eyes with less than 30 DD of ischaemia are at low risk of iris and angle neovascularisation. Hayreh suggests using a combination of criteria to diagnose ischaemic CRVO, including presenting VA 20/200 or worse, moderate or severe visual field loss, relative afferent pupillary defect and electroretinographic abnormalities.[4]

The natural history of the two forms is different, with ischaemic being associated with a poorer prognosis.[5] About 20% of initial presentations are ischaemic, but about 30% of non-ischaemic cases may convert to ischaemic over three years[5] though this depends on definition, with the conversion rate being lower if Hayreh's stricter definition is used. The CVOS group 1997,[1] reported that about 34% of initially perfused eyes converted to ischaemic over three years. The distinction between ischaemic and non-ischaemic CRVO is based on fluorescein angiography (FA), a process wherein a dye is injected into the blood stream through a vein, and then the back of the eye is photographed whilst the dye progresses through the retinal blood vessels. In normal eyes, the dye is seen passing through arteries, capillaries and veins in turn. Fluorescein angiography can show filling defects due to blocked vessels, areas of ischaemia, and leakage from damaged blood vessels.

The natural history of CRVO has been the subject of a good quality systematic review by McIntosh and colleagues.[5] One caveat with this study is that the definition used for ischaemic CRVO varied amongst studies, and this may explain the quite variable outcomes that they found. In half the eyes in the studies that McIntosh et al reviewed, the ischaemic sub-type was not defined.

McIntosh and colleagues[5] noted that the outlook after CRVO was poor. In most studies, VA declined. In the minority of studies in which VA was reported to improve, it did not reach better than 20/40. Ischaemic CRVO (variably defined) did worse, with a loss of 35 letters by one year, compared to a loss of only 3 in non-ischaemic. In most included studies, VA at baseline for all CRVO including non-ischaemic CRVO was poor (<20/40). McIntosh and colleagues reported that mean baseline VA in non- ischaemic CRVO was 31 letters and in ischaemic CRVO, it was 9 letters. This may reflect time from onset since earlier presentation is associated with better VA. Hayreh has reported that depending

on the time from onset to first assessment, up to 41% of patients with non-ischaemic CRVO may have VA of 20/30 or better.

Ischaemic CRVO was followed by the development of abnormal new vessels (neo-vascularisation) in about a quarter of cases over an 8 to 9 month period. Neovascularisation is rare in non-ischaemic CRVO. In ischaemic CRVO, about 23% developed neo-vascular glaucoma (NVG) within 15 months.

McIntosh and colleagues reported that MO often resolved spontaneously over time, but this did not lead to improved VA. In ischaemic CRVO, the proportion of patients achieving resolution of MO ranged from 0% to 73% which occurred from 2 to 15 months following CRVO. In non-ischaemic CRVO, approximately 30% (36% by 6 months and 31% by 15 months) achieved resolution of MO. When MO disappears slowly over time, it can be associated with the development of macular atrophy, with deterioration in vision. Hence reduction in retinal thickness is not always a good sign.

After CRVO in one eye, 5% of patients developed an RVO in the other eye (known as fellow eye involvement or FEI) in the next year, of which most were BRVO.

A natural history study by Hayreh and colleagues [4] was published after the McIntosh review, based on a series of 667 consecutive patients with CRVO. Hayreh reported that of eyes seen within 3 months, VA was 20/100 or better in 78% with non-ischaemic CRVO but in only 1% of ischaemic CRVO. Hayreh argues[6] that non-ischaemic CRVO is relatively benign, but that ischaemic "is a malignant disease with about half the eyes ultimately developing neovascular glaucoma (NVG) and consequent blindness". In his series of patients, vision was badly affected in those with ischaemic CRVO, with 80% reduced to counting fingers, and almost all the rest in the 20/200-400 range. 16% presented with ischaemic CRVO and another 7% who initially had non-ischaemic, converted to ischaemic.

Neovascular glaucoma developed in about a third,[4] and was associated with worsening of visual fields and a much lower chance of spontaneous improvement. Those who get ischaemic CRVO tend to be older, and have more hypertension and diabetes, than those who develop non-ischaemic. In Hayreh's series of 667 patients, 4% developed bilateral CRVO.

In summary, the outlook after CRVO is often poor without treatment, especially in ischaemic cases. Unlike in BRVO, laser treatment is not helpful for patients with MO following CRVO, though it can be used for treating neovascularisation. Until recently there has been no effective treatment for MO after CRVO.

Treatments

Currently, there are two NICE recommended treatments for CRVO, dexamethasone (Ozurdex) (TA229) and ranibizumab (Lucentis), the latter recommended by NICE only recently (May 2013).

The guidance on dexamethasone (TA229)[7] states that
1.1 Dexamethasone intravitreal implant is recommended as an option for the treatment of macular oedema following central retinal vein occlusion.

The guidance on ranibizumab for CRVO (TA283)[8] states
1.1 Ranibizumab is recommended as an option for treating visual impairment caused by macular oedema:

- *following central retinal vein occlusion* ***and***
- *only if the manufacturer provides ranibizumab with the discount agreed in the patient access scheme revised in the context of NICE technology appraisal guidance 274.*

Aflibercept solution for eye injection (Eylea, Bayer) is a potent VEGF-A inhibitor, and can also attach to other proteins such as placental growth factor (PIGF) and VEGF-B.[9] In CRVO, the main effect of anti-VEGF treatment is the anti-permeability effect. The increased venous pressure leads to leakage and increased VEGF, which leads to further increased permeability of the vessel wall and increased leakage of fluid. By blocking VEGF, aflibercept reduces the leakage and the swelling due to oedema. A study from Regeneron, the developer of aflibercept, states that ranibizumab has lower affinity to VEGF-A than aflibercept.[9]

Bevacizumab, an anti-VEGF, is used off-licence in the NHS. Triamcinolone, a steroid, is also used in some areas, but is also unlicensed for eye use. The triamcinolone used in the UK is Kenalog which is licensed for joint use but not for eye use. Another form, Trivaris, was used in trials and was approved for eye use by the FDA in June 2008, but is no longer available – it was produced by Allergan who manufactures Ozurdex.

Aflibercept has already been approved in the UK for the treatment of adults with neovascular wet age-related macular degeneration (AMD).[10]

The manufacturer of aflibercept, Bayer, states that the Committee for Medicinal Products for Human Use (CHMP) at the European Medicines Agency (EMA) was expected to give a positive opinion to aflibercept solution for injection for the treatment of macula oedema (MO) secondary to CRVO in July 2013.[11] Marketing authorisation was approved via the centralised European regulatory procedure in September 2013. Eylea received marketing approval from the Food and Drug Administration (FDA) in the USA in September 2012 (http://www.fda.gov/Drugs/default.htm).

2.1 Critique of manufacturer's description of underlying health problem

In sections 2.1 and 2.2 (pages 16 and 17) of the manufacturer's submission (MS), Bayer gives a brief accurate description of the disease, its aetiology and the number of patients affected by the condition in England and Wales. They report that

- the presentation of CRVO is usually acute and the most frequent symptom is an abrupt decrease of central vision which is distressing to many patients. However there are a few patients in whom CRVO resolves quickly and spontaneously.
- In the classical case, there are superficial and deep intraretinal haemorrhages in all four quadrants of the retina, which may be accompanied by retinal venous engorgement and tortuosity, optic disc swelling, cotton wool spots, and cystoid MO.
- the severity of the venous occlusion is reflected by the baseline VA, which is influenced by intra-retinal haemorrhages, ischaemia and cystoid macular oedema.
- there are several risk factors for CRVO, but it is most closely associated with cardiovascular risk factors such as hypertension, diabetes mellitus, and arteriosclerotic vascular disease.
- CRVO is also associated with thrombophilia and glaucoma. There is no association between smoking and CRVO
- there are currently approximately 12 new patients with MO secondary to CRVO eligible for treatment per 100,000 of the population in England and Wales each year. This equates to 6,840 eligible for treatment overall in a population of 57 million.

Comments on the manufacturer description

The ERG considers Bayer's description of the underlying health problem to be appropriate. In addition, the manufacturer could have included the following points in this section (though they are mentioned in later sections).

- CRVO is mostly unilateral
- CRVO is categorised into ischaemic and non-ischaemic; the prognosis of ischaemic CRVO is much poorer than that of non-ischaemic CRVO.
- There is spontaneous resolution of MO in some cases (McIntosh et al report 30%)[5] especially if it is non-ischaemic.

The impact of CRVO on vision varies partly due to the amount of MO. The more the accumulation of fluid, the more effect on the vision. It also varies according to the presence or not of ischaemia.

2.2 Critique of manufacturer's overview of current service provision

The manufacturer's overview of the current service provision is given in section 2.6 (page 18 and 19) of the MS. The manufacturer states that the standard of care is now ranibizumab, which requires monthly monitoring. Bayer adds that monthly monitoring after ranibizumab treatment requires additional resource use and thus has a direct impact on capacity available in ophthalmology, especially as services are under pressure because of recent developments in treatment of wet AMD and diabetic macular oedema (DMO). The manufacturer thus argues that there is a need for effective treatments without the burden of monthly monitoring. However it should be noted that the dexamethasone insert, Ozurdex, need only be given every 4 months.

The manufacturer mentions other treatments in section 2.7, where Bayer includes their rationale for not considering bevacizumab and dexamethasone as appropriate comparators for this appraisal.

The ERG agrees with the manufacturer that observation should not be the standard of care in patients with CRVO. Currently, NICE recommends two treatments, ranibizumab and dexamethasone. The ERG agrees that ranibizumab will probably be used more often, given its better safety profile, than dexamethasone, in the NHS. Bevacizumab has been widely used and is much cheaper, but it is likely that in the NHS, bevacizumab use will decline now that ranibizumab has been approved by NICE, taking into account the GMC disapproval of the use of unlicensed drugs when a licensed one is available, and the absence of any recommendation from NICE.

2.3. Critique of manufacturer's definition of decision problem

The manufacturer presents the decision problem issued by the National Institute for Health and Care Excellence (NICE) and the rationale for any deviation from the decision problem on page 24 and section 2.7 (pages 19 to 21) of the submission. For convenience, the table has been reproduced below.

	Final scope issued by NICE	**Rationale if submission differs from the scope**
Population	Adults with visual impairment due to macular oedema caused by CRVO	Not applicable.
Intervention	Aflibercept solution for injection	Not applicable
Comparator(s)	Ranibizumab Dexamethasone Bevacizumab Clinical observation	See Section 2.7
Outcomes	Visual acuity (the affected eye) Visual acuity (the whole person) Need for pan-retinal photocoagulation Adverse effects of treatment Health-related quality of life.	Not applicable
Economic analysis	Incremental cost per quality-adjusted life year. Lifetime horizon Costs will be considered from an NHS and Personal Social Services perspective	Not applicable
Subgroups to be considered	If the evidence allows, consideration will be given to subgroups according to: •the presence or absence of ischaemia •baseline visual acuity •central retinal thickness. Guidance will only be issued in accordance with the marketing authorisation.	We believe that aflibercept is clinically and cost effective in all patients with macular oedema secondary to CRVO. Therefore, we do not believe such an analysis will be required.
Special considerations	None	Not applicable

The manufacturer's approach differs from the NICE decision problem in only three aspects, comparators, subgroup analysis and VA results. The manufacturer does not present VA results for whole person.

2.3.1 Population

The patients in the two trials were adults with visual impairment due to MO caused by CRVO. Those aged ≥18 years with CRVO diagnosed not more than 9 months before study initiation were included. Mean central subfield retinal thickness in all study eyes was ≥250 µm using OCT and an Early Treatment Diabetic Retinopathy Study (ETDRS) best-corrected visual acuity (BCVA) of 73 to 24 letters (20/40 to 20/320) in the study eye.

2.3.2 Intervention

Aflibercept solution (Eylea) for intravitreal injection is designed to deliver 0.05 ml containing 2 mg aflibercept. The recommended dose is 2 mg every 4 weeks (monthly) initially. According to the draft SmPC, it is expected that after the initial injection, treatment is initially given monthly. The interval between two doses should not be shorter than one month. If there is no improvement in visual and anatomic outcomes over the course of the first three injections, continued treatment is not recommended. Monthly treatment continues until visual and retinal thickness outcomes are stable after three monthly assessments. Thereafter the need for continued treatment should be considered. If necessary, treatment may be continued with gradually increasing intervals as long as visual acuity and CRT are stable. If treatment has been discontinued, VA and central retinal thickness (CRT) should be monitored and treatment should be resumed if they deteriorate. Usually, monitoring should be done at the injection visits, but if treatment intervals are extended, the monitoring schedule should be based on the individual patient's response and may be more frequent than the schedule of injections. So extra visits for monitoring may be required.

2.3.3 Comparators

In the NICE final scope, the comparators considered were ranibizumab, dexamethasone, bevacizumab and clinical observation.

In section 2.7 (page 19) of the MS, the manufacturer provides reasons for excluding some of the comparators mentioned above. The manufacturer considered ranibizumab to be the main comparator for this appraisal following the recent recommendation by NICE.

Bayer has included dexamethasone in the submission but they argue that it is not the main comparator for several reasons. Firstly, in the recent appraisal of ranibizumab for CRVO dexamethasone was found to be dominated by ranibizumab.[8] (Bayer also say (page 19) that "dexamethasone was extended dominated by both best supportive care and ranibizumab " – this may be based on a statement in the NICE ranibizumab guidance, paragraph 4.22 which says,

"…dexamethasone is dominated by a combination of two other alternatives, in this case best supportive care and ranibizumab"…
This in turn may be based on a statement from the BMJ ERG report, section 5.3.10;[12]
"When incremental analysis was done including all comparators, dexamethasone intravitreal implant is ruled out by extended dominance for patients with CVRO."

The Bayer wording may be a little misleading, because it implies that dexamethasone may be dominated by best supportive care (BSC), which is incorrect. The dominance arises when both ranibizumab and dexamethasone are compared with BSC, when the ICER for dexamethasone compared to BSC is larger than for ranibizumab compared to BSC.

Secondly, steroids cause substantial side effects such as increased intraocular pressure (IOP) and cataract. There is also a risk associated with the larger needle needed to insert the Ozurdex implant. The manufacturer argues that dexamethasone should be a second line drug in macular oedema (MO) secondary to CRVO but will remain useful in pseudophakic patients as there is no risk of cataract.

Bayer also excluded bevacizumab. They state that bevacizumab is not recommended by NICE and is no longer considered routine or best practice in the NHS especially given the availability of two drugs recommended by NICE. The manufacturer argues that bevacizumab was not considered appropriate by the Committee during the appraisal of ranibizumab as there was insufficient evidence to make robust comparisons with ranibizumab. Bayer undertook literature searches to see if any new studies on bevacizumab have been published since the Committee's decision not to include it in the ranibizumab appraisal. The manufacturer found two more studies (Epstein et al 2012[13-15] and Wittstrom et al 2012[16]) of bevacizumab. The manufacturer excluded them on the grounds that trials were small and there was not enough detail to quality assess and compare baseline characteristics of patients.

Bayer also excluded observation as a comparator for this appraisal because they consider that patients with CRVO are unlikely not to be treated when there are two NICE recommended treatments available. Rarely, patients may be kept under observation if there were contra-indications to anti-VEGF and steroid treatment, or if they refused intravitreal treatment. Contraindications would be allergy and eye infections.

ERG comments.
The ERG agrees that standard care is now by intra-vitreal drugs. Laser treatment is ineffective in CRVO.[3] The ERG regards ranibizumab as the key comparator. The place of dexamethasone is in doubt, for several reasons;

- in the recent appraisal of ranibizumab for RVO, dexamethasone was dominated by ranibizumab
- being a steroid, prolonged use will lead to cataract, and there is also a risk of raised IOP. The duration of effect of dexamethasone means that repeated insertions would be required.
- the large needle size required to insert Ozurdex is a disadvantage
- there is no PAS with dexamethasone so the expected savings from treatment every four months, compared to more frequent administration of the anti-VEGF drugs, will be less than appears from published prices.

However, not all patients respond to anti-VEGF drugs, so there may still be a place for dexamethasone after anti-VEGF failure. This might be especially the case in pseudophakic patients in whom there is no risk of cataract.

2.3.4 Outcomes

The primary and secondary outcomes recommended in the NICE final scope were reported in the MS. The primary aim of the two studies was to assess the efficacy of aflibercept in BCVA in eyes with MO secondary to CRVO. The secondary outcomes included safety and tolerability and the effects on CRT of aflibercept compared with standard of care. The manufacturer states that the standard of care at the time of study was observation until progression to anterior segment neovascularisation, when treatment with panretinal photocoagulation (PRP) would be given. The NICE final scope also considered quality of life (QoL) as an outcome, which has been reported in the MS.

The ERG does not regard CRT as an outcome of importance to patients, but recognises it as a guide to treatment, since the presence of fluid is likely to trigger further treatment. The aim of treatment is sometimes described as to "dry out" the retina. Clinicians will treat if fluid is present; if not they will observe.

It is worth noting that QoL depends largely on vision in the better-seeing eye (BSE) and that treatment that improves visual acuity in the worse-seeing eye (WSE) may have only a modest effect on quality of life. The question of utility gain from treating WSE has been a recurring problem in NICE appraisals, and there is a lack of evidence on this. In the ERG report on fluocinolone,[17] a range of illustrative sensitivity analyses were provided, from improving vision in the WSE have no effect on QoL, to it having as much as treatment of the BSE. Neither of these extremes was considered plausible by the ERG. The Appraisal Committee considered that a 30% weighting might be appropriate – i.e. that gains in vision in the WSE would results in 30% of the utility gain from the same gain in vision in the BSE.

In the NICE scope, subgroup analyses were suggested including according to the presence or absence of ischaemia, baseline VA and CRT. Bayer states that such subgroup analyses were not required because aflibercept is both clinically and cost-effective in all patients with MO secondary to CRVO. The manufacturer reports subgroup analyses of the primary endpoint from page 57 to 60 and table 13 and 14 for all subgroups except CRT.

2.3.5 Other factors

The manufacturer has reduced the price through a patient access scheme (PAS). This price reduction is confidential. The manufacturer of ranibizumab has also reduced its price through a PAS, again confidential.

3. CLINICAL EFFECTIVENESS

The ERG does not consider that any important trials of aflibercept, ranibizumab or dexamethasone in CRVO have been omitted. Bevacizumab is discussed later.

The two trials of aflibercept – COPERNICUS[18, 19] and GALILEO[20] - are described in section 6.2.4, section 6.2.5 and Table 3 on pages 30 and 31. For convenience, Table 3 has been reproduced below. The one year results from COPERNICUS and the six months results from GALILEO have been published. Some data from the two trials were also available from a published abstract[21] which had proportions gaining 15 or more letters at 52 weeks.

Trial no. (acronym)	Intervention	Comparator	Population	Primary study ref.
COPERNICUS (NCT00943072)	n=114 **Year 1** **Week 0-week 24:** Aflibercept 2 mg given intravitreally every 4 weeks (2q4) **Week 24-week 52**: (evaluated monthly) aflibercept 2mg intravitreally as needed (prn) according to protocol retreatment criteria or a sham injection if retreatment not indicated. **Year 2 (extension phase)** aflibercept 2mg intravitreally as needed (prn) according to protocol retreatment criteria (evaluated quarterly).	n=73 **Year 1** **Week 0-week 24:** sham injections every 4 weeks **Week 24-week 52**: (evaluated monthly) aflibercept 2mg intravitreally as needed (prn) according to protocol retreatment criteria or a sham injection if retreatment not indicated. **Year 2 (extension phase)** aflibercept 2mg intravitreally as needed (prn) according to protocol retreatment criteria (evaluated quarterly).	Macular oedema secondary to central retinal vein occlusion (CRVO)	6-month data: Boyer 2012[18] 12 month data: Brown 2013[19]
GALILEO (NCT01012973)	n=103 **Year 1** **Week 0-week 24:** Aflibercept 2 mg given intravitreally every 4 weeks (2q4) **Week 24-week 52**: aflibercept 2mg intravitreally as needed (prn) or a sham treatment according to protocol	n=68 **Year 1** **Week 0-week 24:** sham injections every 4 weeks **Week 24-week 52**: sham injection according to protocol retreatment criteria (evaluated monthly).		6-month data: Holz 2013[20]

Trial no. (acronym)	Intervention	Comparator	Population	Primary study ref.
	retreatment criteria (evaluated monthly). **Year 2** **Week 52-week 76:** follow-up visits every 8 weeks. Aflibercept 2mg intravitreally as needed (prn) or a sham treatment according to protocol retreatment criteria.	**Year 2** **Week 52-week 76:** follow-up visits every 8 weeks. Aflibercept 2mg intravitreally as needed (prn) or a sham treatment according to protocol retreatment criteria.		

3.1 Summary and critique of submitted clinical effectiveness evidence

3.1.1 Quality of included RCTs

The manufacturer presented quality assessment results in Table 10 (page 50) of the submission. The ERG has used the Cochrane risk of bias score[22] as shown below, and considers both trials to be of good quality.

Table 1. Study Quality (COPERNICUS)

Items	Description	Risk of bias
Adequate sequence generation	Patients randomised in a 3:2 ratio using a centralised interactive voice randomised system (IVRS), and stratified by geographic region (North America vs. rest of the world), and by using a baseline BVA score.	Low
Allocation concealment	Randomised using a centralised interactive voice randomised system (IVRS)	Unclear
Masking	Double- blind Assessing physicians, examiners and personnel masked to treatment.	Low
Incomplete outcome data addressed	Primary efficacy analysis conducted using FAS. Missing values were imputed using LOCF analysis	Low
Free of selective reporting	All pre-defined outcomes were reported	Low
Free of other bias (e.g. similarity at baseline, power assessment)	The study was designed to have 90% power to detect a difference of 25% in the proportion of eyes gaining at least 15 letters of vision at week 24 at the 5% significance level using a 2-sided Fisher exact test or a Cochran-Mantel-Haenszel test. Estimated proportions of eyes meeting the primary endpoint were 15% in the sham group and 40% in the aflibercept group. The planned sample of 165 eyes (99 in the aflibercept group and 66 in the sham group) was based on a dropout rate of 9%	Low
Funder	Bayer HealthCare, Regeneron Pharmaceuticals	

Table 2. Study Quality (GALILEO)

Items	Description	High/Low/Unclear
Adequate sequence generation	Patients randomised in a 3:2 ratio using [redacted] and stratified by region (Europe vs. Asia/Pacific), and by baseline BCVA	Low
Allocation concealment	Randomised using [redacted]	Unclear
Masking	Double-blind	Low
Incomplete outcome data addressed	Primary efficacy analysis conducted using FAS. Missing values were imputed using LOCF analysis	Low
Free of selective reporting	All pre-defined outcomes were reported	Low
Free of other bias (e.g. similarity at baseline, power assessment)	The study was designed to have 90% power to detect a difference of 25% in the proportion of eyes gaining at least 15 letters of vision at week 24 using a s-sided Fisher exact test. The planned sample size of 165 eyes (99 in the aflibercept group and 66 in the sham group) was based on a dropout rate of 10%)	Low
Funder	Bayer HealthCare, Regeneron Pharmaceuticals	

The ERG wondered if at the end of the trials, patients were asked what treatment they thought they had been allocated to. Were they able to distinguish between an injection into the eye, and the sham of pressure without puncture? Asking them would have provided a useful check on the security of masking. The manufacturer reported during clarification that patients were not asked.

Three groups were defined for analysis. For analysis of primary efficacy data, the full analysis set (FAS) was used. FAS was defined as all randomised patients who received any study medication and had a baseline assessment and at least one efficacy assessment after baseline (analysed as randomised). For safety, a safety population (SAF) was used, defined as all randomised patients who received any study medication (analysed as treated). Lastly, a sensitivity analysis was carried out using a per protocol (PP) population which included all patients in the FAS who received at least five injections of study medication and did not have any major protocol violations or deviations (analysed as treated).

The analysis did not include an intention-to-treat (ITT) analysis. Instead, a FAS was reported. The FAS included all randomised patients who received any study drug and had a baseline and at least one

post-baseline assessment, and the difference in numbers between true ITT and FAS were trivial – COPERNICUS ITT 115 aflibercept and 74 sham; FAS 114 and 73. GALILEO ITT 106 and 72; FAS 103 and 68. The ERG regards the FAS as suitable for analysis.

For primary analysis, patients who discontinued prematurely (before 24 weeks) and had fewer than five injections of aflibercept or sham were classed as non-responders. Missing data were imputed using last observation carried forward (LOCF) analysis. The manufacturer mentions that 'pure last observation forward' analyses and 'observed case' analyses were also performed as sensitivity analyses (page 46). In COPERNICUS, sensitivity analyses included: *'LOCF', 'observed case', 'pure LOCF' and 'dropouts counted as non-responders' analyses in both the FAS and PPS populations for the primary endpoint and observed case analyses in the FAS and PPS populations for the secondary endpoints of change from baseline in BCVA score, CRT and NEI VFQ-25 total score at week 24, 52 and 100'*. In GALILEO, *'sensitivity analyses included: 'LOCF', 'observed case', 'discontinued patients before week 24 with < 5 injections as failures', 'discontinued patients before Week 52 as failures', 'discontinued patients before week 24 as failures' (week 52 and week 76 results) analyses, in both the FAS and PPS populations for the primary endpoint; and observed case analyses in the FAS and PPS populations for the secondary endpoints of change from baseline in BCVA score, CRT and NEI VFQ-25 total score at week 24, 52 and 76'*.The ERG asked Bayer to clarify what was meant by 'pure' and 'observed' LOCF methods that were used to impute missing data. The manufacturer's response has been reproduced below

'In the primary efficacy analyses, in COPERNICUS, it was assumed that all subjects who discontinued prematurely prior to Week 24 and have less than 5 injections of study drug or sham have been evaluated as failures. In GALILEO, all subjects who discontinued prematurely prior to Week 24 have been also evaluated as failures. Otherwise, missing values were imputed carrying forward the last post-baseline value.

The sensitivity analysis used the pure LOCF approach where all subjects who discontinued prematurely prior to Week 24 have also been evaluated with their last post-baseline value (LOCF)'.

Following the clarification process, the definitions of 'pure' and 'observed' LOCF are still unclear to ERG.

3.1.2 Overview of included RCTs

The overview of the included trials is given in section 6.3 and section 6.4.

The ERG has summarised the two trials below.

Table 3. Baseline characteristics in the GALILEO and COPERNICUS trials (FAS data set)

	GALILEO		**COPERNICUS**		**Integrated**	
	Aflibercept	***Sham***	***Aflibercept***	***Sham***	***Aflibercept***	***Sham***
N	103	68	114	73	217	141
Mean age	59.9 SD12.4	63.8 SD13.3	65.5 SD13.6	76.5 SD14.3	62.9	65.7
Sex (% female)	43.7%	45.6%	39%	48%	41.5%	46.8%
Ethnicity						
White	71.8%	72.1%	77.2%	80.8%	74.7%	76.6%
Black			4.4%	6.8%	2.3%	3.5%
Asian	25.2%	22.1%	6.1%	2.7%	15.2%	12.1%
Other / not reported	2.9%	5.9%	12.3	9.6%	7.8	7.7
BCVA (EDTRS letters)	53.6 SD15.8	50.9 SD15.4	50.7 SD13.9	48.9 SD14.4	52 SD 14.9	49.9 SD 14.9
>20/200	83.5%	82.4%	75.4%	75.3%	82.9%	81.6%
CRT (µm)	683.2 SD234.5	638.7 SD224.7	661.7 SD237.4	672.4 SD245.3	672.0 SD 235.7	655.7 SD 235.1
Intraocular pressure (mmHg)	15.1 SD2.8	14.4 SD2.7	15.1 SD3.3	15.0 SD2.8	15.1 SD 3.0	14.7 SD 2.8
Retinal perfusion status						
*Perfused **	86.4%	79.4%	67.5%	68.5%	76.5%	73.8%
Non-perfused	6.8%	10.3%	14.9%	16.4%	11.1%	13.5%
Indeterminate	6.8%	10.3%	17.5%	15.1%	12.4%	12.8%
Time since diagnosis (months)	2.56 SD2.95	2.88 SD2.60	2.73 SD3.09	1.88 SD2.19		
≤ (COP) / < (GAL) 2 months	53.4%	51.5%	56.1%	71.2%	54.8%	61.7%
≥ (GAL) / > (COP) 2 months	44.7%	48.5%	43.0%	28.8%	43.8%	38.3%

* Non-perfused was defined based on a 10 disk diameter area.

Note that the mean time from diagnosis was quite short – this may not happen in NHS clinics. Results are better if treatment is given soon after the thrombosis.

Settings

The COPERNICUS and the GALILEO trials were multicentre studies. GALILEO was conducted at 63 centres in Europe, Asia and Australia (Austria 3, France 5, Germany 21, Hungary 5, Italy 7, Latvia

2; Australia 6, Japan 6, Singapore 2, South Korea 6). COPERNICUS was carried out at 70 sites in the United States, Canada, India, Israel, Argentina, and Colombia.

Populations in GALILEO and COPERNICUS.

GALILEO included 177 eyes of 177 patients (average 2.8 per centre), and COPERNICUS included 189 eyes of 189 patients (average 2.7 per centre). Patients had reduced visual acuity due to centre-involved macular oedema secondary to CRVO for a maximum of nine months, with a CRT of ≥250 µm on OCT. Baseline best corrected visual acuity (BCVA) had to be between 73 and 24 EDTRS letters (Snellen equivalent 20/40 to 20/320) in both trials.

The World Health Organization[23] uses the following classifications of visual impairment. When the vision in the better eye with best possible glasses correction is:

- 20/30 to 20/60: is considered mild vision loss, or near-normal vision
- 20/70 to 20/160: is considered moderate visual impairment
- 20/200 to 20/400: is considered severe visual impairment

There are also levels of visual impairment based on visual field loss (loss of peripheral vision).

Patients were excluded if they had a variety of ocular conditions or previous treatments as shown in Box 1.

Box 1. Reasons for exclusion

A history of vitreoretinal surgery in the study eye, previous laser photocoagulation, other causes of decreased VA, ocular inflammation, uncontrolled glaucoma) or a range of systemic conditions. Patients with bilateral RVO were excluded. Exclusion criteria with respect to both eyes included: previous use of intraocular corticosteroids or use of periocular corticosteroids within 3 months prior to day 1; iris neovascularisation, vitreous haemorrhage, traction retinal detachment, or preretinal fibrosis involving the macula; history or presence of AMD (dry or wet form) that significantly affected central vision; DMO or DR and infectious blepharitis, keratitis, scleritis or conjunctivitis.

In both studies, demographic characteristics were generally well balanced across groups (see Table 3). The mean visual acuity at baseline was between 50 (COPERNICUS) and 52 (GALILEO) EDTRS letters, with an average CRT of 666 µm in both trials. Over 50% of participants in both trials had a duration of MO of two months or less. In the COPERNICUS trial, there was a larger proportion of patients with a shorter duration of CRVO in the sham group than in the intervention group (71 versus 56% with duration ≤2 months: ERG calculate 95% CIs to be 61-81% and 47 to 65%, so some overlap, and any bias would favour sham), while in the GALILEO trial, more participants in the intervention group had a perfused status than in the sham group (86 versus 79%).

The manufacturer states that patients with ischaemic (non-perfused) or non-ischaemic (perfused) CRVO were included in the study. Baseline perfusion status was determined by FA and classified using the following criteria.

- Non-perfused: ≥10 DA of capillary non-perfusion of FA
- Perfused: <10 DA of capillary non-perfusion of FA

Note that this is not a strict definition of ischaemic CRVO. It would have been useful if details of mean or median extent of non-perfused areas had been given. The percentage of patients with VA > 20/200 suggests that few had ischaemia by a stricter definition as suggested by Hayreh, since VA <20/200 seems a good indicator of ischaemia. This point should be borne in mind when considering the generalizability of the trials.

Patients with ischaemic CRVO generally have a poorer prognosis. Hayreh[4] found that resolution of MO had a significant effect on visual improvement in non-ischaemic CRVO but not in ischaemic CRVO – even after resolution of the oedema, vision may not improve because of ischaemic damage in the retinal layers.

The ERG note that majority of the patients in the trials were non-ischaemic (68% in COPERNICUS and 83% in GALILEO, Table 6 of the MS). There were 16.3% of patients in COPERNICUS and 8.5% in GALILEO whose perfusion was indeterminate. The manufacturer categorised the indeterminate groups as non-perfused. 15.6% and 8.5% patients were categorised as non-perfused in COPERNICUS and GALILEO respectively, not including indeterminate.

The ERG wondered whether patients with more severe ischaemia were excluded from the study. The manufacturer was asked to clarify this. The manufacturer stated that severely ischaemic patients were not excluded from the study. Patients were included if they met all inclusion criteria.

The ERG has some concerns about the proportion categorised as non-perfused. The definition of ischaemia is not as strict as some would suggest, so the non-perfused group are at the milder end of the ischaemic spectrum. Adding the indeterminate group further dilutes this group. Furthermore, the rates of neovascularisation were very low – 6.8% in the sham group in COPERNICUS by 52 weeks and 4.4% in GALILEO at 24 weeks. No cases of NVG are reported, whereas the work of Hayreh would suggest that 36% of those with true ischaemia would develop that.

This suggests that the proportions with significant ischaemia may have been lower than the proportion described as non-perfused, and this may have implications for the applicability of the trials to

ischaemic CRVO. In what follows, we will use the manufacturer's term "non-perfused" when reporting trial results.

Interventions and comparators

In the COPERNICUS trial, intravitreal injections of 2 mg of aflibercept (VEGF Trap-Eye, n=114) were given every 4 weeks for 24 weeks to the intervention group, while the comparison group received a sham injection (n=73). During weeks 24 to 52, patients in both groups received aflibercept if they met protocol-specified retreatment criteria, and received a sham injection if retreatment was not indicated (3.9 SE 0.3 injections in the sham group and 2.7 SE 0.2 injections in the aflibercept group). From week 24 to week 52, all patients were assessed monthly using retreatment criteria. After the first year, patients continued in a one year extension phase (up to 100 weeks) with as needed dosing (no sham injections). From week 52 to week 100, all patients were assessed every 12 weeks using retreatment criteria. Over 100 weeks, the aflibercept group received 11.8 aflibercept injections the sham group 6.4 aflibercept injections.

The summary of study design for the two studies is given in Figure 2 of the manufacturer submission (MS). For convenience, the figure has been reproduced below.

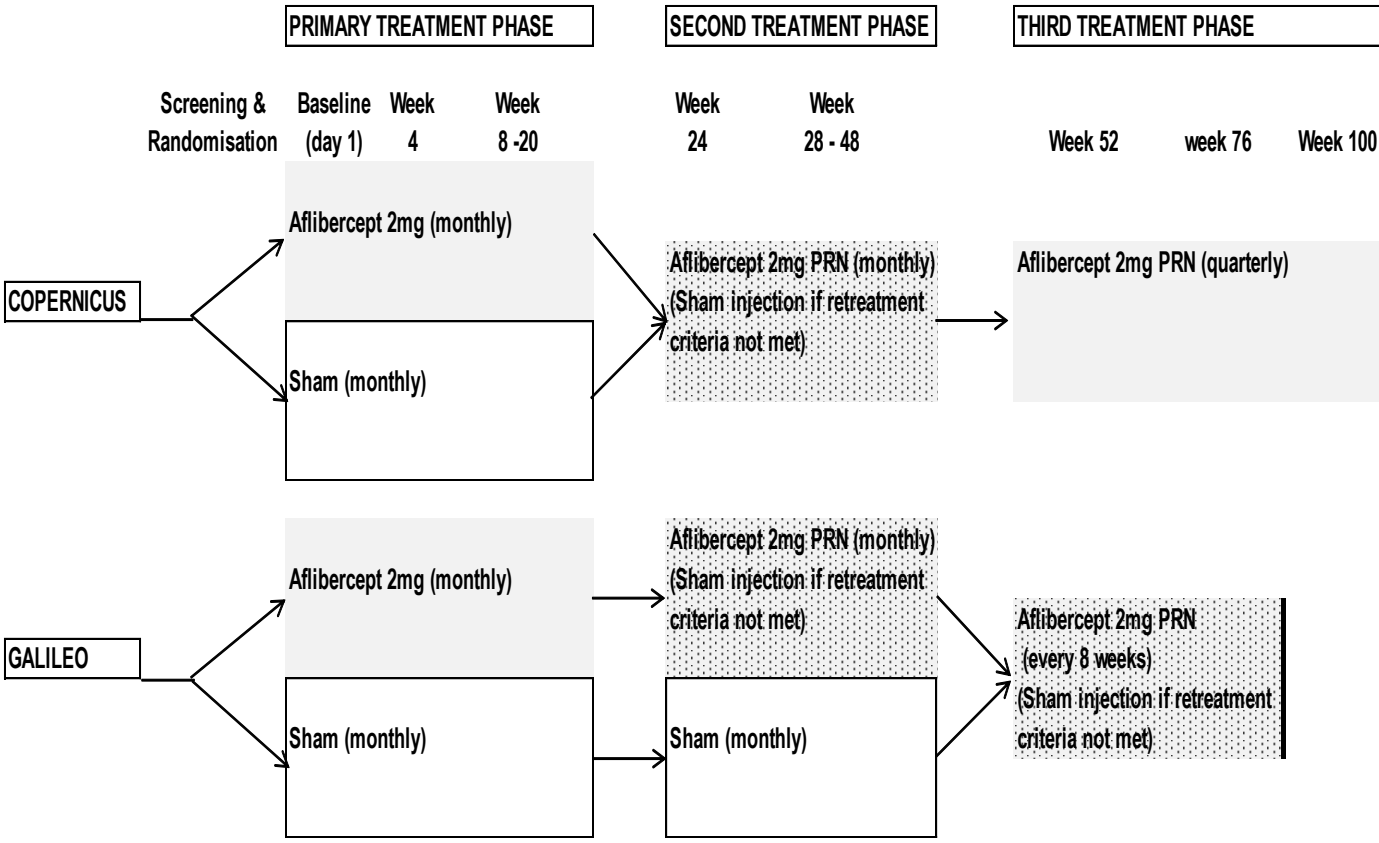


Figure 1. Summary of study design for COPERNICUS and GALILEO studies

The retreatment criteria were as follows:

- More than 50µm increase in CRT on OCT compared to lowest previous measurement
- new or persistent cystic retinal damages of sub-retinal fluid on OCT or persistent diffuse oedema ≥250 µm in the central subfield on OCT
- a decrease of VA of ≥5 letters between the current and most recent visit
- an increase of VA ≥ 5 letters between the current and most recent visit.

In the GALILEO trial, intervention patients also received intravitreal injections of 2 mg of aflibercept (n=103) every 4 weeks over 24 weeks, while the comparison group was given sham injections (n=68). During weeks 24 to 52, patients remained in their original treatment groups but received their allocated treatment as needed (patients were assessed monthly using retreatment criteria). From week 52 to week 76, both groups received the study drug every 8 weeks [redacted]. After week 24, sham injections were given in both groups, if active treatment was not needed. The aflibercept group received1.3 aflibercept injections and the sham group 1.7 aflibercept injections between weeks 52 and 76)

All patients were eligible to receive pan retinal photocoagulation (PRP) at any time if they developed neovascularisation. In GALILEO, use of PRP meant that a patient was withdrawn from study treatment but could undergo safety follow-up to week 76. No other systemic or local medications for treating CRVO were permitted in the study eye during the study (in GALILEO, until completion of week 76 for an early termination of study visit). [redacted]

Outcomes

The primary endpoint of both trials was the proportion of eyes with a gain of 15 or more EDTRS letters (≥3 lines) from baseline to week 24. Additional outcomes in both trials included mean change from baseline in BCVA (EDTRS), CRT, EDTRS letter gain or loss at various cut-off points, the proportions of patients progressing to ocular neovascularisation, vision-related QoL (National Eye Institute Visual Functioning Questionnaire, NEI-VFQ-25), EQ-5D (in GALILEO only), and safety parameters.

Subgroup analyses were carried out by age, sex, ethnicity, geographic location, baseline BCVA, baseline perfusion status, and time since CRVO diagnosis.

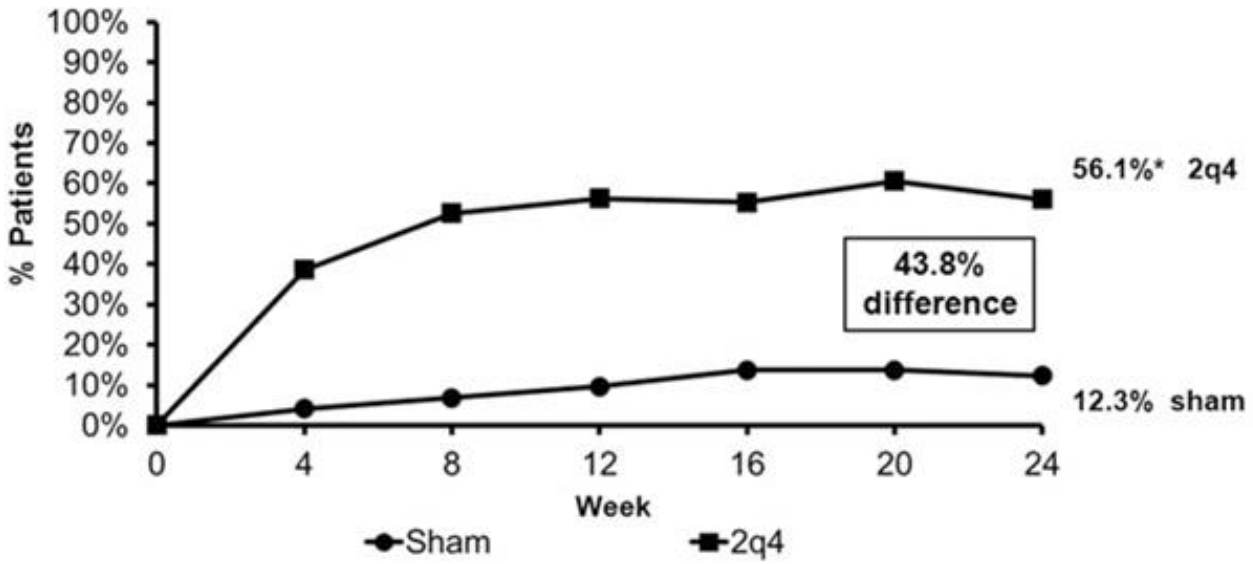
3.2 Results

In the submission, the primary and secondary outcomes are reported in section 6.5.3 (page 51 to 83).

3.2.1 Visual acuity in the treated eye.

Proportion of patient with a gain of 15 EDTRS letters or more. For convenience, the ERG has simplified Table 11 reported in the MS and results are shown in Table 4. In both the GALILEO and the COPERNICUS trial, significantly more patients in the aflibercept group gained 15 or more EDTRS letters than in the sham groups. The difference was maintained at all time points (despite aflibercept being given in all groups from week 24 in the COPERNICUS trial and from week 52 in the GALILEO trial). At week 24, between 38% (GALILEO) and 44% (COPERNICUS) more patients in the aflibercept than in the sham groups had gained 15 or more letters. The difference was 25% in the COPERNICUS trial after 52 weeks (all groups on aflibercept as needed) and 28% in the GALILEO trial (interventions maintained). During the extension period (up to week 100), when all patients received aflibercept as needed, the difference between the original groups was still 28% in the GALILEO trial (at 76 weeks), and 26% in the COPERNICUS trial (at 100 weeks).
The failure to close the gaps suggests that early treatment is more effective.
In the MS, the 24 weeks results were also presented as figures 6 and 7. For convenience, the two figures have been reproduced below.

Figure 2. Percentage of patients who gained ≥15 letters over the course of 24 weeks in the COPERNICUS study



*p<0.0001 vs sham

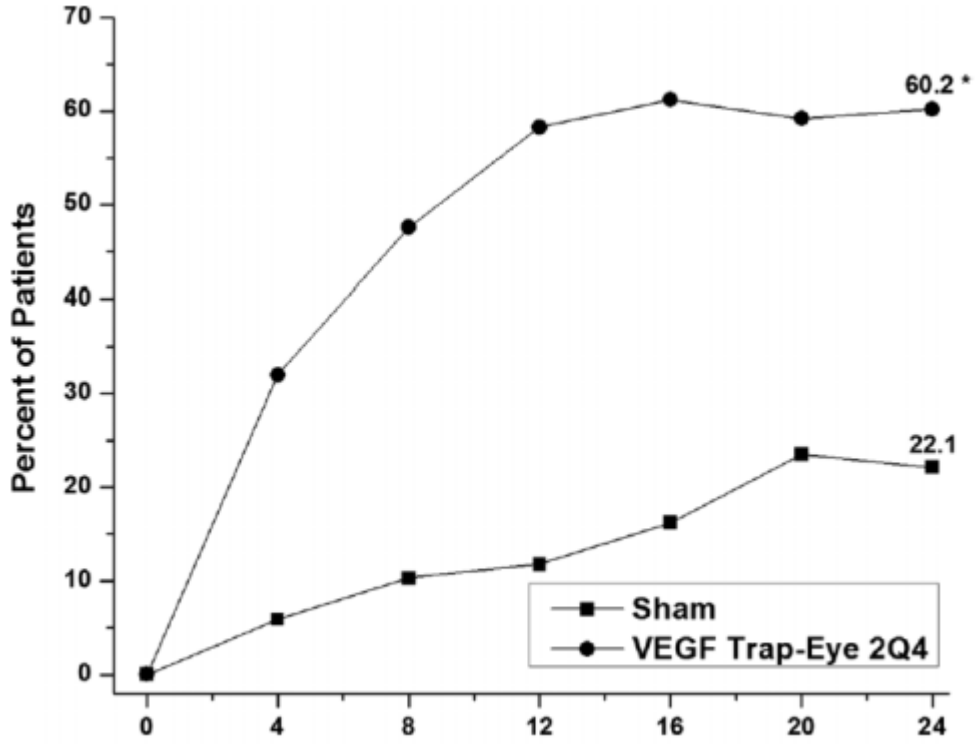


Figure 3. Percentage of patients who gained ≥15 letters over the course of 24 weeks in the GALILEO study

*p<0.0001 vs sham. VEGF Trap-Eye 2Q4 = aflibercept group

The ERG noted that in COPERNICUS, the plateau was reached by around 8 weeks, with only about a 2% increase between 8 and 12 weeks, whereas in GALILEO the plateau was reached after 12 weeks, with a 10% rise between weeks 8 and 12. During clarification process, the manufacturer was asked to explain this. The manufacturer stated that:

"No specific reason is known to explain the difference between studies. We believe that this could be because of an inherent variability in the study population, possibly reflecting the differences in trial design."

The ERG also asked Bayer to provide data on how many patients who gained fewer than 5 letters by week 8 later went on to gain more than 10 letters This was done in order to consider earlier stopping rules. The manufacturer had not undertaken an analysis by 10 letters gain so an additional subgroup data analysis for those gaining fewer than 5 letters by week 8 was provided. This did not answer the question posed, but in the group with a gain of less than 5 letters at week 8, the mean gain at later time points did not reach 5 letters, let alone 10. However the SD was quite large (█ to ██), implying that within the "futility group" there might have been some patients who later gained 10 letters. Note that the futility group comprised only ██ patients, showing that most patients responded well.

The results were similar in response to a range of sensitivity analyses (based on varying the way in which drop-outs were handled).

The results of subgroup analyses (based on age, sex, ethnicity, baseline BCVA, geographic location, baseline perfusion status, time since CRVO diagnosis) were consistent with the results for the overall population [redacted]. The proportion of patients gaining 15 or more EDTRS letters at 24 weeks after treatment with aflibercept was greater in patients beginning treatment within 2 months of diagnosis compared to those with longer disease duration (69 versus 39% in COPERNICUS; 71% vs. 50% in GALILEO), and in those with a baseline BCVA of ≤20/200 compared to those with a baseline BCVA of >20/200 (68 versus 52% in COPERNICUS; 65% vs. 59% in GALILEO) (p-values not reported)

Table 4. Primary endpoint – gain of ≥15 EDTRS letters

	GALILEO				**COPERNICUS**			
≥15 EDTRS letters gained	**Aflibercept**	**Sham**	**diff**	**p**	**Aflibercept**	**Sham**	**diff**	**p**
24 weeks	60.2%	22.1%	38.1%	<0.0001	56.1%	12.3%	43.8%	<0.001
52 weeks	60.2%	32.4%	27.8%	0.0004	55.3%	30.1%	25.2%	<0.001
76 weeks	57.3%	29.4%	27.9%	0.0004				
100 weeks					49.1%	23.3%	25.8%	0.0003

The manufacturer also presented a pooled meta-analysis result for three outcomes namely proportion of patients gaining ≥15 letters of BCVA improvement from baseline to 6 months, proportion of patients losing ≥15 letters of BCVA from baseline to 6 months and change in BCVA/number of letters read from baseline to 6 months. The pooled estimates were used in the indirect comparison with ranibizumab. The two trials are similar in design (and dosing of aflibercept) until 6 months therefore 6 months results were pooled together in the meta-analysis. The pooled estimates were presented both as OR and RR. Results are given in Table 26, Table 27 and Table 28 of the MS. The ERG was able to replicate the meta-analysis results. [Results for other outcomes are reported in respective section]. The results are shown in Table 5 and Figure 4 below.

Table 5. Comparison of meta-analysis results - patients gaining ≥15 letters of BCVA from baseline to 6 months

Study	OR (MS)	RR (MS)
Patients gaining ≥15 letters of BCVA from baseline to 6 months		
COPERNICUS	9.10 (95% CI 4.13 to 20.05)	4.55 (2.42 to 8.58)
GALILEO	5.34 (95% CI 2.66 to 10.72)	2.73 (1.70 to 4.38)
M-H pooled	6.85 (95% CI 4.08 to 11.51)	3.28 (95% CI 2.25 to 4.79)

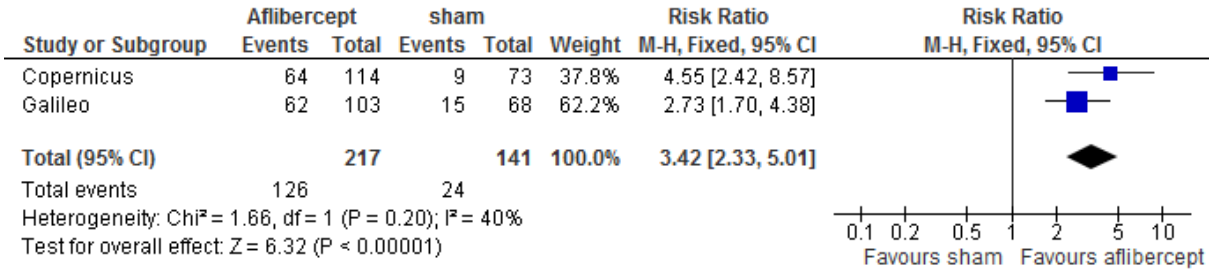


Figure 4. RR - proportion of patients with improvement of ≥15 letters (COPERNICUS and GALILEO) The pooled results confirm that more patients in the aflibercept arm achieved an improvement of 15 letters or more from baseline to 6 months than in the sham arm.

BCVA. Changes in BCVA are shown in Table 6. In both trials, patients in the aflibercept group had a significant improvement in BCVA at 6 months, and this was maintained at 12 months and was significantly greater than the improvements in the sham groups (difference to sham 21.70 letters in COPERNICUS and 14.70 letters in GALILEO). The difference between the aflibercept and sham groups was 12.71 letters in the COPERNICUS trial after 52 weeks (all groups on aflibercept as needed) and 13.2 letters in the GALILEO trial (interventions maintained). During the extension period (up to week 100), when all patients received aflibercept as needed, the difference between the original groups was still 7.6 letters in the GALILEO trial (at 76 weeks), and 11.81 letters in the COPERNICUS trial (at 100 weeks).

The results of subgroup analyses were consistent with those seen in the whole population. In the COPERNICUS trial, BCVA improvements were larger in patients with time from diagnosis to treatment of two months or less compared to those with a diagnosis of more than two months (24 weeks).It should be noted that results in the sham group were also better in the COPERNICUS trial in those recruited within 2 months of onset, with proportions achieving 15 or more letters 15% if diagnosed within less than 2 months, and 5% for later recruitment (MS Table 13, COPERNICUS study). Differences were much less, and results much better, in GALILEO (20% and 24%). [redacted]

[redacted]

Table 6. Change in BCVA (EDTRS letters)

	GALILEO			COPERNICUS		
BCVA (EDTRS letter change)	**Aflibercept**	**Sham**	**p**	**Aflibercept**	**Sham**	**p**
24 weeks	+18.0	+3.3	<0.0001	+17.3	-4.0	<0.001
52 weeks	+16.9	+3.8	0.0004	+16.2	+3.8	<0.001
76 weeks	+13.7	+6.2	0.007			
100 weeks				+13.0	+1.5	<0.0001

The manufacturer also presented pooled results for aflibercept and dexamethasone (GENEVA 008 and 009) for this outcome (Table 28 of the MS). The ERG was able to replicate results for aflibercept. SDs were not available for GENEVA trials therefore, the ERG was not able to reproduce this result. Part of table 28 where manufacturer reports pooled RR of dexamethasone has been reproduced below.

Table 7. Dexamethasone compared to sham

Study	RR	[95% Conf. Interval]		% Weight
GENEVA 008 & 009	1.44	0.82	2.54	100

Table 8. Comparison of meta-analysis results - change in BCVA/number of letters read from baseline to 6 months

Study	**WMD (MS)**
COPERNICUS	21.30 (95% CI 16.55 to 26.05)
GALILEO	14.70 (95% CI 10.60 to 18.80)
pooled WMD	17.52 (95% CI 14.41 to 20.62)

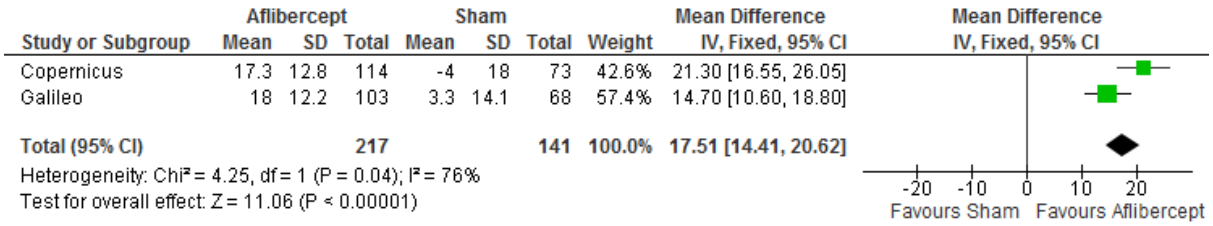


Figure 5. Change in BCVA/number of letters read from baseline to 6 months (COPERNICUS and GALILEO)

The meta-analysis results show that patients treated with aflibercept gained 17.5 more letters from baseline to 6 months than the sham group.

Gain or loss of EDTRS letters. Table 9 shows the results for gains of ≥10 letters (≥2 lines) and losses of ≥10 letters (≥2 lines) and ≥15 letters (≥3 lines) in the two trials. In both trials, most patients (over 90% in both trials at week 24, [redacted]) did not lose any EDTRS letters. Between 1 and 5% lost up to 15 letters in the aflibercept groups up to week 52, compared to between 15 and 24% in the original sham groups. In the COPERNICUS trial, the proportion of patients with losses of up to 15 EDTRS letters slightly [redacted] between week 52 and the end of the study, from 5% to [redacted], whereas in the GALILEO trial, slightly fewer patients in the original sham groups had losses of 10 letters or more at study end than at week 52, while slightly more patients in the aflibercept group had losses of 10 letters or more at study end compared to week 52 (6% vs. 1%). [p-values were not reported for these measures]

Table 9. Loss and gain of EDTRS letters – various thresholds

	GALILEO			**COPERNICUS**		
Letter gains	**24 weeks**	**52 weeks**	**76 weeks**	**24 weeks**	**52 weeks**	**100 weeks**
≥10 letters						
Aflibercept	75.7%	71.8%	68.0%	76.3%	77.2%	[redacted]
Sham	30.9%	38.2%	47.1%	21.9%	46.6%	[redacted]
Loss of letters						
≥10 letters						
Aflibercept	1.0%	1.0%	5.8%	1.8%	5.3%	[redacted]
Sham	13.2%	23.5%	17.6%	30.1%	17.8%	[redacted]
≥15 letters						
Aflibercept	1.0%	1.0%	4.9%	1.8%	5.3%	[redacted]
Sham	7.4%	14.7%	10.3%	27.4%	15.1%	[redacted]

In the table above, it can be seen that there was a large difference between the two trials in the number of patients losing 15 or more letters in the sham treatment arms. At 24 weeks, 27% of patients in COPERNICUS had lost 15 or more letters compared with 7.4% in GALILEO. The manufacturer was asked for a reason for this difference. The manufacturer response has been reproduced below.

'Regarding the difference in response between sham groups in GALILEO and COPERNICUS, more patients in COPERNICUS had disease duration longer than 2 months and also had a slightly worse BCVA at baseline, compared to GALILEO. It is possible that this is simply a chance variation between study populations. However, it is suspected that there may also have been some differential

recruitment into the two pivotal trials, because of differences in study design. In GALILEO, active treatment was not permitted in patients randomised to sham until 52 weeks in the sham arm. Therefore, clinicians may have been more reluctant to recruit severely affected patients into GALILEO than into COPERNICUS, where active treatment was an option in the sham arm after only 24 weeks. This may explain why the sham arm in GALILEO did much better than in COPERNICUS.

Even if clinicians did, as hypothesised, select 'better' patients for GALILEO, non-perfused patients are more likely to have a poor clinical outcome if they are not treated effectively. Non-perfused patients were included in both the COPERNICUS and GALILEO trials. This is in contrast to ranibizumab where the pivotal studies excluded non-perfused patients

Aflibercept has, therefore, been shown to work as well in non-perfused patients as in perfused patients. The breakdown between perfused and non-perfused sham arms shows that the 'better' sham arm performance in GALILEO was driven mainly by perfused patients doing well, whilst the non-perfused patients did worse. '

As mentioned previously, the definition of non-perfused in the trials was not a very strict one. We note that in the published papers, it is said that patients with afferent pupillary defect (indicative of considerable ischaemia) were excluded.

In the CRUISE trial,[24, 25] retinal ischaemia was not an exclusion criterion, but patients with afferent pupillary defects, suggesting more severe ischaemia, were excluded. We note that in the BMJ Evidence ERG report for the ranibizumab appraisal (page 10, section 1.3),[12] it is assumed that patients with ischaemia were not included.

As noted earlier, the ERG has doubts about the true proportion of patients in the aflibercept trials with ischaemia, and we do not feel that the Bayer submission provides evidence that aflibercept is effective in severely ischaemic eyes. It would have been useful if more detail on ischaemic state had been given, such as median or mean areas of non-perfusion for each arm in both trials.

The results were also pooled and reported in Table 27 of the MS. The ERG has checked these figures and gets the same results.

Table 10. Number (%) of patients losing 15 letters or more

Number (proportion) of patients losing 15 or more letters		
Study	**Aflibercept 2 mg**	**Sham**
COPERNICUS	2 (1.8%)	20 (27.4%)
GALILEO	8 (7.8%)	15 (22.1%)
	Ranibizumab 0.5 mg	**Sham**
CRUISE	2 (1.5%)	20 (15.4%)

Table 11. Comparison of meta-analysis results - patients losing ≥15 letters of BCVA from baseline to 6 months

Study	**OR (MS)**	**RR (MS)**	**ERG**
Patients losing ≥15 letters of BCVA from baseline to 6 months			
COPERNICUS	0.05 (95% CI 0.01 to 0.21)	NR	-
GALILEO	0.30 (95% CI 0.12 to 0.75)	NR	-
M-H pooled*	0.15 (95% CI 0.07 to 0.31)	NR	-
Patients losing ≥15 letters of BCVA from baseline to 6 months			
CRUISE	NR	2.82 (95% CI 1.85 to 4.30)	0.10 (95% CI 0.02 to 0.42)

*Mantel-Haenszal

The ERG was able to replicate results for aflibercept but got different results for the CRUISE study. The results show that more patients in the sham arm lost 15 letters or more from baseline to 6 months, while the number of patients on ranibizumab losing vision is very small during this time period.

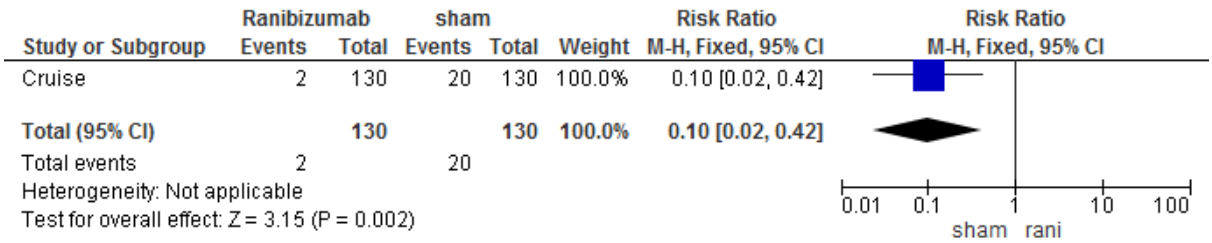


Figure 6. RR- Patients losing ≥15 letters from baseline to 6 months (CRUISE)

3.2.2 Central retinal thickness

In both trials there were significantly greater reductions in CRT at 6 months in the aflibercept group than in the control group (difference between means 311.9 µm in COPERNICUS ($p<0.001$) and 239.4 µm in GALILEO ($p<0.0001$)), but this difference was only maintained in the GALILEO trial, where patients continued their assigned treatment up to 12 months, and not in the COPERNICUS trial, where patients in the sham group also received aflibercept in the extension period, which caused a similar decrease in CRT as in the original intervention group.

3.2.3 Vision-related quality of life

The 25-item National Eye Institute Visual Function Questionnaire (NEI-VFQ 25) has 25 questions covering 12 topics: general health, general vision, near vision, distance vision, driving, peripheral vision, colour vision, eye pain, role limitation, social functioning and mental health. Scores range from 100 for best to 0 for worst. VHQ-25 results correlate more with vision in the BSE.[26]

Results for vision-related QoL (NEI-VFQ25) are shown in Table 12 and Figure 7 and

Figure 8. NEI VFQ-25 total scores increased (i.e. improved) significantly more in the aflibercept group at 6 months in both trials (mean change of [redacted] in aflibercept vs. [redacted] in sham). In both trials there were also significantly greater improvements in the distance activities sub-score ([redacted] vs. [redacted]) at

6 months (but no significance was reached in the near activities and vision dependency sub-scores). [redacted] In the GALILEO trial, where intervention groups were maintained up to 52 weeks, total NEI VFQ-25 scores continued to be significantly more improved in the aflibercept group than in the sham group at 52 weeks, and improvements were also significantly greater in the near and distance activities sub-scales (but not in the vision dependency sub-scale) [redacted] In the COPERNICUS trial, patients in the sham group who received aflibercept in the extension period had a similar increase in vision-related quality of life as patients in the original intervention group by 12 months (no significant difference between groups). [redacted]

Table 12. INTEGRATED analysis - Mean change NEI VFQ-25 subscale scores from baseline to Week 24 in (FAS LOCF) [from manufacturer submission]

Integrated analysis							
Week 24	**Aflibercept**			**Sham**			**Difference in LS mean change 95% CI [1] p-value**
NEI VFQ-25 score (SD)	**Baseline**	**Week 24**	**Mean Change from baseline**	**Baseline**	**Week 24**	**Mean Change from baseline**	
	N=217	**N=200**	**N=200**	**N=140**	**N=125**	**N=124**	
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Near-activities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Distance-activities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vision dependency	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Figure 7. Mean change from baseline in NEI VFQ-25 scores at weeks 24, 52 and 100 (COPERNICUS study) [from manufacturer submission]

[redacted]

Figure 8. Mean change from baseline in NEI VFQ-25 scores at weeks 24, 52 and 76 (GALILEO study) [from manufacturer submission]

[redacted]

In both GALILEO and COPERNICUS, mean change in NEI VFQ-25 for all domains was greater in the aflibercept group than in the sham arm.

There was no significant change over time and no significant difference between intervention groups at any of the time points in EQ-5D scores.

The MS did not provide data on EQ-5D results, but only a brief 8-line mention on page 78 that EQ-5D scores were similar. This rather contrasts with the more than 5 pages of data given on VFQ-25. The ERG asked question at clarification, and question and reply are given in Box 2.

Box 2. Clarification question and response

Question B1. Please outline what variables the EQ-5D data was adjusted for and how this adjustment was derived and applied. The EQ-5D data and analysis on page 78 of the submission does not contain actual values for EQ-5D. Please also provide the adjusted mean EQ-5D values by treatment arm and adjusted difference at weeks 24, 52 and 76 of GALILEO, together with the significances of the adjusted differences.

Answer

The utility values used in the cost effectiveness (CE) model were derived from EQ-5D scores from the European GALILEO population and were not adjusted for any covariate.

Therefore, Table below provides unadjusted EQ5D values from the European GALILEO population for each treatment arm and at four different points in time (baseline, week 24, 52, 76 and early termination). P values are indicated for differences between treatment arms.

Table B1. Unadjusted EQ5D values from the European subset of the GALILEO population

	Aflibercept	Sham
Baseline		
n	[redacted]	[redacted]
Mean	[redacted]	[redacted]
SD	[redacted]	[redacted]
P-value	[redacted]	
Week 24		
n	[redacted]	[redacted]
Mean	[redacted]	[redacted]
SD	[redacted]	[redacted]
P-value	[redacted]	
Week 52		

n	[redacted]	[redacted]
Mean	[redacted]	[redacted]
SD	[redacted]	[redacted]
P-value	[redacted]	
Week 76		
n	[redacted]	[redacted]
Mean	[redacted]	[redacted]
SD	[redacted]	[redacted]
P-value	[redacted]	

Source: Galileo European dataset, observed case analyses

Please note that the values presented above in Table B1 were derived from the same dataset that was used to produce the utility values applied in the CE model. However, in the model, the utility observations were analysed based on the patients' WSE and were applied to the health states (HS) based on the BCVA in the two eyes.

In summary, there were no significant differences in EQ-5D.

Note that it has been argued that EQ-5D is not sensitive enough to reflect changes in vision that matter to patients with eye conditions. One key function, driving, is specifically asked about in VFQ-25, whereas EQ-5D asks only about normal activities.

3.2.4. Adverse events

Details of adverse events (AEs) are given in section 6.8 (page 109 to 125) of the MS.
The evidence on safety and tolerability of aflibercept comes from COPERNICUS and GALILEO. In GALILEO, the safety of aflibercept is compared against sham injections for up to 76 weeks and in COPERNICUS, the safety is reported for 100 weeks, though no sham injections were given after the first year.

Ocular (in the study and fellow eye) and non-ocular AEs were recorded at each visit, and reported as treatment-emergent adverse events (TEAEs) i.e. AEs which occurred or worsened after the first administration of study drug. Adverse events were summarised using the Medical Dictionary for Regulatory activities (MedRA) (version 13.1) and were assessed for seriousness, intensity, pattern, causal relationship to study drug, and causal relationship to the injection procedure.

The safety analysis population (SAF) included all randomised patients who had received any medication. Table 42 has been reproduced below for convenience.

Table 13. Safety analysis population – COPERNICUS, GALILEO and Integrated (to week 24)

	Aflibercept (n)	**Sham (n)**
COPERNICUS	114	74
GALILEO	104	68
INTEGRATED (to week 24 only)	218	142

In both studies, patients received monthly aflibercept injections for 24 weeks. But after 24 weeks, all patients in COPERNICUS were assessed using retreatment criteria – monthly from 24 to 52 weeks, then 12-weekly from week 52 to week 100) and received 2 mg aflibercept, as necessary, otherwise a sham injection was administered (week 24 to week 52 only). Therefore, safety data for COPERNICUS is presented for 0-24 weeks, 24 to 52 weeks and 24 to 100 weeks.

In GALILEO, from week 24 to week 52, patients continued to receive either aflibercept or sham treatments, as randomised, except that the aflibercept group received aflibercept on a PRN basis. From week 52 to week 76, all patients were assessed every 8 weeks using retreatment criteria and received 2 mg aflibercept, as necessary, otherwise a sham injection was administered. Thus, safety data for GALILEO has been presented for 0-24 weeks, 0 to 52 weeks, and 52 to 76 weeks.

For convenience, Table 43 has been reproduced below but split into two tables.
The first table reports any TEAEs observed in COPERNICUS and GALILEO in the first 24 weeks. The integrated data has also been presented here. The second table reports any TEAEs observed after 24 weeks. In both studies, at 24 weeks the proportion of patients reporting any TEAEs, both non-ocular (systemic) or ocular, was slightly higher in patients receiving sham compared to those receiving aflibercept. [redacted] The most common injection-related TEAEs (occurring in ≥10% of all patients) were conjunctival haemorrhage, eye pain and eye irritation. More patients in the sham group discontinued because of any TEAE (7.7% vs. 1.8%). [redacted]
A very few TEAE SAEs were related to study drug and the incidence was similar in the two groups.

The manufacturer believes most SAEs were related to the disease state or injection procedure. The only deaths were 2 in the COPERNICUS sham group.

Note that in the tables below, possible AEs unrelated to the drugs or injections have been removed. Full details are in table 43 of the MS.

Table 14. Summary of safety data TEAEs during the COPERNICUS and GALILEO studies (INTEGRATED 24 week analysis)(SAF)

	COPERNICUS		**GALILEO**		**INTEGRATED**	
	Aflibercept	**Sham**	**Aflibercept**	**Sham**	**Aflibercept**	**Sham**
	0-24 weeks	**0-24 weeks**	**0-24 weeks**	**0-24 weeks**	**0-24 weeks**	
	N=114 n (%)	**N=74 n (%)**	**N=104 n (%)**	**N=68 n (%)**	**N=218 n (%)**	**N=142 n (%)**
Any study drug-related TEAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocular (study eye)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-ocular	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any injection-related TEAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any TEAE causing treatment discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any TEAE SAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-ocular (systemic)	6 (5.3)	6 (8.1)	[redacted]	[redacted]	12 (5.5)	11 (7.7)
Ocular (study eye)	4 (3.5)	10 (13.5)	[redacted]	[redacted]	[redacted]	[redacted]
Any study drug-related TEAE SAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any injection-related TEAE SAE (study eye)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 15. Summary of safety data TEAEs during the COPERNICUS and GALILEO studies (after 24 week analysis)(SAF)

NB. The hatched areas indicate when the sham group has crossed over to receive aflibercept PRN

	COPERNICUS				**GALILEO**			
	Aflibercept		**Sham**		**Aflibercept**		**Sham**	
	24-52 weeks[a]	**24-100 weeks[a]**	**24-52 weeks[a]**	**24-100 weeks[a]**	**0-52 weeks**	**52-76 weeks**	**0-52 weeks**	**52-76 weeks**
	N=110 ***n (%)***	**N=110** **n (%)**	***N=60*** ***n (%)***	**N=60** **n (%)**	**N=104** **n (%)**	[redacted] **n (%)**	**N=68** **n (%)**	[redacted] **n (%)**
Any study drug-related TEAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocular (study eye)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-ocular	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any injection-related TEAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any TEAE causing treatment discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any TEAE SAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-ocular (systemic)	*7 (6.4)*	[redacted]	*5 (8.3)*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocular (study eye)	*3 (2.7)*	[redacted]	*2 (3.3)*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any study drug-related TEAE SAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any injection-related TEAE SAE (study eye)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] week 24 completers within safety analysis set

[redacted] The incidence of any study drug-related TEAE was similar in the two groups.

Table 16. Ocular TEAEs in the study eye occurring in ≥3.0% of patients at preferred term level in any treatment in the COPERNICUS and GALILEO studies (an integrated 24 weeks analysis)

	COPERNICUS		GALILEO		INTEGRATED	
	Aflibercept	Sham	Aflibercept	Sham	Aflibercept	Sham
	0-24 weeks	0-24 weeks	0-24 weeks	0-24 weeks	0-24 weeks	
	N=114 n (%)	N=74 n (%)	N=104 n (%)	N=68 n (%)	N=218 n (%)	N=142 n (%)
Any ocular TEAE (study eye) Patients with at least 1 preferred term ≥3% in any group	[redacted]	[redacted]	[redacted]	[redacted]	NR	[redacted]
Conjunctival haemorrhage	[redacted]	[redacted]	9 (8.7)	3 (4.4)	26 (11.9)	[redacted]
Visual acuity reduced	[redacted]	[redacted]	[redacted]	[redacted]	8 (3.7)	[redacted]
Eye pain	[redacted]	[redacted]	12 (11.5)	3 (4.4)	28 (12.8)	[redacted]
Intraocular pressure increased	[redacted]	[redacted]	[redacted]	4 (5.9)	17 (7.8)	[redacted]
Maculopathy	[redacted]	[redacted]			13 (6.0)	[redacted]
Retinal vascular disorder	[redacted]	[redacted]	[redacted]	[redacted]	12 (5.5)	[redacted]
Retinal exudates	[redacted]	[redacted]	[redacted]	[redacted]	14 (6.4)	[redacted]
Optic disc vascular disorder	[redacted]	[redacted]	[redacted]	[redacted]	12 (5.5)	[redacted]
Vitreous floaters	[redacted]	[redacted]	[redacted]	[redacted]	11 (5.0)	[redacted]
Retinal haemorrhage	[redacted]	[redacted]	[redacted]	[redacted]	7 (3.2)	[redacted]

Maculopathy is not defined in either the published studies or the Bayer submission but in response to a clarification question, Bayer reported that it was primarily epiretinal membrane. The ERG notes that it occurs more often with aflibercept. An epiretinal membrane is a very thin layer of scar tissue that forms on the surface of the macula. This can impair vision. The only way to deal with it is to remove it surgically via a vitrectomy. After this it may take some time for vision to improve again. The surgery is not without risk – about 2% end up with worse vision and there is a very small (about 1 in 1000) risk of blindness in that eye. Surgery may also accelerate cataract.

Retinal vascular disease is not defined in the submission but Bayer report that it covers a range of conditions such as development of collateral vessels, shunt vessels and tortuosity.

The most common ocular adverse events reported at 24 weeks in the two studies were conjunctival haemorrhage, decreased visual acuity, eye pain, increased intraocular pressure and retinal vascular

disease. More patients in the aflibercept arm complained of eye pain, increased IOP, maculopathy, retinal exudates, optic disc vascular disorder and vitreous floaters than in the sham arm, whereas more patients in the sham arm had reduction in visual acuity, and retinal haemorrhage. The incidence of conjunctival haemorrhage was similar in the two groups.

Table 17. Ocular TEAEs in the study eye occurring in ≥3.0% of patients at preferred term level in any treatment in the COPERNICUS and GALILEO studies (52 weeks and 100 weeks –COPERNICUS and 52 weeks and 76 weeks – GALILEO)

NB. The hatched areas indicate when the sham group has crossed over to receive aflibercept PRN

	COPERNICUS				**GALILEO**			
	Aflibercept		**Sham**		**Aflibercept**		**Sham**	
	24-52 weeks[a]	**24-100 weeks[a]**	**24-52 weeks[a]**	**24-100 weeks[a]**	**0-52 weeks**	**52-76 weeks**	**0-52 weeks**	**52-76 weeks**
	N=110 ***n (%)***	**N=110** **n (%)**	***N=60*** ***n (%)***	**N=60** **n (%)**	**N=104** **n (%)**	**n (%)**	**N=68** **n (%)**	**n (%)**
Any ocular TEAE (study eye) Patients with at least 1 preferred term ≥3% in any group	***62 (56.4)***		***33 (55.0)*** ***29 (48.3)***					
Conjuctival haemorrhage			*8 (13.3)*					
Visual acuity reduced			*3 (5.0)*					
Eye pain			*3 (5.0)*					
Intraocular pressure increased			*5 (8.3)*					
Cystoid macular oedema			*2 (3.3)*					
Macular oedema			*0*					
Maculopathy			*4 (6.7)*					
Retinal haemorrhage			*3 (5.0)*					
Retinal vascular disease								
Vitreous detachment								
Optic disc vascular disorder			*2 (3.3)*					
Macular fibrosis								
Retinal exudates			*4 (6.7)*					

After 24 weeks, the most commonly reported TEAE ocular adverse events were conjunctival haemorrhage, reduction in VA, eye pain, increased IOP and macular oedema. Other commonly seen ocular TEAEs were retinal haemorrhage, retinal vascular disease, vitreous detachment, optic disc

vascular disorder, macular fibrosis and retinal exudates. The manufacturer stated that the occurrence of increased macular oedema was observed once patients switched to PRN dosing of aflibercept, thereby suggesting a destabilisation of the disease with PRN dosing.

More patients in the sham arm experienced ocular SAEs than in the aflibercept arm. The manufacturer state that most SEAs were related to the disease state or injection procedure. Ocular SAEs included vitreous haemorrhage, macular oedema, cataract, glaucoma, iris neovascularisation, reduced VA, cystoid macular oedema, retinal haemorrhage and retinal tear (Please see table below)

Table 18. Number of patients experiencing ocular SAEs

	COPERNICUS		GALILEO	
	Aflibercept	Sham	Aflibercept	Sham
Vitreous haemorrhage	[redacted]	[redacted]	1	1
Macular oedema	[redacted]	[redacted]	4	2
Cataract	[redacted]	[redacted]	[redacted]	[redacted]
Glaucoma	[redacted]	[redacted]	-	2
Iris neovascularisation	[redacted]	[redacted]	1	[redacted]
Reduced VA	[redacted]	[redacted]	[redacted]	[redacted]
Cystoid macular oedema	[redacted]	[redacted]	[redacted]	[redacted]
Retinal haemorrhage	[redacted]	[redacted]	[redacted]	[redacted]
Retinal tear	-	2	1	-
Endophthalmitis	[redacted]	[redacted]	[redacted]	[redacted]

The numbers of patients experiencing at least one drug related TEAEs were low in both trials.

It is note-worthy that no cases of NVG, the most devastating complication of ischaemic CRVO, are reported in the sham arms. This implies to the ERG that the recruits to the trials did not have aggressive ischaemic disease. We asked Bayer if there were any cases of NVG, but the reply was that “glaucoma” as reported was not further divided.
Neovascular glaucoma causes pain, and patients need multiple medications including eye drops and oral acetazolamide because the pressure can be very high – 2-3 times normal. Because the pressure is high, the cornea can become oedematous, making it difficult to visualise the retina. Anti-VEGF

therapy is required to make the neovessels regress, the IOP to drop and the cornea to clear, after which laser therapy may be carried out. Neovascular glaucoma can be a very difficult problem to deal with.

[redacted]

Non-ocular TEAEs and SAEs

The proportion of patients experiencing ≥1 non-ocular TEAE during the entire period of the study was slightly higher in the sham groups than aflibercept group [redacted] but the events were mostly mild to moderate, very unlikely to be related to study drug, consistent with events expected within this older patient population.

The overall incidence of non-ocular SAEs was also low and similar between the two treatment groups. The events included [redacted]

In COPERNICUS, there were two vascular deaths (in sham), one non-fatal MI (in aflibercept) [redacted].

The EMA noted some concerns about the relative safety of aflibercept compared to ranibizumab in AMD, noting that there were more cerebrovascular events with aflibercept (35) than with ranibizumab (2) in the first year of treatment.[27] The difference was most marked in patients 85 and over - 20 events versus 1). The two-year data were similar - 53 events with aflibercept versus 12 with ranibizumab. It should be noted that the AMD population is older than the CRVO one.

The EMA commented that;

'*Taking into account the fact that almost 20% of drug substance goes through the systemic circulation, systemic effects of VEGF Trap-eye on the circulation cannot be excluded, and appropriate monitoring is foreseen in the RMP'*.

and,

The higher proportion of TIAs and cerebrovascular events reported within the pooled data is of concern and will be carefully considered within further assessments of ATEs during routine pharmacovigilance procedures and PSURs.'

but nevertheless the EMA concluded that the overall safety profiles of the two drugs were similar.

NICE TA 294[10]

Data on adverse events of aflibercept and ranibizumab can be drawn from the appraisal of aflibercept for the treatment of wet AMD (NICE TA294),[10] in which data on the safety and tolerability of aflibercept and ranibizumab for up to 96 weeks came from the two trials VIEW 1 and VIEW 2. The ERG and the committee agreed with the manufacturer's assertion stated that there was no clinically meaningful difference in the safety of the two drugs. The incidences of TEAEs were similar. The most common TEAEs in at least 5% of patients treated with aflibercept were: conjunctival haemorrhage (26.7%), eye pain (10.3%), vitreous detachment (8.4%), cataract (7.9%), vitreous floaters (7.6%), and increased intraocular pressure (7.2%). The incidences of arterial thromboembolic events (including non-fatal myocardial infarction, non-fatal stroke or vascular stroke) were similar in the aflibercept (3.3%) and ranibizumab (3.2%) groups. The Appraisal Committee concluded that aflibercept was safe and well tolerated.

In the present appraisal of aflibercept for the treatment of CRVO, the most commonly observed TEAEs in at least 3% of patients with aflibercept were very similar to that observed in the VIEW trials of aflibercept for the treatment of wet AMD. The most commonly reported TEAEs were conjunctival haemorrhage, eye pain, reduced VA and increased IOP. In addition, adverse events like retinal haemorrhage, cataract and vitreous detachment were also observed but total numbers were small.

Based on the findings from this appraisal and the appraisal of aflibercept for wet AMD, the safety profile of aflibercept appears similar to ranibizumab. As is usual with the anti-VEGFs, the main AEs come from the injection rather than the drug.

3.3 Independent systematic review

The ERG has access to an independent systematic review of current drug treatments in the treatment of MO secondary to CRVO (Ford et al, submitted for publication: academic in confidence). This confirmed that the Bayer submission omitted no relevant trials.

3.4. Indirect comparison

In the absence of a head to head comparison of aflibercept against ranibizumab in CRVO, the manufacturer undertook a network meta-analysis (NMA) to assess the effects of the two treatments on VA. Details are given in section 6.7 (pages 89 to 108). The manufacturer carried out a systematic

search to find relevant clinical data on ranibizumab given in a PRN or 'reactive dosing' regimen. Eight studies were identified on the efficacy and safety of aflibercept, ranibizumab, dexamethasone and bevacizumab. Two studies (CRUISE[24, 25] and ROCC[49]) investigated ranibizumab, two studies (COPERNICUS and GALILEO) aflibercept, two studies dexamethasone (GENEVA 008 and GENEVA 009)[28-30] and two studies [13-16] investigated bevacizumab. Bevacizumab was not included in the NMA. The reasons given by Bayer included: not a standard treatment in CRVO; Wittstrom et al was a small study (n=19), included laser treatment and was poorly reported; Epstein et al was also a small study (n=60) of moderate quality that was insufficiently robust for evaluating clinical and cost effectiveness. The manufacturer added that Epstein et al (2012) was insufficiently powered to report on all AEs for bevacizumab in CRVO as this would have required 300 rather than 60 participants. (ERG. It could still have been included for efficacy) This was also the reason given for why a mixed treatment comparison undertaken during the appraisal of ranibizumab (TA283) did not include this study.

The manufacturer states that because of the cross over design of the COPERNICUS, CRUISE and GENEVA trials at 6 months (24 weeks), , the NMA was conducted on 6-month trial data only. Thus, five studies reporting the 6-month results of the trials of interest were included in the NMA.

The network of evidence is presented as Figure 16 in the MS. For convenience, this has been reproduced below. The common treatment arm in studies was sham.

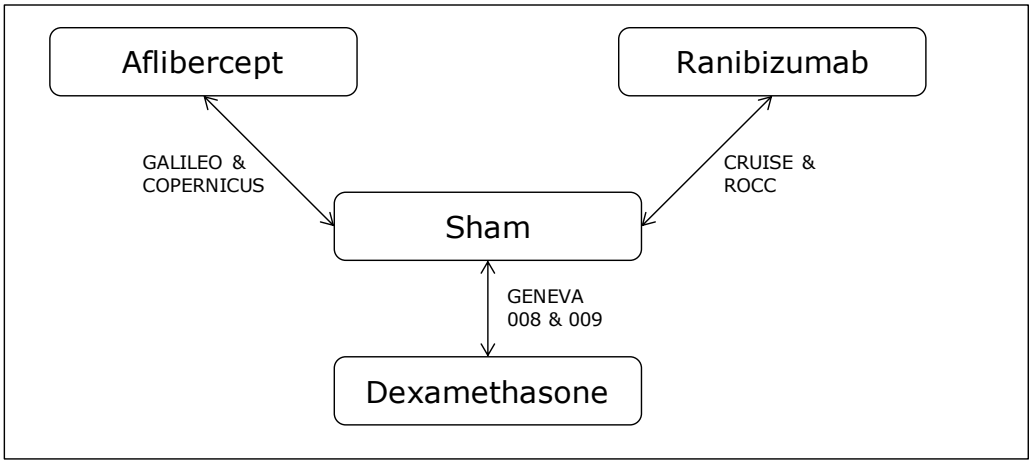


Figure 9. Network diagram (MS)

Please see below a table comparing baseline similarities and results of all the studies included in the NMA.

Table 19. Studies included in the NMA

	COPERNICUS[18, 19]	GALILEO[20]	CRUISE[24, 25]	ROCC[49]	GENEVA[28-30]
BASELINE SIMILARITIES					
Number (%) of patients					
	Aflib 2 mg: 114 Sham: 73	Aflib 2 mg: 103 Sham: 68	Rani 0.5 mg: 130 Sham: 130	Rani 0.5 mg: 15 Sham: 14	Dexa0.7 mg: 136 Sham: 147
Age (years)					
	Aflib 2 mg: 65.5 SD13.6 Sham: 67.5 SD14.3	Aflib 2 mg: 59.9 SD12.4 Sham: 63.8 SD13.3	Rani 0.5 mg: 67.6 SD12.4 Sham: 65.4 SD13.1	Rani 0.5 mg: 72 (range 55-88) Sham: 72 (range 52-88)	Dexa 0.7 mg: mean 64.3 (33 to 90) Sham: 63.9 (31 to 91)
BCVA at baseline (SD)					
	Aflib 2 mg: 50.7 SD13.90 Sham: 48.9 SD14.42	Aflib 2 mg: 53.6 SD15.8 Sham: 50.9 SD15.4	Rani 0.5 mg: 48.1 SD14.6 Sham: 49.2 SD14.7	Rani 0.5 mg: 45 SD23 Sham: 41 SD22	Dexa 0.7 mg: 54.3 SD 9.93 Sham: 54.8 SD 9.86
Duration of |CRVO from diagnosis to screening					
	Aflib 2 mg: 2.73 SD 3.09 (in months) Sham: 1.88 SD2.19 (in months)	Aflib 2 mg: 2.56 SD 2.95 (in months) Sham: 2.88 SD 2.60 (in months)	Rani 0.5 mg: 3.3 SD 3.7 Sham: -2.9 SD2.9	Rani 0.5 mg: 78 days (10 to 163 days) Sham: 78 days (10 to 163 days)	Dexa 0.7 mg: Mean 157 days (19 to 374) Sham: 156 days (19 to 374)
Ischaemia,n(%)					
	Aflib 2 mg: 17 (19.9) non-perfused Sham: 12 (16.4)	Aflib 2 mg: 7 (6.8) non-perfused Sham: 7 (10.3)	Rani 0.5 mg: NR Sham: NR	Rani 0.5 mg: 1 (7) Sham: 4 (29) Nonperfusion in area of >5 disc areas	Dexa 0.7 mg: NR Sham: NR
RESULTS					
Number (%) of patients gaining ≥15 letters improvement from baseline					
	Aflib 2 mg: 64 (56.1) Sham: 9 (12.3)	Aflib 2 mg: 62 (60.2) Sham: 15 (22.1)	Rani 0.5 mg: 62 (47.7) Sham: 22 (16.9)	Rani 0.5 mg: NR Sham: NR	Dexa 0.7 mg: 24 (18) Sham: 18 (12)
Number (%) of patients losing ≥15 letters of BCVA from baseline					
	Aflib 2 mg: 2 (1.8) Sham: 20 (27.4)	Aflib 2 mg: 8 (7.8) Sham: 15 (22.1)	Rani 0.5 mg: 2 (1.5) Sham: 20 (15.4)	Rani 0.5 mg: NR Sham: NR	Dexa 0.7 mg: NR Sham: NR
Mean change (SD) from baseline in BCVA					
	Aflib 2 mg: 17.3 (12.8) Sham: -4 (18)	Aflib 2 mg: 18.0 (12.2) Sham: 3.3 (14.1)	Rani 0.5 mg: 14.9 (13.2) Sham: 0.8 (16.2)	Rani 0.5 mg: 12 (20) Sham: -1 (17)	Dexa 0.7 mg: 0.1 (NR) Sham: -1.8 (NR)

CRUISE was a phase III, randomised, double-blind, sham-controlled trial of ranibizumab (0.3 mg and 0.5 mg) in patients with MO secondary to CRVO. Only the licensed dose, 0.5 mg ranibizumab was

included in the NMA. Patients received monthly injections of ranibizumab or sham injections for the first 6 months and during the observation period i.e. 6 to 11 months all patients could receive monthly ranibizumab according to retreatment criteria.

ROCC was a prospective, multicentre, randomized, double-masked, 6 month placebo-controlled trial where 32 patients with MO secondary to CRVO were randomised to receive monthly intravitreal ranibizumab 05 mg or sham injections for 3 consecutive months. This study was regarded as exploratory given the low number of patients included (29 patients completed the study; 15 and 14 patients on ranibizumab and sham respectively), and it was excluded in a sensitivity analysis

GENEVA 008 and 009 were two identical, prospective, multicentre, phase III clinical trials that investigated the efficacy of dexamethasone, 0.7 mg and 0.35 mg, in patients with MO secondary to RVO. The 0.35 mg dose of dexamethasone was not considered in the NMA as this is not the licensed dose. Randomization was stratified by the underlying cause of RVO (BRVO or CRVO). Each trial consisted of a 6-month, randomized, sham-controlled, parallel-group, double-masked phase followed by a 6-month open-label extension. Patients could receive dexamethasone 0.7 mg, 0.35 mg or sham at day 0 and could be retreated at day 180 according to pre-specified criteria.

The five studies reported results for the three key common trial efficacy endpoints:

- Proportion of patients gaining ≥15 letters of BCVA from baseline at 6 months
- Proportion of patients losing ≥15 letters of BCVA from baseline at 6 months
- Mean change in BCVA/number of letters read from baseline at 6 months

Therefore, trial results of these three endpoints were used as inputs for the NMA. One of the ranibizumab studies, ROCC only reported the mean change in BCVA from baseline.
The NMA did not examine safety endpoints as the occurrence of AEs in the studies was low and thus, it would have led to uncertain results with wide confidence intervals.
(ERG: This conflicts with the reason given by Bayer for excluding the bevacizumab trial by Epstein and colleagues.)

Box 3 reproduces the methods section from the Bayer submission.

Box 3. Methods of NMA

The NMA were conducted using the Bayesian approach. Odds ratios are the natural outputs of a Bayesian NMA. The NMA was performed using WinBUGS version 1.4.3 following the methodology promoted by the DSU of NICE. WinBUGS is Bayesian analysis software that, through the use of Monte Carlo Markov chains, calculates posterior distributions for the parameters of interest, given likelihood functions derived from data and prior probabilities. The Monte Carlo Markov Chain simulation begins with an approximate distribution and, if the model is a good fit to the data, the distribution converges to the true distribution(42).

Both fixed and random effects models were conducted with the latter being preferred in the presence of heterogeneity. Further, a comparison was made by observing the Deviance Information Criterion (DIC) statistics and the total residual deviance, to ensure that the selected model's overall fit is adequate. The DIC provides a measure of model fit that penalizes model complexity – lower values of the DIC suggest a more parsimonious model; however, differences of less than 3 are not considered to be important(43).

To check formally whether a model's fit is satisfactory we consider an absolute measure of fit: the overall residual deviance. We compared the value of the overall residual deviance to the number of independent data points to check if the model fit can be improved. As the rule of the thumb each data point should contribute about 1 to the posterior mean deviance, hence these two values should be very close in the presence a model that is a good predictor.

Convergence was assessed by using the Brooks-Gelman-Rubin diagnostic in WinBUGS. In all cases a burn-in of at least 20,000 simulations were discarded. And all results are presented based on a further sample of at least 50,000 simulations. Lastly, the Monte Carlo error, which reflects both the number of simulations and the degree of autocorrelation, was observed. This should be no more than 5% of the posterior standard deviation of the parameters of interest. All baseline and intervention effect parameters were given flat (uninformative) Normal (0, 10000) priors and the between-study standard deviation flat Uniform distributions with an appropriately large range given the scale of measurement. While ORs are the natural outcomes of an NMA using a Bayesian approach, odds ratios (ORs) can be converted to relative risks (RRs) providing that a baseline treatment effects for the reference treatment (sham) is available. This baseline treatment effects can be obtained via different ways such as cohort studies, a single trial or set of trials considered to reflect contemporary outcomes under treatment, expert opinion, etc. In order to generate RRs, we have "modelled" the sham baseline treatment effects across the 6 clinical trials included.

The results of the NMA are presented in Tables 33, 34, 35, 36, 37 and 41. The first table presents RRs of patients gaining ≥15 letters of BCVA from baseline at 6 months , the next table presents RRs of patients losing ≥15 letters of BCVA from baseline at 6 months and, the last table present mean changes in BCVA/number of letters read from baseline at 6 months with ROCC study.

For convenience, the tables of the RRs are reproduced below. The tables of ORs and mean change in BVA without ROCC study are in Appendix 1.

Table 20. Relative risk - Patients gaining ≥15 letters of BCVA from baseline at 6 months

Treatments	Fixed Effects			Random Effects		
	Relative Risk	lCr.Int.	uCr.Int.	Relative Risk	lCr.Int.	uCr.Int.
Dexamethasone 0.7mg vs. Aflibercept 2mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ranibizumab 0.5mg vs. aflibercept 2mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sd	n.a.			0.67	0.03	1.90

lCr.Int – lower credible interval; uCr.Int – upper credible interval; sd – between study standard deviation

The NMA found that aflibercept was significantly superior to dexamethasone in terms of proportion of patients gaining at least ≥15 letters from baseline to 24 weeks but non-significantly superior to ranibizumab.

The MS appears to show that the NMA found that the proportion of patients losing 15 letters from baseline to 6 months was lower with ranibizumab than with aflibercept ([redacted]) (Table 21) In the CRUISE trial, 1.5% of patients receiving ranibizumab lost 15 letters or more at 6 months while 1.8% and 7.8% of patients receiving aflibercept in COPERNICUS and GALILEO respectively lost 15 letters or more at the same time point.

Table 21. Relative risks - Patients losing >15 letters of BCVA from baseline at 6 months

Treatments	Fixed Effects			Random Effects		
	Relative risk	lCr.Int.	uCr.Int.	Relative risk	lCr.Int.	uCr.Int.
Ranibizumab 0.5mg vs. aflibercept 2mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sd				1.18	0.15	1.96

lCr.Int – lower credible interval; uCr.Int – upper credible interval; sd – between study standard deviation

Table 22 reports that patients on aflibercept gained significantly more letters at six months than those on dexamethasone. There was no significant difference between aflibercept and ranibizumab. In the GENEVA trial, mean change in BCVA with dexamethasone was 0.1 (SD NR), in CRUISE the

corresponding figure with ranibizumab 0.5 mg was 14.9 SD 13.2 while in COPERNICUS and GALILEO, mean change in BCVA was 17.3 SD 12.8 and 18.0 SD 12.2 respectively. Excluding the ROCC trial made no difference (data in appendix).

Table 22. Mean Change in BCVA/number of letters read from baseline at 6 months

Treatments	Fixed Effects			Random Effects		
	Mean Change	lCr.Int.	uCr.Int.	Mean Change	lCr.Int.	uCr.Int.
Aflibercept 2mg vs. dexamethasone 0.7mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Aflibercept 2mg vs. ranibizumab 0.5mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
sd	n.a.			2.86	0.23	4.88

lCr.Int – lower credible interval; uCr.Int – upper credible interval; sd – between study standard deviation; totresdev – total residual deviance; DIC – deviance information criterion

Critical assessment of the manufacturer's NMA

The ERG critically appraised the manufacturer's indirect comparison's using a checklist suggested by Donegan and colleagues.[50]

	Yes/No/Unclear/Not applicable
Indirect comparison method	
Is the method applied to undertake the indirect comparison adequate?	Yes
If an adequate method is used, is a treatment effect estimate and measure of precision reported?	Yes
Similarity	
Is the assumption of similarity stated?	Yes
Is a method described to assess the similarity assumption within the review methods section?	Yes
Is a reasonable approach used to assess the assumption of similarity?	Yes
Are patient or trial characteristics reported for all trials in the indirect comparison?	Yes
Are patient or trial characteristics compared across the two trial sets involved in the indirect comparison?	Yes
Are patient or trial characteristics reported to be comparable for the two trial sets involved in the indirect comparison?	Yes
Homogeneity across trials within each of the two trials set involved in the indirect comparison	
Is the method used to determine the presence of statistical homogeneity adequate?	Yes
Is the homogeneity assumption satisfied or is statistical heterogeneity accounted for if present?	Yes
If the homogeneity assumption is not satisfied, is clinical or methodological homogeneity across trials in each trial set involved in the indirect comparison investigated by an adequate method?	
Consistency	
Is consistency of effects assessed?	Yes
If the direct and indirect evidence is reported to be consistent, is the evidence combined and the result presented?	Not applicable; only indirect evidence
If consistency is reported, is this accounted for by not combining the	Not applicable

direct and indirect evidence?	
Are patient or trial characteristics compared between direct and indirect evidence trials?	Not applicable
Are any included 3-arm trials correctly analysed?	Not applicable
Is justification given for using indirect evidence and direct evidence?	Yes
Does the review present results from all trials providing direct evidence?	Not applicable
Interpretation	
Is a distinction made between direct and indirect comparisons?	Yes (only indirect evidence used)
Does the review state that more trials providing direct evidence as needed?	Yes
Reporting	
Does the review present both of the meta-analysis results from each of the two trial sets involved in the indirect comparison?	Yes
Was it highlighted which results were from indirect evidence?	Yes
Are the individual trials treatment effect estimates reported?	Yes

The ERG found that the methods used by the manufacturer to undertake NMA were appropriate. Adequate description of the trials were given. Baseline characteristics of all the studies were presented and the manufacturer gave appropriate reasons for including these studies. The manufacturer has correctly used the Bayesian approach using WinBUGS to analyse the data. Heterogeneity was also tested appropriately. The findings were also presented correctly.

Independent NMA.

The ERG had access to a NMA undertaken by an academic group (Ford et al submitted for publication) which gave similar results to the Bayer NMA.

4 CONCLUSION

4.1 Summary of clinical effectiveness

The COPERNICUS and GALILEO trials provide evidence that aflibercept is effective in improving vision after CRVO. There are inevitably some AEs after any eye injection, but safety is acceptable, especially taking into account the effects on untreated CRVO.

The manufacturer's NMA suggests that aflibercept is better than dexamethasone and as good as, and possibly a little better than, ranibizumab. The ERG has access to an independent NMA that confirms this but the current evidence base does not provide grounds for preferring one drug over the other, and having both will encourage price competition.

4.2 Any issues related to clinical effectiveness section

One issue concerns the representativeness of the recruits, in that it appears that the proportion of patients with ischaemic CRVO, and especially with more serious ischaemia, may be lower than is seen in routine care. The ERG thinks that trial evidence may not support the Bayer assertion that all subgroups will respond to aflibercept.

Stopping rules.
The ERG think there may be case for having some stopping rules, which might include;
- deterioration in VA after three injections
- no fall in oedema fluid or CRT. The current re-treatment criterion mentions a 50 µm rise in CRT, but this implies that it had fallen previously.

Place of administration
The ERG would expect all aflibercept to be given on an outpatient basis and not charged as a day case.

5 COST EFFECTIVENESS

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

Bayer has appropriately provided adequate description of their cost-effectiveness systematic review including search strategy, inclusion/exclusion criteria and description of included and excluded studies

5.2 Summary and critique of manufacturer's submitted economic evaluation by the ERG

5.2.1 NICE reference case checklist

Attribute	Reference case and TA Methods guidance	Does the *de novo* economic evaluation match the reference case
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice	The main comparison is with ranibizumab, but an additional comparison with dexamethasone is also undertaken. Bevacizumab and observation are not considered.
Patient group	As per NICE scope. "*Adults with visual impairment due to macular oedema caused by central retinal vein occlusion.*"	Yes.
Perspective costs	NHS & Personal Social Services	Yes.
Perspective benefits	All health effects on individuals	Yes.
Form of economic evaluation	Cost-effectiveness analysis	Cost utility.
Time horizon	Sufficient to capture differences in costs and outcomes	Yes.
Synthesis of evidence on outcomes	Systematic review	Yes. The relative risks of improving by at least 15 letters of [redacted] for ranibizumab and [redacted] for dexamethasone are drawn from the manufacturer NMA. But the relative risk of losing at least 15 letters of [redacted] that is in favour of ranibizumab of the NMA is not included within the model.
Outcome measure	Quality adjusted life years	Yes.
Health states for QALY	Described using a standardised and validated instrument	Yes. The main health BCVA states are evaluated using the EQ-5D data

		collected during GALILEO.
Benefit valuation	Time-trade off or standard gamble	The standard UK EQ-5D tariff is used, which is based upon time-trade off.
Source of preference data for valuation of changes in HRQL	Representative sample of the public	Yes.
Discount rate	An annual rate of 3.5% on both costs and health effects	Yes.
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes.
Probabilistic modelling	Probabilistic modelling	Yes.
Sensitivity analysis		A range of sensitivity and scenario analyses are presented.

The manufacturer develops a de novo cost utility model with a four week cycle length and a lifetime horizon. Health states are defined in terms of 15 ETDRS letter wide bands, resulting in five health states for the treated eye and five health states for the fellow eye: 25 health states in total. The model assumes that the BCVA of the fellow eye is constant. The base case assumes one year of treatment.

The initial patient distribution is taken from the pooled COPERNICUS and GALILEO patient level data. For each of the six cycles from baseline to week 24:

- The probabilities of the treated eye improving and worsening for aflibercept drawn from the pooled COPERNICUS and GALILEO patient level data.
- The probabilities of the treated eye improving for ranibizumab are calculated by applying the [redacted] relative risk of improving by at least 15 letters at week 24 to the corresponding aflibercept probabilities of improving. The probabilities of worsening for ranibizumab are assumed to be the same as those of aflibercept. The probabilities of remaining in the same health state are the residuals such that for a given start of cycle health state the transition probabilities sum to 100%.
- The probabilities for dexamethasone are calculated in the same manner as those for ranibizumab, only applying the [redacted] relative risk of improving by at least 15 letters at week 24.

For weeks 24 to 52 treatment continues, but given a lack of comparative clinical efficacy data it is assumed that the BCVA of the treated eye is constant. Thereafter a slow visual worsening is modelled using data drawn from the literature, with 0.0296% worsening by one health state each 4 week cycle.

Quality of life values for the base case are drawn from EQ-5D data collected during the GALILEO trial. This is augmented by a scenario analysis that applies quality of life values drawn from Czoski-Murray et al (2009).[51]

The number of administrations during for baseline to 24 weeks and for 24 weeks to 52 weeks are

- 5.75 and 2.55 to give a total of 8.30 for aflibercept, at a direct drug cost of £816.00 excluding the PAS and [redacted] including the PAS;
- 5.50 and 3.30 to give a total of 8.80 for ranibizumab, at a direct drug cost of £742.17 excluding the PAS; and,
- 1.85 and 2.15 to give a total of 4.00 for dexamethasone, at a direct drug cost of £870.00.

Administrations also incur a cost of £257 for aflibercept and ranibizumab based upon 48% requiring day case administration, and £321 for dexamethasone due to a higher 75% proportion requiring day case administration. Unfortunately, the PAS inclusive price for ranibizumab has not been communicated for this assessment and as a consequence the manufacturer applies ranibizumab PAS percentages from 10% to 50% in 5% increments.

A one-stop monitoring model is applied, where administration visits can double as monitoring visits. The number of dedicated monitoring visits for baseline to 24 weeks are 0.00 for aflibercept, 0.00 for ranibizumab and 0.92 for dexamethasone, and for 24 weeks to 52 weeks are 2.43 for aflibercept, 2.03 for ranibizumab and 1.08 for dexamethasone. These incur a cost of £197.

The base case does not include adverse events, but these are included within a scenario analysis.

A blindness mortality multiplier of 1.54, a first year cost of blindness of [redacted] and a subsequent annual cost of blindness of [redacted] are applied.

5.2.2 Model structure

The manufacturer develops a de novo cost utility markov model with a four week cycle length. The model defines health states in terms of the BCVAs of patients' eyes with this being banded into five health state, these bands in general being 15 ETDRS letters wide.

Table 23. Visual acuity bands within the model

Health state	ETDRS letters
HS1	> 80
HS2	66 – 80
HS3	51 – 65
HS4	36 – 50
HS5	<36

Given two eyes, this result in 25 health states as below.

Table 24. Model health states

		Treated eye				
		HS1	HS2	HS3	HS4	HS5
Fellow eye	HS1	1-1	2-1	3-1	4-1	5-1
	HS2	1-2	2-2	3-2	4-2	5-2
	HS3	1-3	2-3	3-3	4-3	5-3
	HS4	1-4	2-4	3-4	4-4	5-4
	HS5	1-5	2-5	3-5	4-5	5-5

The model assumes there is no involvement in the fellow eye and that the BCVA of the fellow eye is constant. As a consequence, only changes in the BCVA of the treated eye are modelled. Patients can transition along the rows of the above table, but not between rows. Blindness applies to those in the 5-5 health state.

5.2.3 Population

The population modelled is as per the pooled COPERNICUS and GALILEO trials: adult patients with visual impairment with macular oedema secondary to central retinal vein occlusion.

The baseline distribution of the patient population between the 25 health states of the model is inferred from the pooled COPERNICUS and GALILEO baseline distributions of the treated eye and the fellow eye, as below.

Table 25. Baseline distribution of treated eye and fellow eye

	Treated eye	Fellow eye
HS1	0.30%	74.69%
HS2	21.34%	20.31%
HS3	39.94%	2.50%
HS4	21.65%	0.63%
HS5	16.77%	1.88%

The model assumes that the distributions are independent, resulting in the following inferred baseline two-eyed patient distribution.

Table 26. Inferred baseline two-eyed distribution of the patient population

		Treated eye				
		HS1	HS2	HS3	HS4	HS5
Fellow eye	HS1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note that the submission states that the BCVA of the fellow eye remained constant over the first 24 weeks of the trials. It is not entirely clear whether this is based upon patient level data or is a modelling assumption.

5.2.4 Interventions and comparators

Aflibercept is compared with ranibizumab and with dexamethasone.

5.2.5 Perspective, time horizon and discounting

The perspective is as per the NICE 2008 *Guide to the methods of technology appraisal*, with benefits being from the patient perspective and costs being from the NHS/PSS perspective.

The time horizon of the model is 30 years, which is effectively a lifetime time horizon given the baseline age of 64 years.

Costs and benefits are discounted at an annual 3.5%.

5.2.6 Treatment effectiveness and extrapolation

Treatment effectiveness: Aflibercept

Since the fellow eye is assumed to have a constant BCVA, only the BCVA of the treated eye needs to be modelled. The transitions for this for the first six months of the model are based upon the pooled individual patient level data of COPERNICUS and GALILEO. For instance, the individual patient level data for the transitions for baseline to the end of week 4 are as below.

Table 27. Individual patient transitions baseline to week 4: COPERNICUS and GALILEO pooled

		End of cycle				
		HS1	HS2	HS3	HS4	HS5
Start of cycle	HS1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Due to there being no patients with a treated eye in HS1 at baseline, it is assumed that there are no transitions out of this health state. This is more for neatness than for any other reason and has no impact upon the modelling. This results in the following transition probability matrix (TPM) for baseline to the end of week 4 for aflibercept.

Table 28. Transition probability matrix baseline to week 4: Aflibercept

		End of cycle				
		HS1	HS2	HS3	HS4	HS5
Start of cycle	HS1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The pooled individual patient level data of COPERNICUS and GALILEO results in six TPMs for the first 24 weeks of the model:

- cycle 1: start of week 0 to end of week 4;
- cycle 2: start of week 5 to end of week 8;
- cycle 3: start of week 9 to end of week 12;
- cycle 4: start of week 13 to end of week 16;
- cycle 5: start of week 17 to end of week 20; and,

- cycle 6: start of week 21 to end of week 24.

The patient numbers underlying these TPMs are given in tables 54 to 59 on pages 158-160 of the submission.

Treatment effectiveness: Ranibizumab

The fixed effects estimate of [redacted] for the relative risk of improving of improving by at least 15 letters at week 24 of the NMA is applied to the aflibercept TPMs' probabilities of improvement. The probabilities of worsening under ranibizumab are assumed to be the same as those for aflibercept. The probability of remaining in the same health state is the residual of these values, such that the rows sum to 100%.

For instance, this results in the following TPM for baseline to the end of week 4 for ranibizumab.

Table 29. Transition probability matrix baseline to week 4: Ranibizumab

		End of cycle				
		HS1	HS2	HS3	HS4	HS5
Start of cycle	HS1	100%	0%	0%	0%	0%
	HS2	35%	59%	6%	0%	0%
	HS3	11%	45%	41%	2%	0%
	HS4	0%	26%	41%	33%	0%
	HS5	0%	15%	17%	22%	46%

Treatment effectiveness: Dexamathasone

The fixed effects estimate of [redacted] for the relative risk of improving of improving by at least 15 letters at week 24 of the NMA is applied to the aflibercept TPMs' probabilities of improvement. As for ranibizumab, the probabilities of worsening are those of aflibercept, and the probability of remaining in the same health state is the residual.

For instance, this results in the following TPM for baseline to the end of week 4 for ranibizumab.

Table 30. Transition probability matrix baseline to week 4: Dexamethasone

		End of cycle				
		HS1	HS2	HS3	HS4	HS5
Start of cycle	HS1	100%	0%	0%	0%	0%
	HS2	17%	77%	6%	0%	0%
	HS3	5%	22%	70%	2%	0%
	HS4	0%	13%	20%	67%	0%
	HS5	0%	7%	8%	11%	74%

Discontinuations

Discontinuations are not taken into account within the model. The manufacturer justifies this on the basis that there was a low overall pooled discontinuation rate of 6.8% in COPERNICUS and GALILEO, the previous ranibizumab STA for RVO had a higher discontinuation rate and the assessment committee for the previous ranibizumab STA for RVO accepted modelling that did not explicitly account for discontinuations.[8]

Adverse events

Adverse events are not included in the base case. The manufacturer justifies this on the basis that aflibercept and ranibizumab used for wet AMD during the VIEW studies[52] showed similar safety profiles with any differences possibly being due to trial design or chance.

A scenario analysis that does include adverse events is presented. Adverse events for the baseline to week 24 are drawn from the pooled COPERNICUS and GALILEO trial data, the Novartis submission for the STA of ranibizumab for RVO and from Haller et al (2010)[28] for dexamethasone.

Table 31. Scenario analysis adverse event rates: Baseline to week 24

	Aflibercept	Ranibizumab	Dexamethasone
Cataract	0.00%	3.30%	7.30%
Raised IOP	7.80%	5.00%	24.0%
Retinal tear	0.50%	0.00%	0.24%

Adverse events are assumed to be proportionate to the number of injections. For instance, the base case applies 5.50 aflibercept injections during baseline to week 24 and the 2.55 aflibercept injections during weeks 24 to 52. This results in the adverse events for aflibercept during weeks 24 to 52 being 2.55/5.50 = 46.4% of those modelled during baseline to week 24. A similar approach is adopted for the comparators.

Extrapolation

During the period from week 24 to end of active treatment stable visual acuity is assumed for all treatments.

Subsequent to the end of treatment a 4 weekly probability of worsening by one health state of 0.0296% is applied. The submission states that this is based upon 7.4% worsening by at least 15 letters over 20 years, as drawn from the Beaver Dam study as reported in Klein et al (1991).[53]

Blindness mortality multiplier

A mortality multiplier of 1.54 drawn from Christ et al (2008)[54] is applied for those modelled as having both eyes falling into HS5. No additional mortality multiplier for CRVO is included.

5.2.7 Health related quality of life

Health states' quality of life

The base case uses the EQ-5D data of the GALILEO European subset of patients to derive quality of life values. EQ-5D data was collected at baseline, week 24, week 52, week 76 and early termination. This data was pooled across the arms and time points and evaluated using the UK social tariff. This was then split by the contemporaneous BCVA of the treated eye to result in the following average quality of life values and standard errors.

Table 32. Base case quality of life values: One-eyed health states

Health state	Quality of life
HS1	[redacted]
HS2	[redacted]
HS3	[redacted]
HS4	[redacted]
HS5	[redacted]

The manufacturer applies these quality of life values to the two-eyed health states as below.

Table 33. Base case quality of life values: Two-eyed health states

		Treated eye				
		HS1	HS2	HS3	HS4	HS5
Fellow eye	HS1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

If the BCVA of the treated eye worsens, the patient moves from left to right along one of the rows. For instance if the fellow eye is in HS1, as the treated eye moves from HS1 to HS5 so the quality of life worsens from [redacted] to [redacted].

But if the fellow eye is in HS3, as the treated eye moves from HS1 to HS3 there is no impact and the quality of life remains at [redacted]. Quality of life is only affected when the treated eye falls below the BCVA of the fellow eye into HS4 and HS5, so becoming the WSE. This causes the quality of life to fall from [redacted] to [redacted] and to [redacted] respectively.

If the fellow eye is in HS5 despite the treated eye being the BSE, changes in its BCVA have no impact upon quality of life.

An additional scenario analysis that uses quality of life values derived from Czoski-Murray et al (2009) is presented.[51] This was an experimental study that used contact lenses to simulate the effects of AMD for an hour among members of the general public. Note that CRVO can affect the whole retina so may have a greater quality of life impact than AMD.

Table 34. Czoski-Murray scenario quality of life values

		Treated eye				
		HS1	HS2	HS3	HS4	HS5
Fellow eye	HS1	0.828	0.828	0.828	0.828	0.828
	HS2	0.828	0.735	0.735	0.735	0.735
	HS3	0.828	0.735	0.627	0.627	0.627
	HS4	0.828	0.735	0.627	0.519	0.519
	HS5	0.828	0.735	0.627	0.519	0.469

The approach adopted for the Czoski-Murray scenario analysis differs noticeably from the base case analysis. If the fellow eye is in HS1, changes in the BCVA of the treated eye have no impact upon quality of life.

If the fellow eye is in HS3, changes in the BCVA of the treated eye affect quality of life when the treated eye is the BSE. As the treated eye moves from HS1 to HS3, the quality of life falls from 0.828 to 0.627. But when the treated eye falls into either HS4 or HS5 and becomes the WSE, it has no impact upon quality of life, which remains at 0.627.

If the fellow eye is in HS5, the treated eye is the BSE and changes in its BCVA affect quality of life over the entire range of health states. The treated eye worsening from HS1 to HS5 worsens the quality of life from 0.828 to 0.469.

Adverse events' quality of life

The disutilities for adverse events are drawn from the literature.

Table 35. Adverse event quality of life impacts

	Disutility
Cataract	0.1420
Raised IOP	0.0003
Retinal tear	0.2700

The model structure divides these amounts by 13, the number of 4 week cycles within a year, the implicit assumption being that the disutility of the adverse events only last for one cycle of 4 weeks.

5.2.8 Resources and costs

Number of administrations

The mean number of aflibercept injections is based upon the average exposure divided by 2mg, the dose size. For the first 24 weeks the pooled COPERNICUS and GALILEO mean exposure of 11.5mg results in an estimate of 5.75 injections on average. Due to cross-over in COPERNICUS, for the subsequent 28 weeks only the mean exposure in GALILEO of 5.1mg is used resulting in an estimate of 2.55 injections on average. This gives a total of 8.30 aflibercept doses during the first year.

The mean number of ranibizumab injections was drawn from Campochiaro et al (2011),[25] with 5.5 injections in the first 24 weeks and 3.3 during the PRN dosing phase of the subsequent 28 weeks. This gives a total of 8.80 ranibizumab doses during the first year.

The mean number of dexamethasone injections is stated as being drawn from the STA of ranibizumab for macular oedema secondary to retinal vein occlusion (TA283),[8] with 1.85 injections in the first 24 weeks and 2.15 injections during the subsequent 28 weeks. This gives a total of 4.00 dexamethasone doses during the first year.

Note that deaths during the first year of the model will tend to slightly reduce the number of administrations. But the effect is minor, given the all-cause mortality of 1.1% in the first year.

Cost of administrations

There is an administration cost of £257.45 outlined in table 88[1] for the administration of aflibercept and ranibizumab. This is based upon 52% outpatient administration and 48% day-case administration. This appears to be based upon Health Episode Statistics, as reviewed later in section 5.3.4. A higher administration cost of £321.49 is applied for dexamethasone, based upon 25% outpatient administration and 75% day-case administration, this being drawn from the Novartis submission for the STA of ranibizumab for RVO (TA283).[8]

Number of monitoring visits

The calculation of the number of monitoring visits for aflibercept and ranibizumab assumes that from baseline to week 24 treatment visits can double as monitoring visits. A one stop model is also adopted for weeks 24 to 52, though the calculation for this is slightly more convoluted.

For week 24 to week 52 it is assumed that 3.50 monitoring visits are required for aflibercept and 4.40 monitoring visits for ranibizumab, based upon the manufacturer survey of experts. These are added to the number of administrations for baseline to week 24 of 5.75 and 5.50 to result in a total year 1 monitoring requirement of 9.25 and 9.90 for aflibercept and ranibizumab respectively. These are then divided by 13, the number of 4 week cycles in a year, to give a per cycle monitoring requirement of 0.71 for aflibercept and 0.76 for ranibizumab during weeks 24 to 52. The number of administrations during weeks 24 to 52 averages to 0.36 and 0.47 per cycle, and as a consequence there is a per cycle dedicated monitoring visit requirement of 0.71-0.36 = 0.35 and 0.76-0.47 = 0.29 for aflibercept and ranibizumab respectively: totals of 2.43 and 2.03 dedicated monitoring visits.

For dexamethasone 6 monitoring visits are assumed to be required from baseline to 52 weeks, based upon the Novartis submission for the STA of ranibizumab for RVO (TA283). The one stop model is applied rather more transparently, with a per cycle administration frequency of 0.31 and a per cycle

[1] Table 98 suggests a cost of £233.

monitoring frequency of 0.46 resulting in a per cycle dedicated monitoring visit frequency of 0.15 throughout the first year: a total of 2.00 dedicated monitoring visits

Cost of monitoring visits

Dedicated monitoring visits are costed at £197.00, being composed of:

- OCT at a cost of £117.26: NHS reference cost for outpatient procedure BZ23Z – Minor Vitreous Retinal Procedures; and,
- An outpatient cost of £79.74: NHS reference cost for ophthalmology consultant led follow up face to face non-admitted.

Note that a common one off cost of £117.26 for fluorescein angiography is applied at the start of treatment for all treatments.

A one stop model is applied, in that it is assumed that treatment visits can double as monitoring visits. The above results in the following first year treatment, administration and monitoring costs.

Table 36. Modelled 1st year drug, administration and monitoring costs summary

	Baseline to week 24			Week 24 to week 52			1st year totals		
	Afli.	Rani.	Dexa.	Afli.	Rani.	Dexa.	Afli.	Rani.	Dexa.
Administrations	5.75	5.50	1.85	2.55	3.30	2.15	8.30	8.80	4.00
Drug cost	£4,692	£4,082	£1,606	£2,081	£2,449	£1,874	£6,773	£6,531	£3,480
Admin cost	£1,480	£1,416	£594	£656	£850	£692	£2,137	£2,266	£1,286
Monitoring	5.75	5.50	2.77	3.50	4.40	3.23	9.25	9.90	6.00
Dedicated	0.00	0.00	0.92	2.43	2.03	1.08	2.43	2.03	2.00
Monitor cost	£0	£0	£182	£479	£400	£212	£479	£400	£394

Adverse event costs

100% of cataracts and retinal tears are assumed to require treatment, with all these treatments being as inpatients. Based upon the manufacturer expert survey it is assumed that 43% of cases of raised IOP require treatment, and that of these 3% will require inpatient treatment. The balance between inpatient treatments and between medications for those treated as outpatients is drawn from the Novartis submission for the STA of ranibizumab for RVO (TA283). No additional cost for an outpatient visit is included, presumably on the basis that raised IOP would be picked up and treated during a routine administration or monitoring visit. This results in the following treatment costs.

Table 37. Costs of adverse events

	Treated	As OP	OP Cost	As IP	IP Cost	Mean
Cataract	100%	0%	£0	100%	£851	£851
Raised IOP	53%	97%	£51	3%	£906	£33
Retinal tear	100%	0%	£0	100%	£424	£424

The costs of blindness

The model applies a first year cost of blindness of [redacted] and an annual cost of blindness of [redacted] thereafter, based upon the ERG report for the STA of ranibizumab of retinal vein occlusion (TA283).

5.2.9 Cost effectiveness results

For the comparison with ranibizumab the deterministic base case results are presented below.

Table 38. Base case deterministic results excluding PAS: vs ranibizumab

	Aflibercept	Ranibizumab	Net
Total cost	[redacted]	[redacted]	[redacted]
Drug cost (excl. PAS)	[redacted]	[redacted]	[redacted]
Admin cost	[redacted]	[redacted]	[redacted]
Monitoring cost	[redacted]	[redacted]	[redacted]
AE (incl. blindness) cost	[redacted]	[redacted]	[redacted]
OS undiscounted[2]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	0.054
ICER	[redacted]	[redacted]	[redacted]

The corresponding probabilistic results from the model run over 2,000 iterations are presented below.

[2] Taken from cell AI7 of the relevant cohort flow worksheets of the electronic model.

Table 39. Base case probabilistic results excluding PAS: vs ranibizumab

	Excluding the aflibercept PAS		
	Δ cost	Δ QALY	ICER
Mean	[redacted]	0.050	[redacted]
WTP/QALY	Probability aflibercept cost effective		
£0	34.3%		
£10k	63.5%		
£20k	76.1%		
£30k	81.3%		
£50k	84.5%		
£100k	87.2%		

Aflibercept has had a PAS discount of [redacted] approved, reducing the unit cost from £816 to [redacted]. Unfortunately, the ranibizumab PAS has not been shared with the manufacturer for this submission. As a consequence, scenario analyses have been performed that apply varying PAS percentages for ranibizumab.

Table 40. Base case deterministic results including PAS: vs ranibizumab

	Aflibercept		Ranibizumab			
Ranibizumab PAS	Drug	Total	Drug	Total	net Total	ICER
0%	[redacted]	[redacted]	[redacted]	[redacted]	-£2,937	Dominant
10%	[redacted]	[redacted]	[redacted]	[redacted]	-£2,286	Dominant
15%	[redacted]	[redacted]	[redacted]	[redacted]	-£1,961	Dominant
20%	[redacted]	[redacted]	[redacted]	[redacted]	-£1,636	Dominant
25%	[redacted]	[redacted]	[redacted]	[redacted]	-£1,311	Dominant
30%	[redacted]	[redacted]	[redacted]	[redacted]	-£986	Dominant
35%	[redacted]	[redacted]	[redacted]	[redacted]	-£660	Dominant
40%	[redacted]	[redacted]	[redacted]	[redacted]	-£335	Dominant
45%	[redacted]	[redacted]	[redacted]	[redacted]	-£10	Dominant
50%	[redacted]	[redacted]	[redacted]	[redacted]	£315	£5,871.00

For the comparison with dexamethasone the deterministic base case results are presented below.

Table 41. Base case deterministic results: vs dexamethasone

	Aflibercept	Dexamethasone	Net
Total cost (excl. PAS)	[redacted]	[redacted]	[redacted]
Total cost (incl. PAS)	[redacted]	[redacted]	£612
Drug cost (excl. PAS)	[redacted]	[redacted]	[redacted]
Drug cost (incl. PAS)	[redacted]	[redacted]	[redacted]
Admin cost	[redacted]	[redacted]	[redacted]
Monitoring cost	[redacted]	[redacted]	[redacted]
AE (incl. blindness) cost	[redacted]	[redacted]	[redacted]
OS undiscounted	19.054	19.049	0.005
QALYs	[redacted]	[redacted]	0.189
ICER (excl. PAS)			[redacted]
ICER (incl. PAS)			**£3,236**

The corresponding probabilistic results from the model run over 2,000 iterations are presented below.

Table 42. Base case probabilistic results: vs dexamethasone

	Excluding the aflibercept PAS			Including the aflibercept PAS		
	Δ cost	Δ QALY	ICER	Δ cost	Δ QALY	ICER
Mean	[redacted]	0.190	[redacted]	£598	0.192	£3,109
WTP/QALY	Probability aflibercept cost effective			Probability aflibercept cost effective		
£0	0.0%			5.9%		
£10k	0.5%			98.0%		
£20k	51.6%			99.8%		
£30k	88.4%			100.0%		
£50k	98.7%			100.0%		
£100k	99.9%			100.0%		

5.2.10 Sensitivity and scenario analyses

A number of one way sensitivity analyses for the comparison with ranibizumab are presented. These explore:

- the baseline age;
- the relative risk of gaining letters at week 24;
- the rate of worsening after the end of treatment in the aflibercept arm;
- the rate of worsening after the end of treatment in the ranibizumab arm;
- the mortality multiplier for blindness;

- the health state utilities;
- the frequencies of administrations;
- the frequencies of monitoring;
- the costs of administration and of monitoring; and,
- the costs of blindness.

These one way sensitivity analyses result in the following.

Table 43. One way sensitivity analyses: excluding the PAS

				Low value			High value		
	Base	Low	High	Δ Cost	Δ QALY	ICER	Δ Cost	Δ QALY	ICER
Age	64.0	62.6	65.4	[redacted]	0.057	[redacted]	[redacted]	0.052	[redacted]
RR gain	[redacted]	[redacted]	[redacted]	[redacted]	0.145	[redacted]	[redacted]	-0.048	[redacted]
Prog. Afli.	0.0003	0.0002	0.0004	[redacted]	0.055	[redacted]	[redacted]	0.052	[redacted]
Prog. Rani.	0.0003	0.0002	0.0004	[redacted]	0.052	[redacted]	[redacted]	0.055	[redacted]
HR blind mort	1.54	1.28	1.86	[redacted]	0.053	[redacted]	[redacted]	0.054	[redacted]
Utilities									
HS1	[redacted]	[redacted]	[redacted]	[redacted]	0.040	[redacted]	[redacted]	0.067	[redacted]
HS2	[redacted]	[redacted]	[redacted]	[redacted]	0.042	[redacted]	[redacted]	0.066	[redacted]
HS3	[redacted]	[redacted]	[redacted]	[redacted]	0.066	[redacted]	[redacted]	0.042	[redacted]
HS4	[redacted]	[redacted]	[redacted]	[redacted]	0.067	[redacted]	[redacted]	0.041	[redacted]
HS5	[redacted]	[redacted]	[redacted]	[redacted]	0.068	[redacted]	[redacted]	0.040	[redacted]
Administration frequency									
Afli. 00-24	5.75	[redacted]	[redacted]	[redacted]	0.054	[redacted]	[redacted]	0.054	[redacted]
Afli. 24-52	2.55	[redacted]	[redacted]	[redacted]	0.054	[redacted]	[redacted]	0.054	[redacted]
Rani. 00-24	5.50	[redacted]	[redacted]	[redacted]	0.054	[redacted]	[redacted]	0.054	[redacted]
Rani. 24-52	3.30	[redacted]	[redacted]	[redacted]	0.054	[redacted]	[redacted]	0.054	[redacted]
Monitoring frequency									
Afli. yr1	9.25	[redacted]	[redacted]	[redacted]	0.054	[redacted]	[redacted]	0.054	[redacted]
Rani. yr1	9.90	[redacted]	[redacted]	[redacted]	0.054	[redacted]	[redacted]	0.054	[redacted]
Admin cost	£233	[redacted]	[redacted]	[redacted]	0.054	[redacted]	[redacted]	0.054	[redacted]
Monitor. cost	£197	[redacted]	[redacted]	[redacted]	0.054	[redacted]	[redacted]	0.054	[redacted]
OP admin	52%	[redacted]	[redacted]	[redacted]	0.054	[redacted]	[redacted]	0.054	[redacted]
Vision loss yr1	[redacted]	[redacted]	[redacted]	[redacted]	0.054	[redacted]	[redacted]	0.054	[redacted]
Vision loss yr2	[redacted]	[redacted]	[redacted]	[redacted]	0.054	[redacted]	[redacted]	0.054	[redacted]

Results are sensitive to the relative risk of visual gain, with aflibercept being dominated if the upper bound of 1.18 applies.

There is some sensitivity to the utility values which are applied. But these sensitivity analyses may be of limited usefulness as they vary only one utility at a time with the values applied sometimes resulting in perverse utility values when viewed alongside those of adjoining health states.

As would be expected, results are sensitive to the dosing frequencies that are applied, and to a lesser degree the monitoring frequencies.

Three scenario analyses are also conducted for the comparison with ranibizumab:

- Czoski-Murray et al (2009) quality of life values, as outlined above;
- Including adverse events, as outlined above; and,
- Treatment durations of 2 years and 4 years as stated within the submission, though examination of the electronic model suggests that the latter is 5 years[3].

For the scenario analyses of treatment durations of 2 years and 4 years, administrations in the 2nd year of 3.5 for aflibercept and 3.8 for ranibizumab are drawn from the COPERNICUS week 100 study report and the Novartis submission for the STA of ranibizumab for RVO (TA283). Dosing for years 3, 4 and 5 was drawn from the manufacturer expert survey, with 3.0 doses of both aflibercept and ranibizumab in year 3, and 1.8 doses of aflibercept and 2.2 doses of ranibizumab in year 4. Monitoring frequencies were mainly drawn from the manufacturer expert survey.

Table 44. Administration and monitoring frequencies for scenario analyses

	0-24wk	24-52wk	Year 2	Year 3	Year 4	Year 5
Administrations						
Aflibercept	5.75	2.55	3.50	3.00	1.80	1.00
Ranibizumab	5.50	3.30	3.80	3.00	2.20	1.60
Monitoring						
Aflibercept	5.75	3.50	4.80	3.80	3.20	2.40
Ranibizumab	5.50	4.40	5.80	4.40	3.80	2.80

These result in the following.

[3] The drug costs of column HD of the markov worksheets stretch down to row 75 which corresponds to the end of cycle 64.

Table 45. Scenario analyses versus ranibizumab: excluding the PAS

	Δ Cost	Δ QALY	ICER
Czoski-Murray utilities	[redacted]	0.028	[redacted]
With adverse events	[redacted]	0.054	[redacted]
2 year treatment duration	[redacted]	0.054	[redacted]
4 year treatment duration	[redacted]	0.054	[redacted]

5.2.11 Model validation and face validity check

The submission provides the following validation data for the model in tables 102 and 103 on pages 231-232. The 24 week data is drawn from the pooled results in section 2.3.4 of the submission for aflibercept and from Brown et al (2010)[24] for ranibizumab. The 52 week data is drawn from the GALILEO data in section 6.5 of the submission for aflibercept and from Brown et al (2010)[24] and Campochiaro et al (2011)[25] for ranibizumab. Note that for aflibercept the mean baseline BCVA for the 24 week validation differs from that for the 52 week validation. No validation data is supplied for the comparison with dexamethasone.

Table 46. Manufacturer validation: trial data and model outputs: mean BCVAs of treated eye

	24 week comparison				52 week comparison			
	Baseline	24 week	vs Sham	vs Rani.	Baseline	52 week	vs Sham	vs Rani.
Trial results								
Afli.	52.0	69.7	18.2	4.1	53.6	70.4	13.0	6.4
Sham	49.9	49.4			50.9	54.7		
Rani.	48.1	63.0	14.1		48.1	62.0	6.6	
Sham	49.2	50.0			49.2	56.5		
Manufacturer validation exercise modelling results								
Afli.	53.0	70.7	..	3.1	53.0	70.3	..	3.1
Rani.	53.0	67.6	..		53.0	67.2	..	

The 24 week comparison of the manufacturer suggests that the model outputs are reasonably aligned with the trial data, but that the benefits of aflibercept may be slightly understated by the model.

The 52 week comparison of the manufacturer suggests that the model outputs are quite badly misaligned with the trial data, and that the model considerably understates the benefits of aflibercept. But in common with the COPERNICUS trial, the ranibizumab CRUISE trial also had cross-over to active treatment at 24 weeks and as a consequence this comparison is invalid.

5.3 *ERG cross check and critique*

5.3.1 Base case results

The base case results of the submission cross check with those of the submitted electronic model for the comparison with ranibizumab. But the base case results for the comparison with dexamethasone differ slightly.

Table 47. Electronic model base case results versus dexamethasone

	Aflibercept	Dexamethasone	Net
Total cost (excl. PAS)	[redacted]	[redacted]	[redacted]
Total cost (incl. PAS)	[redacted]	[redacted]	£664
Drug cost (excl. PAS)	[redacted]	[redacted]	[redacted]
Drug cost (incl. PAS)	[redacted]	[redacted]	[redacted]
Admin cost	[redacted]	[redacted]	[redacted]
Monitoring cost	[redacted]	[redacted]	[redacted]
AE (incl. blindness) cost	[redacted]	[redacted]	[redacted]
OS undiscounted	19.054	19.049	0.005
QALYs	[redacted]	[redacted]	0.189
ICER (excl. PAS)			[redacted]
ICER (incl. PAS)			**£3,522**

The with and without PAS ICERs of the electronic model of [redacted] per QALY and £3,522 per QALY contrast with those of the written submission of [redacted] per QALY and 3,236 per QALY respectively. The ICERs of the written submission are for the scenario of adverse events being included within the modelling.

Model validation

The trial values reported in the manufacturer validation exercise cross check with those reported in table 15 of the submission and Brown et al (2011). But it seems to be more appropriate to compare the model results with those of the manufacturer NMA of Table 37 on page 105 of the submission. The ERG also cannot quite replicate the modelled results of the manufacturer validation exercise.

Limiting the lowest value for the worst health state to 20 letters to give a 15 wide letter health state results in a baseline mean of 52.0 letters, the closest the ERG can achieve to the manufacturer's 53.0 letters. This then results in the following central values for the health states' BCVA:

- HS1: (100+80)/2 = 90 letters

- HS2: (79+65)/2 = 72 letters
- HS3: (64+50)/2 = 57 letters
- HS4: (49+35)/2 = 42 letters
- HS5: (35+20)/2 = 27 letters

Applying these values within the model results in the following.

Table 48. ERG validation vs manufacturer validation: model outputs: mean BCVAs of treated eye

	24 week comparison				52 week comparison			
	Baseline	24 week	vs Sham	vs Rani.	Baseline	52 week	vs Sham	vs Rani.
Manufacturer validation exercise modelling results								
Afli.	53.0	70.7	..	3.1	53.0	70.3	..	3.1
Rani.	53.0	67.6	..		53.0	67.2	..	
ERG cross check of validation exercise modelling results								
Afli.	52.0	70.9		3.3	52.0	70.9		3.3
Rani.	52.0	67.6			52.0	67.6		

These values result in modelled gains from aflibercept over ranibizumab of 3.33 letters at both week 24 and week 52. Note that they also result in a modelled mean BCVA of 58.35 letters in the dexamethasone arm at both week 24 and week 52, and a gain from aflibercept of 12.59 letters.

In the light of this, it is unclear what BCVAs the manufacturer has assumed for the health states during its validation exercise. It is also unclear why the manufacturer validation suggests a decline in the modelled mean BCVA between week 24 and week 52.

Table 37 on page 105 of the submission provides a fixed effects estimate for the mean 24 week change in the BCVA of 3.46 letters for aflibercept compared to ranibizumab, and of 15.57 letters compared to dexamethasone.

- The ERG cross check of the model outputs of a 3.33 letter gain for aflibercept compared to ranibizumab is closely aligned with the 3.46 letters of table 37.
- The ERG cross check of the model outputs of a 12.59 letter gain for aflibercept compared to dexamethasone is somewhat less than the 15.57 letters of table 37, suggesting that the model underestimates the gain from aflibercept compared to dexamethasone.

5.3.2 Data Inputs: Correspondence between written submission and sources cited

The following data inputs cross check with the sources cited:

- The adverse event rates for dexamethasone

- The balance between medications for those having their raised IOP treated with medications
- The balance between procedures for those having their raised IOP treated by surgery
- The 1.54 blindness mortality multiplier

Dexamethasone dosing and monitoring

The assumption of 4 doses of dexamethasone during the first year is stated as being drawn from the STA of ranibizumab for RVO (TA283). Table B62 of the Novartis submission for the STA of ranibizumab for RVO suggests only 2 doses of dexamethasone during the first year, a total of 8 visits being required so resulting in 6 dedicated monitoring visits.

Table 109 of the Allergan submission for the STA of dexamethasone for RVO (TA229)[7] provides the pooled GENEVA trials data for CRVO patients for baseline and month 6, and supplements this with expert opinion from the Allergan New York expert panel. This suggested the following:

Table 49. Dexamethasone CRVO dosing for the STA of dexamethasone for RVO

	% dosed
Baseline	100%
6 months	86%
12 months	63%
18 months	63%
24 months	37%
30 months	37%

The SPC for dexamethasone states:

> "*The recommended dose is one OZURDEX implant to be administered intra-vitreally to the affected eye. Administration to both eyes concurrently is not recommended.*
> *Repeat doses should be considered when a patient experiences a response to treatment followed subsequently by a loss in visual acuity and in the physician's opinion may benefit from retreatment without being exposed to significant risk.*
> *Patients who experience and retain improved vision should not be retreated. Patients who experience a deterioration in vision, which is not slowed by OZURDEX, should not be retreated.*
> *There is only very limited information on repeat dosing intervals less than 6 months. There is currently no experience of repeat administrations in posterior segment non-infectious uveitis or beyond 2 implants in Retinal Vein Occlusion.*
> *Patients should be monitored following the injection to permit early treatment if an infection or increased intraocular pressure occurs.*"

In the light of this either 2.00 doses or 1.86 doses of dexamethasone during the first year seems more reasonable. The 1.86 doses from the pooled GENEVA data for the CRVO is aligned with the clinical effectiveness data, and so seems to be the most reasonable to use for the base case.

Table 14 of the ERG report for the STA of dexamethasone for RVO notes that for CRVO patients the effect of the implant peaked at day 60 as measured by both the proportion gaining at least 15 letters and the mean letters gained, 29% and 9 letters. These both declined slightly between day 60 and day 90. Between day 90 and day 180 while the proportion gaining at least 15 letters was maintained at 18%, the mean letters gained had fallen back to zero. This could be seen as suggesting a need for retreatment at day 90 or day 120 among a significant proportion of patients and an average annual dose of perhaps around 3 or 4 administrations. But ERG expert opinion is that this is unlikely due to safety concerns, though these might be slightly allayed if there has been no increase in pressure and if the patient is pseudophakic.

The values from the New York Panel can also be used for sensitivity analyses around the appropriate duration of therapy.

Adverse event rates

The 6 month rates of cataract and raised IOP requiring medication for aflibercept cross check with those of table 44 of the submission. The ERG has not been able to source the 0.50% rate of retinal tears within the submission, the text on page 112 of the submission noting [redacted]. Holz et al (2013)[20] report 1 retinal tear in the aflibercept arm between baseline and week 24 during GALILEO, and Brown et al (2013)[19] report none in the aflibercept arm between baseline and week 24 during COPERNICUS. The 0.50% corresponds with the rate reported by Holz et al for GALILEO, but seems slightly too high for the pooled analysis.

Brown et al (2010) report 1.6% with cataracts, and 0.0% with retinal tears by month 6 in the ranibizumab 0.5mg arm. The 1.6% for cataracts also cross checks with table B33 of the Novartis submission for the STA of ranibizumab for RVO, and is slightly lower than the 3.3% of the base case. The ERG cannot source the proportion with raised IOP from Brown et al, but table B48 of the economics section of the Novartis submission for the STA of ranibizumab for RVO gives a pooled value for the BRAVO and CRUISE trial of 10%. This rate may relate to 12 months, suggesting the 5.0% that is applied for the first 6 months in the manufacturer base case.

Haller et al (2010) report 7.3% with cataracts, 24% requiring IOP medication and 0.24% with retinal detachment for dexamethasone 0.7mg by day 180. They also report that 3 patients out of the 427 randomised to dexamethasone 0.7mg, 0.70%, required surgery to reduce their IOP.

Rate of visual worsening

The text supplied in the manufacturer reference pack for Klein et al (1991)[53] does not report the values used within the submission. But even accepting these figures, it seems likely that some will have worsened by rather more than just 15 letters over 20 years. The 0.296% rate of worsening by 15 letters each 4 week cycle may be a lower bound. Consequently, sensitivity analyses increasing this rate are desirable.

Adverse events quality of life impacts

The adverse event quality of life impacts for cataract and retinal tear cross check with Brown et al (2007),[55] though these are in turn derived from a further study of pegaptinib for AMD. But Brown et al assume that the disutilities will apply for 3 months for cataract and for 4 months for retinal tears.

The ERG could not directly source the 0.0003 four week disutility for raised IOP from Vaahtoranten-Lehtonen et al (2007)[4].[56] It may also be quite low if it includes neo-vascular glaucoma, which occurs in a third of ischaemics. It is unclear how the disutility of 0.0003 could have been derived from the utility data within the reference. The Novartis submission for the STA of ranibizumab for RVO cites the same source but gives an estimate of a 0.01 disutility for raised IOP. This is the also the value given in table 96 of the submission. The manufacturer has multiplied the 0.01 by 0.03 to arrive at the 0.0003 QALY impact. The intention appears to be to divide it by 365 to yield one day's duration of disutility, which would require multiplication by approximately 0.003. This is then further divided by 13 within the model structure.

5.3.3 Data Inputs: Correspondence between written submission and electronic model

Administration and monitoring costs

The electronic model applies an administration cost of £233.34 for aflibercept and dexamethasone and £321.49 for dexamethasone. This compares with £257.45 of table 88 on page 207 of the submission, though table 98 of the submission that summarises the sensitivity analyses does list £233 as the base case value for aflibercept and ranibizumab.

Costs of raised IOP

[4] Accessed online at http://onlinelibrary.wiley.com/doi/10.1111/j.1600-0420.2007.00947.x/full#t7 3 October 2013.

The rates of adverse events are adjusted to give an average per cycle rate. Despite this, the costs of medication for raised IOP are also divided by 13 and the costs of inpatient therapies are also divided by 6. This reduces the cost for raised IOP that is applied within the modelling from £33 to £4.

Overall survival

The modelled average overall survival figures of table 114 on page 254 of the submission is given as 18.977 years for aflibercept and 18.976 years for ranibizumab. For dexamethasone table 120 on page 262 of the submission suggests an overall survival of 18.976 years. This does not appear to correspond with the values in cells AI7 of the relevant cohort flow worksheets which suggest 19.054 years for aflibercept, 19.053 years for ranibizumab and 19.049 years for dexamethasone.

5.3.4 ERG commentary on model structure, assumptions and data inputs

The ERG has rebuilt the manufacturer model on the basis of transition probability matrices being applied to the start of period distributions. Mortality is applied to the end of period distributions, resulting in the next period start of period distribution. Adopting the manufacturer assumptions within this modelling framework as far as is practicable results in the following.

Table 50. Manufacturer deterministic results and ERG model rebuild: excl. PAS

	Manufacturer model			ERG rebuild		
	Aflibercept	Ranibizumab	Dexameth*.	Aflibercept	Ranibizumab	Dexameth*.
Total cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Admin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Monitoring	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blind cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
*Excluding adverse events						

The ERG cross check model rebuild estimates slightly lower total QALYs for all the comparators, but this applies equally with a loss of 0.008 QALYs throughout. The ICERs are in line with those of the manufacturer model.

The only real discrepancy is with the cost of blindness estimate for dexamethasone, with the manufacturer model estimating [redacted] compared to only [redacted] for the ERG cross check model rebuild. This arises due to the manufacturer model only considering incidence events of blindness within the aflibercept and ranibizumab arms, but incident events and the prevalence of blindness in the

dexamethasone cohort flow. The approach used for the dexamethasone cohort flow appears to be more correct. Within the ERG cross check rebuild, adopting this approach increases the costs of blindness to £[redacted] in the aflibercept arm, to £[redacted] in the ranibizumab arm and to £[redacted] in the dexamethasone arm. This improves the cost effectiveness of aflibercept compared to ranibizumab to [redacted] per QALY and improves the cost effectiveness of aflibercept compared to dexamethasone to [redacted] per QALY

Observed data versus LOCF

The clinical effectiveness is based upon missing values having LOCF, as outlined in table 9 on page 45 of the submission. The manufacturer response to ERG clarification question B7 outlines that the transitions underlying the economics are based upon observed data. It also states that "*updated FAS observed data (based on a more recent cut of the data) show a more predictable variation pattern*". The manufacturer then switches to LOCF data for its responses to ERG clarification questions B8 to B20 which further confuses matters.

The impact of and reasons for using the observed data rather than the LOCF that was used for the clinical effectiveness estimates is unclear. The manufacturer response to ERG clarification question B7 also makes it unclear as to what data cut was used for the economics and how this relates to the data cut used for the clinical effectiveness estimates. It would be good to know the date of the data cut the underlies the TPM data within the model, the date of the subsequent data cut alluded to in the manufacturer response to ERG clarification question B7 and the date of the data cut that underlies the clinical effectiveness estimates.

Compounding of the week 24 relative risks

The model applies the week 24 relative risks of improving by at least 15 letters to each of the six the TPMs of the six 4 weekly cycles of baseline to week 24; i.e. the week 24 relative risks are applied 6 times within the model. The possible compounding effect of this reapplication of the week 24 relative risks is not obvious. But it can be explored by comparing the model outputs at week 24 with those that would result from the single use of the baseline to 24 week aflibercept TPM as supplied by the manufacturer in answer to ERG clarification question B20. For reasons that will become clear, this is best combined with the lack of any consideration of the relative risk of losing letters within the modelling.

Relative risk of losing ≥15 letters at 6 months

The model does not incorporate the relative risk of losing 15 or more letters at 6 months. The ranibizumab and aflibercept trials reported the following proportions losing letters, with the

corresponding figure for the CRVO subset of the pooled dexamethasone trials being drawn from table 29 of the Allergan submission for the STA of dexamethasone for RVO.

Table 51. Proportions losing 15 or more letters by month 6

Trial	Active treatment arm	Sham arm
GENEVA (dexamethasone)	14.0%	20.4%
CRUISE (ranibizumab)	1.5%	16.9%
GALILEO (aflibercept)	7.8%	22.1%
COPERNICUS (aflibercept)	1.8%	27.4%

These results in the manufacturer's central estimate for the relative risk of losing 15 or more letters at 6 months of [redacted] with this being in favour of ranibizumab. The confidence interval around this relative risk of losing 15 or more letters is [redacted]. This [redacted] than the confidence interval around the [redacted] relative risk of gaining 15 or more letters [redacted].

The relative risk of losing 15 or more letters at 6 months for dexamethasone was not estimated by the manufacturer, but the above strongly suggests that it would be greater than unity, with this being in favour of aflibercept.

The manufacturer in response to ERG clarification question B6 justifies this since "*applying the RR of losing 15 letters in addition to the RR of gaining 15 letters, we believe would be double counting the effectiveness of aflibercept*". The ERG does not understand this statement.

The manufacturer is correct to note that it is important within the TPMs to ensure that each row sums to unity. Applying the relative risk of losing letters would require that the model catch any instances where this ceased to be the case, as may occur within the probabilistic analysis, and normalise the rows to sum to unity.

A simple means of achieving this, while slightly ad hoc, is to populate the ranibizumab probabilities gaining letters and losing letters. If these sum to less than unity the probability of remaining in the same health state would simply be the residual as per the submitted model. If these sum to more than unity the probability of remaining in the same health state would be zero, with the remaining probabilities being reduced by an equal proportion such that they sum to unity.

It is important to bear in mind that that this adjustment is not required for the deterministic analysis. Within the deterministic analysis, inclusion of the [redacted] relative risk of losing more than 15 letters

never causes the probabilities of moving from one health state to another within the rows of the TPMs to exceed 68%. This adjustment is only required as a failsafe for the probabilistic analysis[5].

The model does not take into account the relative risk of worsening by at least 15 letters at 24 weeks. While the relative risk of gaining letters by week 24 favours aflibercept, the relative risk of losing letters by week 24 favour ranibizumab. Including the manufacturer estimate of [redacted] for the relative risk of losing letters by week 24 causes the estimated patient gains from aflibercept compared to ranibizumab to all but disappear. However, this revision to the manufacturer model, while seemingly correct in principle, suggest a net gain at week 24 of only 0.36 letters. This compares with the unamended model estimate of 3.33 letters, and the NMA estimate of 3.46 letters.

But this is within the context of the six TPMs from baseline to week 24 all having the week 24 relative risks applied to them. If the single aflibercept TPM for baseline to week 24 has the week 24 relative risks applied to it the modelled gain from aflibercept over ranibizumab at week 24 is 3.49 letters if only the week 24 relative risk of gaining letters is applied and is 3.32 letters if both the week 24 relative risk of gaining letters and the week 24 relative risk of losing letters are applied.

[5] Given the width of the confidence interval around the [redacted] relative risk of losing letters, it is also important that it be included in the probabilistic analysis. Note that the log-normal implementation of the distribution for the relative risk of gaining letters, with its standard deviation being inferred from the 95% confidence interval divided by 2*1.96, returns a mean value of [redacted] over 5,000 iterations which is slightly different from the central estimate of [redacted]. The parallel log-normal implementation of the distribution for the relative risk of losing letters returns a mean value of [redacted] over 5,000 iterations which is rather more adrift from the central estimate of [redacted]. This seems likely to be due to the distribution for the relative risk of losing letters being somewhat more skewed, possibly due to it approaching the lower boundary of 0. The proportion of iterations simulated as being less than 1 is [redacted] for the relative risk of gaining letters, and is [redacted] for the relative risk of losing letters. This would apply within any modelled of the relative risks of losing letters, but since the model structure of 6 TPMs in the first six months when applying the relative risk of losing letters does not result in outputs that are aligned with the validation data, this probabilistic modelling has not been undertaken by the ERG.

Table 52. The numbers of TPMs, compounding relative risks and the risk of losing letters

	HS1	HS2	HS3	HS4	HS5	Mean letters	Net letters
Baseline	0.3%	21.3%	39.9%	21.6%	16.8%	52.02	
Aflibercept 24 weeks							
6 TPM	29.9%	41.7%	18.1%	5.7%	4.5%	70.94	
1 TPM	29.5%	40.1%	19.6%	6.2%	4.6%	70.44	
Ranibizumab 24 week: only 24 week RR gain							
6 TPM	**23.4%**	**40.1%**	**22.1%**	**7.8%**	**6.6%**	**67.61**	**3.33**
1 TPM	24.1%	36.5%	23.3%	9.0%	7.1%	66.95	3.49
Ranibizumab: 24 week RR gain and 24 week RR loss							
6 TPM	30.3%	39.3%	19.3%	6.9%	4.3%	70.57	0.36
1 TPM	**24.1%**	**36.7%**	**23.6%**	**9.1%**	**6.6%**	**67.12**	**3.32**

As can be seen from the above, the modelled week 24 distributions for aflibercept are quite similar regardless of whether the six 4 week TPMs are applied or the one 24 week TPM is applied.

The main question is whether the approach of the submitted model week 24 distribution for ranibizumab that applies the six 4 week TPMs and the 24 week relative risk of gaining letters is much different from that which would result from the more conceptually correct application of the one 24 week TPM coupled with both the 24 week relative risk of gaining letters and the 24 week relative risk of losing letters. The main differences arise across HS2 to HS4, but it can be argued that these differences broadly parallel those of the differences in the modelled week 24 distributions for aflibercept. For the deterministic base case, given the TPMs and the relative risks which approach is adopted may not be particularly important for the comparison with ranibizumab.

But never- the-less, the above similarity between the approaches arises by chance and only applies to the base case deterministic comparison of aflibercept with ranibizumab. The correct model structure would seem to be to model the week 24 distribution of patients based upon the baseline patient distribution, the week 24 relative risk of gaining letters and the week 24 relative risk of losing letters. The distributions for the intervening points could have been reasonably interpolated from the resulting baseline and week 24 values, much as occurred within the manufacturer submission for the STA of aflibercept for wet AMD (TA294).[10]

The validation data suggests that the model as submitted quite significantly underestimates the benefit of aflibercept over dexamethasone. This may arise due to the model not taking into account the relative risk of worsening by at least 15 letters at 24 weeks. It seems likely that a formal analysis of

this data would suggest that the risk of losing letters by week 24 is somewhat higher with dexamethasone than with aflibercept. It also seems likely that had the model structure been more closely aligned with the data logic, with the 24 week distributions being based upon the single baseline to 24 week TPM coupled with both a 24 week relative risk of gaining letters and a 24 week relative risk of losing letters, that its outputs for the comparison with dexamethasone would have been more closely aligned with the validation data.

Extrapolation

The model assumes a constant visual acuity in the treated eye during the treatment period after 6 months, followed by a slow decline thereafter. This applies to all treatments and as a consequence any gain modelled at 6 months largely persists for the duration of the model, with the slight proviso of there being the floor effect from HS5. It may not be reasonable to anticipate a lifetime duration of benefit from one year of treatment, and this assumption may tend to exaggerate the QALY gain.

Drop-out rates

The pooled discontinuation rate of 6.8% for aflibercept cross checks with that reported at 24 weeks in figures 4 and 5 on pages 48 and 49 of the submission: 4.3% for COPERNICUS and 9.4% for GALILEO. The manufacturer is also correct to note a higher discontinuation rate for ranibizumab, Campochiaro et al (2011)[25] reporting 119 of 130 patients completing the first six months, implying a drop-out rate of 8.5% at 24 weeks. But Haller et al (2010)[28] reports that 24 of the 427 randomised to 0.7mg dexamethasone had discontinued by day 180, a slightly lower discontinuation rate of 5.6%.

The clinical effectiveness estimates for week 24 and the numbers of doses from baseline to week 24 and from week 24 to week 52 are specific to those randomised to aflibercept and ranibizumab. As a consequence, there is no obvious reason for the slightly lower drop-out rate at week 24 for aflibercept to bias the base case.

The higher drop-out rate at week 24 of 9.4% for GALILEO is mirrored in the drop-out rate at of 14.2% at week 52. This compares with Campochiaro et al (2011) reporting a 114 of 130 patients completing the first twelve months of CRUISE, implying a drop-out rate of 12.3% at 52 weeks for ranibizumab.

It is conceivable that the drop-out rates could suggest some slight bias for the scenario analyses which lengthen the duration of treatment to beyond one year if the assumed number of doses does not reflect drop-out rates. But any effect seems likely to be slight.

EQ-5D values: correspondence between clinical effectiveness and economics sections

The clinical effectiveness section of the submission on pages 77 and 78 reports the adjusted differences in EQ-5D utilities between treatment groups, but only quantifies these at week 24. The ERG clarification question B1 requests further information about what adjustments were made, and also requests the adjusted values at weeks 24, 52 and 76. The manufacturer response does not outline what adjustments were made, and only supplies the unadjusted values.

Note also that the EQ-5D data supplied in response to ERG clarification question B2 is split by two-eyed health states as determined by the BCVA of the treated eye and the BCVA of the fellow eye, this applying to all time points including baseline. But the baseline patient distribution applied within the model is based upon the split in one-eyed health states, it apparently not being possible to arrive at the baseline distribution of two-eyed health states with the manufacturer stating that "*the distribution of patients across the 25 health states is not known*". This raises questions about either the calculation of the baseline patient distribution or the EQ-5D data within the submission and supplied at clarification.

EQ-5D values: implementation within the model

Bearing in mind that patients cannot cross over from one fellow eye health state to another but rather can only travel along the rows, the implementation of the EQ-5D values within the trial appears odd.

Table 53. Base case EQ-5D values: Two-eyed health states

		Treated eye				
		HS1	HS2	HS3	HS4	HS5
Fellow eye	HS1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

For instance, if a patient's fellow eye is in HS5 by definition their treated eye must be the BSE. Changes in the BCVA of the treated eye would consequently be anticipated to have an impact upon the patient's quality of life. But there is none.

The degree to which the above is conservative, as argued by the manufacturer, depends upon the degree to which the treated eye is or crosses over to be the BSE; i.e. to what extent are the values below the principal diagonal are actually applied within the modelling. The baseline distribution suggests that 2.55% of treated eyes are the BSE at baseline, though this is with the caveat as to the calculation of the baseline two-eyed distribution as previously noted. The modelling suggests that,

within the aflibercept arm, the proportion who have their treated eye as their BSE peaks at 24 weeks at 10.20%.

In the light of this, while the implementation is perhaps slightly peculiar, the impact upon the model may not be too severe. It will also tend to be conservative and reduce the estimated QALY gain from the more effective treatment.

EQ-5D values: data supplied at clarification

In response to ERG clarification question B2 the manufacturer supplied the average EQ-5D quality of life values split by the BCVA of the treated eye and the BCVA of the fellow eye. This data can be pooled across time points. With the additional assumption that the quality of life is the same for those whose treated eye is in health state A and whose fellow eye is in health state B as for those whose treated eye is in health state B and whose fellow eye is in health state A[6] this results in the following mean EQ-5D values.

Table 54. EQ-5D data supplied at clarification: European patient subset

	HS1	HS2	HS3	HS4	HS5	Pooled
HS1	[redacted]					[redacted]
n obs.	[redacted]					[redacted]
HS2	[redacted]	[redacted]				[redacted]
n obs.	[redacted]	[redacted]				[redacted]
HS3	[redacted]	[redacted]	[redacted]			[redacted]
n obs.	[redacted]	[redacted]	[redacted]			[redacted]
HS4	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]
n obs.	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]
HS5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
n obs.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[6] This assumption applies to few observations since within the EQ-5D data the fellow eye is typically in no worse a health state than the treated eye. Among the European patient subset only 0, 2, 1 and 1 observations at baseline, week 24, week 52 and week 76 require this assumption, while the corresponding numbers among all patients are 1, 2, 1 and 1 observations.

Table 55. EQ-5D data supplied at clarification: All patients

	HS1	HS2	HS3	HS4	HS5	Pooled
HS1	[redacted]					[redacted]
n obs.	[redacted]					[redacted]
HS2	[redacted]	[redacted]				[redacted]
n obs.	[redacted]	[redacted]				[redacted]
HS3	[redacted]	[redacted]	[redacted]			[redacted]
n obs.	[redacted]	[redacted]	[redacted]			[redacted]
HS4	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]
n obs.	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]
HS5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
n obs.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The pooled data for the European patient subset corresponds with the values used in the manufacturer submission.

Moving down the columns of the above tables shows the pattern of quality of life values for changes in the BCVA of the WSE. Most of the observations fall into the first column, with the BSE being in HS1. This may suggest a slight decline in quality of life as the BCVA of the WSE declines, but the pattern is interrupted by the anomalous values for HS4, with the value for HS5 also being anomalous within the European patient subset. Passing over these values might suggest a utility decrement if the BCVA of the WSE falls from the best health state to the worst of [redacted] for the European subset of patient, and [redacted] across all patients.

Moving across the rows of the above tables shows the pattern of quality of life values for changes in the BCVA of the BSE. Unfortunately, there are relatively few observations within these cells and any pattern is not obvious.

The manufacturer analysis using the pooled data incorporates changes in the BCVA of both eyes, rather than attempting to control for the BCVA of the BSE while changing the BCVA of the WSE. As a consequence, this fails to take into account the inherent structure of the data and the fact that it will always be expected to show a strong positive correlation. Those with a WSE in HS5 can have a BSE in any health state. Those with a WSE in HS1 can only have a BSE in HS1. As a consequence, the average BCVA of the BSE of the former will tend to be worse than that of the latter.

It seems important when analysing the EQ-5D data to determine the impact of changes in the BCVA of the WSE that the BCVA of the BSE is controlled for. The pattern within the first column of the

European patient subset is quite erratic. That for the all patient group is smoother. though there is still a anomalous value for HS4. This could be “finessed” by simply making the value for HS4 equal to the average of the two adjacent values. This data could then populate the first column and first row of the two-eyed quality of life values.

But the question then arises about what is the quality of life impact from changes in the BCVA of the treated eye when the treated eye is the BSE: i.e. what of the remaining values below the principal diagonal. The quality of life data collected during GALILEO may be a poor guide to this, given the limited number of observations and the erratic patterns of the mean values as outlined above. A simplistic approach would be to assume that the absolute quality of life change is the same as if it were the WSE, but recognising that this is a somewhat conservative assumption. This would result in the following for the GALILEO the all patient data.

Table 56. Revised EQ-5D data supplied at clarification: All patients

		Treated eye				
		HS1	HS2	HS3	HS4	HS5
Fellow eye	HS1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The step from HS1 to HS5 of [redacted] is similar to that applied in the manufacturer base case when using the European patient subset data of [redacted].

Czoski-Murray utility values

The manufacturer applies a central ETDRS of 35 letters for the worst health state. It may be more reasonable to apply a central value of 27 letters for the worst health state, and a perhaps optimistic value of 90 letters for the best health state. This will tend to steepen the Czoski-Murray utility function, benefitting the more effective treatment. Including the Czoski-Murray age adjustment for the baseline age of 64 years moves the values down, but does not steepen the curve. These changes result in the following.

Table 57. ERG revisions to Czoski-Murray quality of life values: BSE values

	Base case	ERG revised values		
	QoL	ETDRS	LogMAR	QoL
HS1	0.828	90	-0.1	0.833
HS2	0.735	72	0.26	0.700
HS3	0.627	57	0.56	0.590
HS4	0.519	42	0.86	0.480
HS5	0.469	27	1.16	0.369

This results in the following two-eyed quality of life values.

Table 58. Revised Czoski-Murray utility values: Two-eyed health states

		Treated eye				
		HS1	HS2	HS3	HS4	HS5
Fellow eye	HS1	0.833	0.833	0.833	0.833	0.833
	HS2	0.833	0.700	0.700	0.700	0.700
	HS3	0.833	0.700	0.590	0.590	0.590
	HS4	0.833	0.700	0.590	0.480	0.480
	HS5	0.833	0.700	0.590	0.480	0.369

It can also be argued that it is too pessimistic to suggest that changes in the BCVA of the treated eye when it is the WSE will have no quality of life impacts. A number of NICE STAs for treatments for eye conditions have suggested that it may be reasonable for changes in the BCVA of the WSE to have perhaps 30% of the quality of life impact of the same change in the BCVA of the BSE.

The evidence from Brown (1999)[57] may suggest that this is not the case. Brown et al surveyed 325 patients with impaired vision of at least 20/40 in at least one eye. Among these there were 78 patients with good vision of 20/20 to 20/25 in the other eye. These patients were subdivided by the BCVA in the fellow eye into 5 groups with TTO and SG being applied to them. This resulted in the following patient distribution and HRQoL estimates.

Table 59. HRQoL by BCVA in WSE among patients with good vision in BSE: Brown et al 1999

BCVA in WSE	n	TTO	SG
20/40-20/50	18	0.860	0.930
20/70-20/100	12	0.900	0.960
20/200-20/400	13	0.950	0.940
≤ 20/800 (CF)	28	0.880	0.920
≤ 20/1600 (HM/NLP)	7	0.810	0.950
CF: Counting fingers HM: Detecting hand movement NLP: No light perception			

Brown (1999) found no obvious pattern between changes in the BCVA of the WSE and the average HRQoL measured by TTO or standard gamble.

But were the 30% WSE impact to apply, the following quality of life values might be anticipated.

Table 60. Revised Czoski-Murray utility values with WSE impacts: Two-eyed health states

		Treated eye				
		HS1	HS2	HS3	HS4	HS5
Fellow eye	HS1	0.833	0.817	0.814	0.811	0.808
	HS2	0.833	0.700	0.697	0.693	0.690
	HS3	0.833	0.700	0.590	0.586	0.583
	HS4	0.833	0.700	0.590	0.480	0.477
	HS5	0.833	0.700	0.590	0.480	0.369

Quality of life data: values identified from the literature

The manufacturer literature search for quality of life papers used a 2001 to 2013 date cut-off. This meant that of the two papers which have been extensively used within NICE STAs of treatments for eye conditions, Brown (1999) and Czoski-Murray et al (2009), only Czoski-Murray et al (2009) was identified.

But it seems surprising for the manufacturer not to have considered Brown (1999) given that it was extensively used in both the dexamethasone STA and the ranibizumab STA, and that the current submission shows an extensive awareness of these and draws a number of inputs from them. Brown (1999) was also extensively referenced within the ERG report for the STA of aflibercept for wet AMD.

In response to ERG clarification question B19 the manufacturer also notes that Czoski-Murray et al (2009) was the preferred source for the ranibizumab for RVO STA. This has to be read alongside the modelling suggesting that the Czoski-Murray et al (2009) quality of life values were more conservative than the Brown (1999) quality of life values within the ranibizumab for RVO STA. This may be due to a possible modelling error as highlighted in the ranibizumab for CNV STA. Within this STA the Czoksi-Murray et al (2009) quality of life values were also more conservative than the Brown (1999) quality of life values. But this arose due to the incorrect modelling of eyes crossing over from being the BSE to being the WSE as vision in the eye deteriorated. Had this been correctly modelled, the Brown (1999) quality of life values would have been more conservative. The Brown (1999) quality of life values are also more conservative within the current aflibercept STA. They are also derived from a TTO exercise among patients with visual impairment. The quality of life values of both Brown (1999) and Czoski-Murray relate to the BSE.

The Brown (1999) quality of life values can be mapped onto the health states of the model to result in the following two-eyed quality of life values.

Table 61. Brown 1999 utility values: Two-eyed health states

		Treated eye				
		HS1	HS2	HS3	HS4	HS5
Fellow eye	HS1	0.920	0.920	0.920	0.920	0.920
	HS2	0.920	0.836	0.836	0.836	0.836
	HS3	0.920	0.836	0.753	0.753	0.753
	HS4	0.920	0.836	0.753	0.670	0.670
	HS5	0.920	0.836	0.753	0.670	0.621

Applying the 30% impact for changes in the BCVA of the WSE would revise this as follows.

Table 62. Revised Brown 1999 utility values with WSE impacts: Two-eyed health states

		Treated eye				
		HS1	HS2	HS3	HS4	HS5
Fellow eye	HS1	0.920	0.904	0.901	0.898	0.895
	HS2	0.920	0.836	0.833	0.829	0.826
	HS3	0.920	0.836	0.753	0.749	0.746
	HS4	0.920	0.836	0.753	0.670	0.667
	HS5	0.920	0.836	0.753	0.670	0.621

Dosing frequency

The submission states that the dosing for aflibercept is based upon that recorded during GALILEO and COPERNICUS for the first 24 weeks, and upon that recorded during GALILEO for the subsequent 28 weeks due to cross over in COPERNICUS.

In response to the ERG clarification question B4 the manufacturer supplied the following data on the number of aflibercept doses, based upon the FAS LOCF dataset.

Table 63. Aflibercept dosing data supplied at clarification

Start of week	0	1	5	9	13	17	0	21	25	29	33	37	41	45	21
End of week	0	4	8	12	16	20	20	24	28	32	36	40	44	48	48
GALILEO															
Doses	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients on trial	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean doses (n=103)							[redacted]								[redacted]
COPERNICUS															[redacted]
Doses	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients on trial	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean doses (n=114)							[redacted]								[redacted]
Pooled															[redacted]
Doses	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients on trial	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean doses (n=217)							[redacted]								[redacted]

Given this data, the [redacted] mean number of aflibercept doses for week 0 to week 20 corresponds closely with the 5.75 aflibercept doses of the base case. The [redacted] mean number of aflibercept doses of GALILEO for week 25 to week 48 is slightly lower than the 2.55 aflibercept doses of the base case, though whether there were any administrations during weeks 49, 50 or 51 that might account for this is a moot point. The totals of [redacted] and [redacted] give a total of [redacted] aflibercept administrations, which corresponds reasonably closely with the 8.30 of the base case that was derived from the first year average doses in mg.

It is unclear why the manufacturer could not have analysed the COPERNICUS data for the subset of patients who received aflibercept at baseline. The response to ERG clarification question B4 also states that "*It is not possible to provided data for the COPERNICUS subset of patients who did not cross over at week 24 and were treated with aflibercept throughout during weeks 0-52. Permission to cross-over to active treatment applied to the sham arm only of the COPERNICUS trial at week 24, as*

specified in the protocol". Dosing within COPERNICUS during weeks 0 to 24 was marginally higher than that in GALILEO.

The SPC for aflibercept states:

> *"After the initial injection, treatment is given monthly. The interval between two doses should not be shorter than one month. If there is no improvement in visual and anatomic outcomes over the course of the first three injections, continued treatment is not recommended. Monthly treatment continues until visual and anatomic outcomes are stable for three monthly assessments. Thereafter the need for continued treatment should be reconsidered.*
> *If necessary, treatment may be continued with gradually increasing treatment intervals to maintain a stable visual and anatomic outcome. If treatment has been discontinued, visual and anatomic outcomes should be monitored and treatment should be resumed if these deteriorate."*

In response to the ERG clarification question A9 the manufacturer notes that based upon the pooled data from COPERNICUS and GALILEO [redacted] of patients gained less than 5 letters at week 12 and so would only receive 3 administrations of aflibercept. Of those classed as responders, [redacted] were "*stable*" by week 12, [redacted] by week 16, [redacted] by week 20 and [redacted] by week 24. This left [redacted] of patients whose vision had not reached stability by week 24. The definition of stability used for this assessment is not clear, and it is also not clear from this whether stability was always maintained thereafter. The manufacturer further states that [redacted] though it is not clear how this figure was arrived at. Applying this pro-rata to the periods subsequent to stability suggests the following average number of aflibercept doses during the first year of treatment.

Table 64. Aflibercept dosing by SPC protocol

		Doses administered		
	Percentage	Monthly	PRN	Total
Week 12 non-responders	[redacted]	3.00	..	[redacted]
Week 12 responders				
stable by week 12	[redacted]	3.00	[redacted]	[redacted]
stable by week 16	[redacted]	4.00	[redacted]	[redacted]
stable by week 20	[redacted]	5.00	[redacted]	[redacted]
stable by week 24	[redacted]	6.00	[redacted]	[redacted]
not stable by week 24	[redacted]	12.00	..	[redacted]
Average doses in year 1				[redacted]

This suggests an average of [redacted] aflibercept doses for the first year, which is somewhat lower than the 8.30 aflibercept doses of the base case. While this may be an interesting sensitivity analysis, there may remain a question around the clinical effectiveness that would result from this dosing.

The base case number of ranibizumab administrations of 5.50 during the first six months and 3.30 for the subsequent six months corresponds with that reported in Campochiaro et al (2011). The Novartis submission for ranibizumab for macular oedema secondary to CRVO estimated 9.0 ranibizumab administrations for year 1 based upon the CRUISE trial, and 3.8 ranibizumab administrations for year 2 based upon the HORIZON trial. There is no obvious reason for the slight discrepancy of 0.20 ranibizumab administrations in the first year between Campochiaro et al (2011) and the Novartis submission for ranibizumab for macular oedema secondary to CRVO.

The Novartis submission for ranibizumab for macular oedema secondary to CRVO further states that "*In these studies predefined treatment criteria determined the retreatment rules for ranibizumab in MO secondary to BRVO and CRVO and these are in line with the proposed SPC*", but this may relate more to the post 6 month period. During the initial 6 month period of CRUISE ranibizumab dosing was monthly. In the light of this, the average dose of ranibizumab that would arise from the SPC compared to that observed during the CRUISE trial may be subject to the same considerations as outlined above for aflibercept; i.e. some may cease treatment due to lack of efficacy and some may cease treatment due to efficacy and stability of BCVA.

The SPC for ranibizumab states:

> *"Treatment is given monthly and continued until maximum visual acuity is achieved i.e the patient's visual acuity is stable for three consecutive monthly assessments performed while on ranibizumab treatment. If there is no improvement in visual acuity over the course of the first three injections, continued treatment is not recommended.*
> *Treatment is resumed when monitoring indicates loss of visual acuity due to DME or to macular oedema secondary to RVO. Monthly injections should then be administered until stable visual acuity is reached again for three consecutive monthly assessments (implying a minimum of two injections). The interval between two doses should not be shorter than one month."*

The ranibizumab SPC suggests stopping treatment among non-responders along the same lines as the SPC for aflibercept, and re-starting treatment along the same lines as the SPC for aflibercept. But according to the SPCs, treatment with ranibizumab should cease once maximum visual acuity is reached, presumably synonymous with stability, whereas treatment with aflibercept may either be less frequent than monthly or may cease once stability has occurred. This may suggest that cessation of treatment may be more likely among ranibizumab responders than among aflibercept responders.

Monitoring frequency

The SPC for aflibercept states:

> *"Usually, monitoring should be done at the injection visits. During treatment interval extension through to completion of therapy, the monitoring schedule should be determined by the treating physician based on the individual patient's response and may be more frequent than the schedule of injections."*

This raises the prospect of the initial monthly monitoring requirement being stretched to be in line with any elongation in the treatment interval.

In contract, the SPC for ranibizumab states:

> *"Treatment is given monthly and continued until maximum visual acuity is achieved i.e the patient's visual acuity is stable for three consecutive monthly assessments performed while on ranibizumab treatment. … Thereafter patients should be monitored monthly for visual acuity."*

This appears to suggest that while still on treatment, and possibly thereafter, that monthly monitoring should occur.

In the light of this, among those remaining on treatment there may be a lower monitoring burden for aflibercept compared with ranibizumab.

Administration cost

The £257.45 administration cost is based upon a weighted average of day cases and outpatient appointments, the weights being drawn from the Health Episode Statistics. Full details of this are not provided within the submission, but the £257.45 administration cost is the same as that used in the submission for aflibercept for wet AMD (ID519).

In the light of this, the critique of the £257.45 administration cost of the submission for aflibercept for wet AMD applies[7]. The relevant health episode statistics data of 2010-11 and 2011-12 is summarised below.

[7] http://www.nice.org.uk/nicemedia/live/13720/63979/63979.pdf accessed 14 September 2013

Table 65. HES 2010-11 and HES 2011-12 data

	OP All	Day case
2010-11 HES data		
C79.4 Injection into vitreous body NEC	34,187 (37%)	56,994 (63%)
C89.3 Injection of therapeutic substance into posterior segment of eye NEC	14,329 (85%)	2,622 (15%)
C79.4+C89.3	48,516 (45%)	59,616 (55%)
2011-12 HES data		
C79.4 Injection into vitreous body NEC	61,328 (46%)	70,648 (54%)
C89.3 Injection of therapeutic substance into posterior segment of eye NEC	17,224 (96%)	771 (4%)
C79.4+C89.3	78,552 (52%)	71,419 (48%)

For the administration cost, the 45% outpatient to 55% day-cases split was based upon the OPCS 4 codes C79.4: and C89.3: using 2010-11 HES data. 2011-12 HES data suggests a split of 52% outpatient to 48% day-cases, which is in line with tables 88 and 98 of the submission. Coupled with the 2011-12 NHS reference costs of £79.74 per ophthalmology consultant led non-admitted follow-up and £402.08 per BZ23Z – minor vitreous retinal procedure day case this results in a slightly lower weighted average of £233.24 compared to the manufacturer estimate of £257.45.

NEC: Not Elsewhere Classified would appear to suggest that C89.3 is the more specific coding for injection of a therapeutic substance into the posterior segment of the eye, with C79.4 covering injections into the vitreous that are Not Elsewhere Classified; i.e. excluding those covered by C89.3. This is also in line with ERG expert opinion. If applicable, based upon the 2010-11 HES data would suggest a weighted average administration cost of £129.60, but with C89.3 becoming overwhelmingly an outpatient procedure in 2011-12 this weighted average administration cost would drop to £93.55.

But all the above costings assume that the outpatient administration is costed at the £80 of the Consultant led: Follow up attendance: Non-admitted: 130 Ophthalmology. It seems more reasonable to the ERG that it should be costed at the £117 of the Outpatient procedures: BZ23Z: Minor vitreous retinal procedures. The weighted average of the 2011-12 C79.4 and C89.3 would then result in an average administration cost of £252.90, while the 2011-12 C89.3 alone would result in an average administration cost of £129.46.

But it is also being assumed that administration visits double as monitoring visits, in which case the costs of OCT may be added to this. These have been costed in previous STAs at £51.27 for the outpatient diagnostic imaging code of RA23Z: Ultrasound Scan, less than 20 minutes. This could suggests administration costs of £180.73 based upon the 2011-12 C89.3 alone if the OCT costs are in

addition to those of the administration. While by a different route, the £180.73 is broadly in line with that applied within the STA of ranibizumab for RVO of £192.00.

The STA of ranibizumab for DMO the FAD stated that "administration costs for *ranibizumab monotherapy were estimated at £150 per visit, and heard from clinical specialists that this value underestimates the true costs of ranibizumab administration. The clinical specialists believed that the true cost would be a minimum of £200 and could be as high as £400 per visit."* But further note that Novartis provided a further bottom up costing in response to the FAD that suggested only around £143 per administration which broadly paralleled the £150 cost of the then current BZ23Z - Vitreous Retinal Procedures Category 1: Outpatient procedures. A sensitivity analysis assuming 25% day case administration was also presented.

Costs are based on national reference costs. The ERG notes that the RCO has given approval to intravitreal injections being given by non-medical staff. This might reduce costs a little, if non-medical staff take the same length of time as medical staff. Costs to commissioners would only fall if trusts charged less than the current reference cost.

Monitoring costs

The dedicated monitoring visits are costed at £197.00, being the sum of the outpatient procedure BZ23Z Minor vitreous retinal procedures at £117.26 and the ophthalmology consultant led face to face non-admitted outpatient appointment at £79.74. Applying the £51.27 of the outpatient diagnostic imaging code of RA23Z: Ultrasound Scan, less than 20 minutes for OCT would reduce this monitoring cost to £131.01.

Costs of blindness

The manufacturer has confirmed that the costs of blindness are only applied to incident cases of blindness in the aflibercept and ranibizumab cohort flows. Within the dexamethasone cohort flow the costs of blindness are applied to both newly incident cases and prevalent cases. The ERG views the approach adopted in the dexamethasone cohort flow as the correct approach.

Also, the STA of ranibizumab for CNV from pathological myopia identified a recent Kings Fund report, McCrone et al (2008),[58] that provides a better estimate of the costs of depression than that used in Meads and Hyde (2003).[59] This results in a first year cost for blindness of [redacted] and a subsequent annual cost of blindness of [redacted].

Note that the costing of Meads and Hyde (2003) was intended for an AMD patient group and as such is possibly slightly older than the baseline age assumed in the model of 64 years. The vast majority of

the estimated costs relate to residential care. But within the current modelling, there is a mean additional survival of around 20 years which may make the residential care element more reasonable to apply. It should also be borne in mind that since the fellow eye is assumed to maintain a constant BCVA throughout, only 1.9% of patients are at risk of blindness within the model.

Minor Issue: Blindness mortality multiplier

The implementation of the mortality multiplier for blindness of 1.54 is peculiar. A weighted average mortality risk is calculated and applied to all patients regardless of their health state. While slightly more involved in practise, the intention is to calculate the common mortality risk as a weighted average of:

- the age specific mortality risk multiplied by the proportion who are not blind; and,
- the age specific mortality risk conditioned by the blindness mortality multiplier, multiplied by the proportion who are blind

This weighted average mortality risk is then applied to all health states within the model. But this will tend to raise the mortality rate to above what it should be for most patients and lower the mortality rate to below what it should be for those in blindness. It appears likely that this will tend to bias the analysis slightly towards the more effective treatment[8].

The manufacturer model cannot be easily revised to correct for this error. As a consequence, it seems desirable to remove the blindness mortality multiplier from the modelling.

Minor Issue: Adverse events rates

There is a small error during months 7 to 12 of the modelling of adverse events within the aflibercept arm. The intention is to make the rate of these proportionate to the number of injections within the period. This can be achieved by dividing the per cycle adverse event rate of the first six months by the per cycle number of injections during the first six months, then multiplying this by the per cycle number of injections during months 7 to 12.

This occurs within the ranibizumab arm. But within the aflibercept arm the multiplication is by the total number of injections during months 7 to 12. This overstates the adverse event rates in the aflibercept arm during months 7 to 12 by a factor of seven.

The adverse events rates in the dexamethasone arm after month 6 are inadvertently set to zero.

[8] This is complicated by the proportions not being conditioned by the total proportion of patients remaining alive at that point, so this bias cannot be definitively stated.

Minor Issue: Treatment rates for adverse events

The submission draws the treatment rates of 43% for raised IOP and 68% for cataracts from its expert survey. Within the model the 43% is applied but the 68% is not.

5.4 Exploratory and sensitivity analyses undertaken by the ERG

The ERG has amended the manufacturer model as below.

- Revise the number of dexamethasone administrations in year 1 to be 1.86[9].
- Revise the cost per aflibercept and ranibizumab administration to £180.73[10].
- Revise the cost per dedicated monitoring visit to £130.01[11].
- Revise the number of dedicated monitoring visits during months 7 to 12 to be 0.95 for aflibercept and 1.10 for ranibizumab[12].
- Correct the month 7 to month 12 adverse event rates for aflibercept and dexamethasone[13].
- Revise the rates of cataract in the ranibizumab arm to 1.6% and the durations of the quality of life impacts of raised IOP to one 4 week cycle, of cataracts to 3 months and of retinal tears to 4 months[14].
- Revising the costs of raised IOP by conditioning the medication costs by the proportion of time on treatment rather than dividing by 13 and by not dividing the cost of surgery by 6[15].
- Remove the 1.54 blindness mortality multiplier, on the grounds of its implementation within the model and possible perverse effects[16].
- Apply the costs of blindness to both newly incident cases and prevalent cases within the aflibercept and ranibizumab cohort flows, as in the dexamethasone cohort flow[17].
- Revise costs of blindness to be £[redacted] in the year of incidence and an annual £[redacted] thereafter[18].

[9] Implemented within the Data_Inputs_UK worksheet by setting cells F96 and F101 equal to 1.86/13
[10] Implemented in the *Data_Inputs_UK* worksheet by setting cell F196 to the relevant value.
[11] Implemented in the *Data_Inputs_UK* worksheet by setting cell F207 to the relevant value
[12] Implemented in the *Data_Inputs_UK* worksheet by setting cell F130=0.50 and cell F131=0.63
[13] Implemented in the *Markov_Aflibercept* worksheet in cells GL17:GN23 by replacing ruEyleaPRN with ruEyleaPRN_f and revising cells GL24:GN24 to be of the same form as cells GL25:GN25, and in the *Markov_Dexamethasone* worksheet in cells GL17:GN23 by replacing ruOZPRN with ruOZPRN_f
[14] Implemented in the *Data_Inputs_UK* worksheet by setting cell AB19=1.6%, and in the *EQ5D_Trial_Data* worksheet by multiplying cell L12 by 3, by setting cell L13=0.1 and by multiplying cell L14 by 4.
[15] Implemented in the *Data_Inputs_UK* worksheet by revising cells AG221:AG225 such that the references to cells AD221:AD225 are multiplied by 57% and the references to cells AD228:AD233 are conditioned by 62% and by multiplying cell F227 by 6.
[16] Implemented within the three *Markov* worksheets by simplifying cells AG11:AG491 to be of the form VLOOKUP(AC11,rng_lifetable,3)
[17] Implemented in the *Markov_Aflibercept* and *Markov_Ranibizumab* worksheets by applying the parrallel formulae to those within the *Markov_Dexamethasone* worksheet for cells GV12:GV491.
[18] Implemented in the *Data_Inputs_UK* worksheet be setting cells AB215:AB216 to the relevant values.

The following sensitivity analyses are presented, these being limited to the with PAS scenario for reasons of space.

- SA01: Applying the [redacted] relative risk of losing 15 or more letters by week 24 within the comparison with ranibizumab[19].
- SA02: Apply the lower CI bound for the 24 week relative risks of gain[20].
- SA03: Apply the upper CI bound for the 24 week relative risk of gain[21].
- SA04: Increase the cost of administration to £250 for aflibercept and ranibizumab[22].
- SA05: Assume 2 years of treatment, retaining the manufacturer values for aflibercept and ranibizumab, and for dexamethasone the same year 2 monitoring as for aflibercept and an annual average dose of 1.26 for year 2[23].
- SA06: Assume 5 years of treatment, retaining the manufacturer values for aflibercept and ranibizumab, and for dexamethasone the same year 2-4 monitoring as for aflibercept and annual average doses of 1.26 for year 2 and 0.74 thereafter[24].
- SA07: Equalise the number of doses for ranibizumab to those assumed for aflibercept[25].
- SA08: Equalise the number of doses and dedicated monitoring visits for ranibizumab to those assumed for aflibercept[26].
- SA09: Increase the post treatment 4 weekly rate of worsening from 0.0296% to an arbitrary 0.1%[27].
- SA10: Include adverse events and increasing the percentage of raised IOP requiring treatment to 100%[28].

[19] The implementation of this within the electronic model can be achieved by inserting a set of interim TPMs for ranibizumab in the *SE_Transitions* worksheet. The probabilities of gaining letters is calculated as before by multiplying the aflibercept probabilities of gaining letters by the relative risk [redacted] for the deterministic analysis). The probabilities of losing letters is calculated in a similar manner by multiplying the aflibercept probabilities of losing letters by the relative risk ([redacted] for the deterministic analysis). If the probabilities within a row does not exceed unity, the corresponding probabilities in the live ranibizumab TPM are the same with the probability of remaining in the same health state being the residual. If the probabilities within a row exceed unity, the corresponding probabilities in the live ranibizumab TPM are the probabilities in the interim TPM divided by the sum of the probabilities in the row of the interim TPM, with the probability of remaining in the same health state being zero.
[20] Implemented in the *Data_Inputs_UK* worksheet by setting E32:E33 to the relevant values.
[21] Implemented in the *Data_Inputs_UK* worksheet by setting E32:E33 to the relevant values.
[22] Implemented in the *Data_Inputs_UK* worksheet by setting F196 to the relevant value.
[23] Implemented in the Executive_Summary worksheet by setting N53 and N63 to the relevant values.
[24] Implemented in the *Executive_Summary* worksheet by setting N53:N57 and N63:67 to the relevant values. This also requires that cell F53 be of the form IF(treatment_duration>1 ,IF(UserOzru_2="", ruOz2_default, UserOzru_2),0) and in the Data_Inputs_UK worksheet cell F111 to be divided by 13.
[25] Implemented in the *Executive_Summary* worksheet by setting I51:I75 to be equal to H51:H57.
[26] Implemented in the *Executive_Summary* worksheet by setting I51:I75 to be equal to H51:H57 and I62:I67 to be equal to H62:H67.
[27] Implemented in the *Data_Inputs_UK* worksheet by setting Q37 to the relevant value.
[28] Implemented in the *Data_Inputs_UK* worksheet by setting F160 to the relevant value.

- SA11 to SA15: Setting the utility values to be those drawn from the ERG report data of the All Patients' EQ-5D, Czoski-Murray, Czoski-Murray with WSE effects, Brown 1999 and Brown 1999 with WSE effects[29].
- SA16: Equalising the dexamethasone administration costs to those of aflibercept[30].

The revisions made to the model result in the following outputs.

Table 66. Revised deterministic results excluding PAS: vs ranibizumab

	Aflibercept	Ranibizumab	Net
Total cost	[redacted]	[redacted]	[redacted]
Drug cost (excl. PAS)	[redacted]	[redacted]	[redacted]
Admin cost	[redacted]	[redacted]	[redacted]
Monitoring cost	[redacted]	[redacted]	[redacted]
AE (incl. blindness) cost	[redacted]	[redacted]	[redacted]
OS undiscounted[31]	19.056	19.056	0.000
QALYs	[redacted]	[redacted]	0.053
ICER			[redacted]

Table 67. Revised deterministic results including PAS: vs ranibizumab

	Aflibercept		Ranibizumab			
Ranibizumab PAS	Drug	Total	Drug	Total	net Total	ICER
0%	[redacted]	[redacted]	[redacted]	[redacted]	-£3,049	Dominant
10%	[redacted]	[redacted]	[redacted]	[redacted]	-£2,398	Dominant
15%	[redacted]	[redacted]	[redacted]	[redacted]	-£2,073	Dominant
20%	[redacted]	[redacted]	[redacted]	[redacted]	-£1,748	Dominant
25%	[redacted]	[redacted]	[redacted]	[redacted]	-£1,423	Dominant
30%	[redacted]	[redacted]	[redacted]	[redacted]	-£1,098	Dominant
35%	[redacted]	[redacted]	[redacted]	[redacted]	-£772	Dominant
40%	[redacted]	[redacted]	[redacted]	[redacted]	-£447	Dominant
45%	[redacted]	[redacted]	[redacted]	[redacted]	-£122	Dominant
50%	[redacted]	[redacted]	[redacted]	[redacted]	£203	£3,820

For the comparison with dexamethasone the deterministic base case results are presented below.

[29] Implemented in the *EQ-5D_Trial_Data* worksheet by setting D4:D28 to the relevant values.
[30] Implemented in the *Data_Inputs_UK* worksheet by setting F197 to the relevant value
[31] Taken from cell AI7 of the relevant cohort flow worksheets of the electronic model.

Table 68. Revised deterministic results: vs dexamethasone

	Aflibercept	Dexamethasone	Net
Total cost (excl. PAS)	[redacted]	[redacted]	[redacted]
Total cost (incl. PAS)	[redacted]	[redacted]	£2,285
Drug cost (excl. PAS)	[redacted]	[redacted]	[redacted]
Drug cost (incl. PAS)	[redacted]	[redacted]	[redacted]
Admin cost	[redacted]	[redacted]	[redacted]
Monitoring cost	[redacted]	[redacted]	[redacted]
AE (incl. blindness) cost	[redacted]	[redacted]	[redacted]
OS undiscounted	19.056	19.056	0.000
QALYs	[redacted]	[redacted]	0.186
ICER (excl. PAS)			[redacted]
ICER (incl. PAS)			£12,265

The sensitivity analyses for the comparison with ranibizumab are presented for the ranibizumab PAS varying from 10% to 50%.

Table 69. ERG sensitivity analyses: aflibercept versus ranibizumab

		Ranibizumab PAS									
		0%	10%	15%	20%	25%	30%	35%	40%	45%	50%
Revised Model	Δ Costs	-£3,049	-£2,398	-£2,073	-£1,748	-£1,423	-£1,098	-£772	-£447	-£122	£203
	Δ QALYs	0.053									
	ICER	Dom.	Dom.	Dom.	Dom.	Dom.	Dom.	Dom.	Dom.	Dom.	£3,820
SA01: RR losing letters	Δ Costs	-£3,005	-£2,355	-£2,030	-£1,704	-£1,379	-£1,054	-£729	-£403	-£78	£247
	Δ QALYs	0.003									
	ICER	Dom.	Dom.	Dom.	Dom.	Dom.	Dom.	Dom.	Dom.	Dom.	£86,789
SA02: Lower CI RR gain	Δ Costs	-£3,145	-£2,495	-£2,169	-£1,844	-£1,519	-£1,194	-£869	-£543	-£218	£107
	Δ QALYs	0.143									
	ICER	Dom.	Dom.	Dom.	Dom.	Dom.	Dom.	Dom.	Dom.	Dom.	£749
SA03: Upper CI RR gain	Δ Costs	-£2,981	-£2,331	-£2,006	-£1,680	-£1,355	-£1,030	-£705	-£380	-£54	£271
	Δ QALYs	-0.047									
	ICER	£62,932	£49,202	£42,337	£35,472	£28,607	£21,742	£14,877	£8,012	£1,147	Dom'ted
SA04: Admin £250	Δ Costs	-£3,083	-£2,433	-£2,107	-£1,782	-£1,457	-£1,132	-£807	-£481	-£156	£169
	Δ QALYs	0.053									
	ICER	Dom.	Dom.	Dom.	Dom.	Dom.	Dom.	Dom.	Dom.	Dom.	£3,176
SA05: 2 year treatment	Δ Costs	-£4,422	-£3,502	-£3,043	-£2,583	-£2,124	-£1,664	-£1,204	-£745	-£285	£175
	Δ QALYs	0.053									
	ICER	Dom.	Dom.	Dom.	Dom.	Dom.	Dom.	Dom.	Dom.	Dom.	£3,274
SA06: 5 year treatment	Δ Costs	-£6,838	-£5,476	-£4,796	-£4,115	-£3,434	-£2,754	-£2,073	-£1,392	-£712	-£31
	Δ QALYs	0.053									
	ICER	Dom.	Dom.	Dom.	Dom.	Dom.	Dom.	Dom.	Dom.	Dom.	Dom.
SA07: Equal doses	Δ Costs	-£2,689	-£2,075	-£1,769	-£1,462	-£1,155	-£848	-£541	-£234	£73	£379

	Δ QALYs	0.053									
	ICER	Dom.	Dom.	Dom.	Dom.	Dom.	Dom.	Dom.	Dom.	£1,364	£7,128
SA08: Equal doses & monitor	Δ Costs	-£2,572	-£1,958	-£1,651	-£1,345	-£1,038	-£731	-£424	-£117	£190	£496
	Δ QALYs	0.053									
	ICER	Dom.	Dom.	Dom.	Dom.	Dom.	Dom.	Dom.	Dom.	£3,562	£9,326
SA09: Faster worsening	Δ Costs	-£3,052	-£2,402	-£2,076	-£1,751	-£1,426	-£1,101	-£776	-£450	-£125	£200
	Δ QALYs	0.051									
	ICER	Dom.	Dom.	Dom.	Dom.	Dom.	Dom.	Dom.	Dom.	Dom.	£3,899
SA10: Adverse events	Δ Costs	-£3,066	-£2,415	-£2,090	-£1,765	-£1,440	-£1,114	-£789	-£464	-£139	£187
	Δ QALYs	0.053									
	ICER	Dom.	Dom.	Dom.	Dom.	Dom.	Dom.	Dom.	Dom.	Dom.	£3,489
SA11: All patients EQ-5D	Δ Costs	-£3,049	-£2,398	-£2,073	-£1,748	-£1,423	-£1,098	-£772	-£447	-£122	£203
	Δ QALYs	0.065									
	ICER	Dom.	Dom.	Dom.	Dom.	Dom.	Dom.	Dom.	Dom.	Dom.	£3,144
SA12: Czoski	Δ Costs	-£3,049	-£2,398	-£2,073	-£1,748	-£1,423	-£1,098	-£772	-£447	-£122	£203
	Δ QALYs	0.037									
	ICER	Dom.	Dom.	Dom.	Dom.	Dom.	Dom.	Dom.	Dom.	Dom.	£5,519
SA13: Czoski with WSE	Δ Costs	-£3,049	-£2,398	-£2,073	-£1,748	-£1,423	-£1,098	-£772	-£447	-£122	£203
	Δ QALYs	0.053									
	ICER	Dom.	Dom.	Dom.	Dom.	Dom.	Dom.	Dom.	Dom.	Dom.	£3,851
SA14: Brown	Δ Costs	-£3,049	-£2,398	-£2,073	-£1,748	-£1,423	-£1,098	-£772	-£447	-£122	£203
	Δ QALYs	0.024									
	ICER	Dom.	Dom.	Dom.	Dom.	Dom.	Dom.	Dom.	Dom.	Dom.	£8,440
SA15: Brown with WSE	Δ Costs	-£3,049	-£2,398	-£2,073	-£1,748	-£1,423	-£1,098	-£772	-£447	-£122	£203
	Δ QALYs	0.040									

	ICER	Dom.	Dom.	Dom.	Dom.	Dom.	Dom.	Dom.	Dom.	Dom.	£5,076

Most of the sensitivity analyses change the net costs or net QALYs in the predictable direction. But most also do not particularly affect the conclusions that would be drawn.

Sensitivity analysis SA01 that applies the relative risk of losing letters within the model framework where these are compounded six times during the first six months has a dramatic effect upon the modelled patient gain from aflibercept over ranibizumab. It all but eliminates it. But as previously outlined, this compounding for relative risks when both the relative risk of gaining letters and the relative risk of losing letters are applied results in model outputs that are not aligned with the validation data.

Sensitivity analysis SA03 that applies the upper confidence interval for the relative risk of gaining 15 or more letters at 6 months of [redacted] results many of the cost effectiveness estimated falling into the SW quadrant, due to the 0.047 QALY gain from ranibizumab over aflibercept. These are best read as the cost effectiveness of ranibizumab relative to aflibercept. If the PAS for ranibizumab is equal to or more than 25% ranibizumab is estimated as being cost effective at the £30,000 per QALY threshold. If the PAS for ranibizumab is a little more than 30% ranibizumab is estimated as being cost effective at the £20,000 per QALY threshold. As for the other analyses, if the PAS for ranibizumab is 50% aflibercept ceases to be cost saving and so is dominated by ranibizumab.

Sensitivity analysis SA08 that equalises the dosing and monitoring frequencies between aflibercept and ranibizumab still results in aflibercept being estimated to be cost effective relative to ranibizumab, though additional costs are anticipated if the PAS for ranibizumab is 45% or more.

Similarly, while varying the source of the quality of life data changes the net QALY gain in the predictable directions, the broad conclusions remain unchanged.

Table 70. ERG sensitivity analyses: aflibercept versus dexamethasone

	Δ costs	Δ QALYs	ICER
Revised Model	[redacted]	0.186	£12,265
SA02: Lower CI RR gain	[redacted]	0.250	£9,023
SA03: Upper CI RR gain	[redacted]	0.090	£24,991
SA05: 2 year treatment	[redacted]	0.187	£14,034
SA06: 5 year treatment	[redacted]	0.187	£18,699
SA09: Faster worsening	[redacted]	0.180	£12,631
SA10: Adverse events	[redacted]	0.192	£11,116
SA11: All patients EQ-5D	[redacted]	0.234	£9,760
SA12: Czoski	[redacted]	0.122	£18,740
SA13: Czoski with WSE	[redacted]	0.178	£12,868
SA14: Brown	[redacted]	0.080	£28,523
SA15: Brown with WSE	[redacted]	0.136	£16,833
SA16: Equal admin cost	[redacted]	0.186	£13,664

The sensitivity analyses for the comparison with dexamethasone are more variable, in part due to the revised first year dosing for dexamethasone of 1.86 administrations somewhat worsening the cost effectiveness estimate to £12,265 per QALY.

The sensitivity analysis SA02 that applies the lower confidence interval limit of [redacted] results in some improvement in the cost effectiveness estimate to £9,023 per QALY but sensitivity analysis SA03 that applies the upper confidence interval limit of [redacted] somewhat worsens the cost effectiveness estimate to £24,991 per QALY.

Of more concern may be sensitivity analyses SA05 and SA06 that lengthen the assumed duration of treatment, coupled with the dexamethasone dosing proposed by Allergan from a survey of experts it undertook for the STA of dexamethasone for RVO. These analyses also equalise the monitoring frequency for years 2 to 5 between aflibercept and dexamethasone. The 5 year treatment duration worsens the cost effectiveness estimate to £18,699 per QALY.

As in the comparison with ranibizumab, the choice of the source of utilities changes the net QALY gains in the predictable direction. Sensitivity analysis SA15 that applied Brown et al (1999) with WSE effects worsens the cost effectiveness estimate to £16,833 per QALY. Combining this with a lengthening of the time horizon to 5 years worsens the cost effectiveness estimate to £25,621 per QALY.

While probably a worst case scenario analysis, the sensitivity analysis that equalises the administration cost between aflibercept and dexamethasone worsens the cost effectiveness estimate to £13,644 per QALY.

5.5 Conclusions of the cost effectiveness section

The manufacturer submission considers ranibizumab as the main comparator, with dexamethasone as a secondary comparator. It does not consider bevacizumab or clinical observation.

The model does not incorporate any stopping rules. Some patients will not respond and so will cease treatment before month 6. Some may also respond and be stable prior to month 6, and so go onto PRN dosing before the point allowed during the trials. While the manufacturer has this information for aflibercept, implementing any stopping rule for ranibizumab may be more problematic.

The model structure only applies the 24 week relative risk of gaining letters, and compounds this six times between baseline and week 24 to arrive at the 24 week patient distribution. This seems conceptually incorrect. The obvious approach would be to apply the 24 week relative risks of gaining letters and of losing letters to the aflibercept TPM for baseline to 24 weeks coupled with the baseline distribution to arrive at the 24 week patient distribution. By coincidence the two approaches yield roughly the same 24 week patient distributions for the central estimates of the deterministic modelling that compares aflibercept with ranibizumab.

The impact of the model approach that compounds the 24 week relative risk of gaining letters within the probabilistic modelling is unknown. For this reason the ERG does not have confidence in the probabilistic estimates, even within the comparison of aflibercept with ranibizumab.

For the comparison of aflibercept with dexamethasone, it seems possible that applying the 24 week relative risks of gaining letters and of losing letters to the baseline distribution to arrive at the 24 week patient distribution may result in model outputs that are more aligned with the validation data than the approach of the model. The approach of the model that compounds the 24 week relative risk of gaining letters results in outputs which appear to somewhat underestimate the benefits of aflibercept compared to dexamethasone.

Key related assumptions within the model are

- while any patients remain on treatment after the first six months there is no change in the BCVA of the treated eyes;

- the duration of treatment is the same for each treatment; and,
- subsequent to treatment patients experience the same slow rate of visual worsening.

This will cause the week 24 estimated gains from aflibercept over ranibizumab, and over dexamethasone, to be maintained over the patient lifetime despite there only being one year of treatment. This may be optimistic.

The base case of the manufacturer for the comparison with dexamethasone applies 4.00 doses during the first year. This is too high and biases the analysis in favour of aflibercept. It would be more reasonable to assume only 2.00 doses, or the average of 1.86 doses as within the pooled GENEVA data for CRVO patients.

The base case of the model assumes only one year of treatment. The scenario analyses that lengthen this to 2 years and to 5 years rely upon expert opinion about dosing. If the dosing and monitoring frequency for aflibercept is no more than that for ranibizumab during the increase in the modelled treatment duration, as may be reasonable, this seem unlikely to affect conclusions for the comparison with ranibizumab. Dosing with dexamethasone during the increases in the modelled treatment duration are more problematic. If the values suggested by Allergan in their submission for the STA of dexamethasone for RVO are applied, this worsens the cost effectiveness of aflibercept compared to dexamethasone.

5.6 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

Aflibercept versus ranibizumab

The ERG revisions to the modelling, excluding both the aflibercept PAS and the ranibizumab PAS, result in a net cost estimate of [redacted], a net gain of 0.053 and a cost effectiveness estimate of [redacted] per QALY. The net costs of the original manufacturer estimates were a bit higher at [redacted], the net gain is similar at 0.054, with these resulting in a cost effectiveness estimate of [redacted] per QALY.

Within the ERG analyses that apply the aflibercept PAS, the ranibizumab PAS can be varied from 0% to 50% in 5% increments. The [redacted] for aflibercept remain below those of ranibizumab up to and including a ranibizumab PAS of [redacted]%. The total costs in the aflibercept arm remain below those of ranibizumab up to and including a ranibizumab PAS of 45%. As a consequence, aflibercept is estimated to dominate ranibizumab up to and including a ranibizumab PAS of 45%. A ranibizumab PAS of 50% results in the total costs of the aflibercept arm being £203 more than those of the ranibizumab arm, and a cost effectiveness estimate of £3,820 per QALY.

The following sensitivity analyses all include the aflibercept PAS.

Applying the relative risk of losing letters within the model framework where these are compounded six times during the first six months has a dramatic effect upon the modelled patient gain from aflibercept over ranibizumab. It all but eliminates it. But as previously outlined, this compounding of relative risks when both the relative risk of gaining letters and the relative risk of losing letters are applied results in model outputs that are not aligned with the validation data.

Applying the upper confidence interval for the relative risk of gaining 15 or more letters at 6 months of [redacted] results in many of the cost effectiveness estimates falling into the SW quadrant, due to the estimated gain from ranibizumab over aflibercept of 0.047 QALYs. If the PAS for ranibizumab is equal to or more than 25% ranibizumab is estimated as being cost effective at the £30,000 per QALY threshold. If the PAS for ranibizumab is a little more than 30% ranibizumab is estimated as being cost effective at the £20,000 per QALY threshold. If the PAS for ranibizumab is 50% aflibercept ceases to be cost saving, and so is dominated by ranibizumab.

Equalising the dosing and monitoring frequencies between aflibercept and ranibizumab still results in aflibercept being estimated to be cost effective relative to ranibizumab, though it now ceases to be cost saving if the PAS for ranibizumab is 45% or more.

Varying the source of the quality of life data changes the net QALY gain in the predictable directions, but the broad conclusions remain unchanged.

Aflibercept versus dexamethasone

ERG revisions to the modelling of aflibercept compared to dexamethasone result in a net cost including the aflibercept PAS of [redacted], a net gain of 0.186 QALYs and a cost effectiveness estimate of £12,265 per QALY. The net costs are somewhat greater than the manufacturer estimate of £612, but the net QALYs are broadly in line with the manufacturer estimate of 0.189. The difference in the net costs estimate mainly arises from the number of administrations of dexamethasone during the first year being revised from the 4.00 of the manufacturer base case to the 1.86 suggested by the pooled analysis of the GENEVA trials' CRVO subset of patients.

The sensitivity analyses for the comparison with dexamethasone are presented in more detail in Table 70 of section 5.4 above. The results of these are more variable than those of the comparison with ranibizumab, in part due to the revised cost effectiveness estimate being £12,265 per QALY.

Applying the lower confidence interval limit of [redacted] for the relative risk of gaining at least 15 letters at 24 weeks results in some improvement in the cost effectiveness estimate to £9,023 per QALY, but applying the upper confidence interval limit of [redacted] somewhat worsens the cost effectiveness estimate to £24,991 per QALY.

Of more concern may be lengthening the assumed duration of treatment, coupled with the dexamethasone dosing proposed by Allergan from a survey of experts it undertook for the STA of dexamethasone for RVO. These analyses also equalise the monitoring frequency for years 2 to 5 between aflibercept and dexamethasone. The 5 year treatment duration worsens the cost effectiveness estimate to £18,699 per QALY.

As in the comparison with ranibizumab, the choice of the source of utilities changes the net QALY gains in the predictable direction. Applying Brown et al (1999) with WSE effects worsens the cost effectiveness estimate to £16,833 per QALY. Combining this with a lengthening of the time horizon to 5 years worsens the cost effectiveness estimate to £25,621 per QALY.

While probably a worst case scenario analysis for this variable, the sensitivity analysis that equalises the administration cost between aflibercept and dexamethasone worsens the cost effectiveness estimate to £13,644 per QALY.

5.7 Overall conclusions

ERG revisions to the comparison of aflibercept with ranibizumab slightly improve the estimates of overall cost savings. This manly arises from the changes to the number of monitoring visits required during the first year of treatment. The net QALY estimates are in line with those of the manufacturer.

A sensitivity analysis that applies the same dosing and administration frequency for aflibercept compared to ranibizumab still results in cost savings given the aflibercept PAS up to and including a ranibizumab PAS of 40%. Increasing the ranibizumab PAS further to 50% results in a net cost estimate of £203 for aflibercept, and a cost effectiveness estimate of £3,820 per QALY.

It appears that a more logical structure for the model would be to apply the week 24 relative risk of gaining letters and the week 24 relative risk of losing letters to the baseline to week 24 aflibercept TPM coupled with the baseline patient distribution in order to estimate the week 24 patient distribution.

The current approach of applying only the week 24 relative risk of gaining letters but compounding it six times over the first six months of the modelling does not seem correct. By chance, it results in week 24 patient distributions for ranibizumab compared to aflibercept for the central estimates of the deterministic model that are not too far out of line with those that would result from the more logical structure for the model. These also both result in a mean gain in BCVA from aflibercept over ranibizumab at week 24 that are quite closely aligned with that of the NMA.

But it is unclear what effect the compounding of the week 24 relative risk of gain has within the probabilistic modelling, and for this reason the probabilistic results need to be treated with caution.

ERG revisions to the comparison of aflibercept with dexamethasone somewhat worsen the estimate of net costs including the aflibercept PAS to £2,285, compared to a manufacturer estimate of £612. This manly arises due to the number of dexamethasone doses in the first year being revised from 4.00 to 1.86, as per that reported within the Allergan submission for the STA of dexamethasone for RVO for the pooled analysis of the CRVO subset of patients of the GENEVA trials. The net QALY estimates are broadly in line with those of the manufacturer. This results in a revised cost effectiveness estimate of £12,265 per QALY compared to the £3,236 per QALY of the manufacturer. The choice of the data source for the quality of life estimates, the duration of treatment and the numbers of administrations during years 2 to 5 affect this cost effectiveness estimate.

The current modelling approach results in week 24 patient distributions for dexamethasone compared to aflibercept for the central estimates of the deterministic model that suggest a mean gain in BCVA from aflibercept over dexamethasone that is somewhat less than that of the NMA. It appears possible that the more logical model structure would result in model outputs that aremore closely aligned with the estimate of the mean gain in BCVA from aflibercept over dexamethasone of the NMA.

6. Discussion and research needs

The clinical effectiveness of aflibercept is not in doubt, but some questions remain.

6.1 Geographic atrophy

A recent paper from the CATT trial,[60] in which ranibizumab and bevacizumab were compared for wet AMD, reported the appearance of geographic atrophy (GA) of the retinal pigment epithelium (RPE) in people who had not had it at the start of the trial. The study reported that GA was more frequent with more frequent dosing of anti-VEGF injections (regular versus PRN) and more frequent with ranibizumab than with bevacizumab. This was not seen in the IVAN trial. However both the CATT and IVAN trials showed that the risk of atrophy increased with increasing number of anti-VEGF injections.

The issue here is whether GA is an adverse effect of anti-VEGF therapy, or whether GA is just part of AMD, possibly accelerated by anti-VEGF treatment. RPE loss is followed by photoreceptor cell loss (because the photoreceptors need the RPE for their survival) and loss of vision. VEGF is required to maintain the choriocapillaris, which nourishes the RPE. There is therefore a theoretical basis for anti-VEGF treatment having a deleterious effect on the RPE especially if the RPE is already unhealthy. However, this may not apply in CRVO where the choroid and RPE should be relatively healthy (apart from changes associated with ageing).

6.2 Dosage and effectiveness issues compared to ranibizumab

The 96-week results from the VIEW trial (of aflibercept versus ranibizumab in wet AMD) reported that results were similar, but that 5 fewer injections of aflibercept were required. The ranibizumab dose was fixed at 4-weekly injections for the first year, whereas the 2q8 aflibercept regimen involved monthly injections for three months then every 8 weeks. It is possible that the frequency of ranibizumab could have been reduced earlier.

However there is some other evidence that aflibercept may be as effective at lower frequency, or even more effective than ranibizumab. Papadopoulos and colleagues (from Regeneron, the original manufacturer of aflibercept) reported that aflibercept had greater affinity for VEGF-A[9] than ranibizumab. Bakall and colleagues[61] report that aflibercept is of benefit in patients with wet AMD

which is resistant to ranibizumab. However this may be due to tachyphylaxis, and we lack data on the effectiveness of ranibizumab in patients who have become resistant to aflibercept. We also have evidence that aflibercept persist in the eye longer than ranibizumab.[62]

Given the present evidence, all we can say is that in wet AMD, which is characterised by neovessel growth and increased permeability of blood vessels, there are suggestions that aflibercept may be more potent than ranibizumab, and stronger evidence for a reduced dosing frequency. Whether this would apply in CRVO, which is a different entity wherein the role of anti-VEGFs is to reduce permeability, we cannot say in the absence of head to head trials.

6.3 Ischaemic RVO

Earlier in this report, we noted the debate around the definition of ischaemic CRVO, and the case made by Hayreh for a stricter definition that the 10 DD one, which he argues would include a lot of people who are not at risk of the serious complications associated with truly ischaemic CRVO, such as NVG. While patients with ischaemia were not excluded from the COPERNICUS and GALILEO trials, the ERG's impression is that not many with serious ischaemia were recruited. This has implications for the Bayer claim that (page 9)
"aflibercept was shown to be clinically and cost-effective in the entire CRVO population, including ischaemic patients"
The ERG regards the evidence base for this statement as somewhat insecure.

Given the paucity of data, should anti-VEGFs be used in ischaemic CRVO? Hayreh has suggested that those with ischaemic CRVO and MO may not have improvements in VA following resolution of the oedema, but anti-VEGFs may reduce the development of neovascularisation. More research is needed but meantime there is no reason not to try aflibercept in ischaemic CRVO, and this would be in line with the lack of any restriction on ranibizumab use in the recent NICE guidance on that drug in CRVO.

6.4 Drop-outs

Very few patients were reported as losing letters in the aflibercept group. The ERG notes that patients who dropped out were evaluated using LOCF forward, which is a method no longer considered optimal, because drop-outs are not at random and may be doing less well than those that continue.

6.5 Comparators

The ERG is aware that triamcinolone is still used in at least one area.

In the appraisal of ranibizumab for RVO, an account is given of the NICE Decision Support Unit's (DSU) consideration of bevacizumab.[63] The key points from the DSU report and other sources are;

- Bevacizumab is available from two major suppliers who hold special licences issued by the MHRA, and therefore quality of product can be assured.
- Based on data from the two major suppliers, and a survey of consultant ophthalmologists, the DSU considered that there is substantial use of bevacizumab for eye conditions in the NHS (and even more in private practice)
- The ERG is aware that the approval of dexamethasone has reduced the use of bevacizumab for CRVO in some hospitals.
- A number of large studies have concluded that bevacizumab is as safe as ranibizumab, most of this evidence coming from use in AMD. Most AEs in anti-VEGF use come from the injection not the drug. The implications of plasma VEGF being lowered for longer by bevacizumab than ranibizumab and aflibercept[64] are uncertain. A slightly increased risk of cardiovascular events with bevacizumab cannot be ruled out, partly because the RCT evidence base for bevacizumab is smaller due to the lack of industry funding.[65] However the recently published 2 -year follow up of the IVAN study[66] found no difference in systemic cardiovascular events - indeed there were slightly fewer with bevacizumab than with ranibizumab (arterial thrombotic event of heart failure 6% ranibizumab, 4% bevacizumab.
- The CATT trial showed an increase that was not statistically significant. The 12-month results IVAN trial[52] showed fewer cardiovascular events with bevacizumab than with ranibizumab but numbers were very small with both drugs (6 with ranibizumab, one with bevacizumab)
- Indirect comparisons have been hampered by the number of patients in bevacizumab trials, but one[67] in DMO found no evidence that ranibizumab was better.
- Bevacizumab is far less expensive than ranibizumab and aflibercept and the NHS would save many £millions if it was used instead, even after taking into account the reduction in the price of ranibizumab and aflibercept. Because these price reductions are confidential, the ERG cannot provide details of how many hundreds of £millions would be saved.
- NICE has declined to issue guidance on bevacizumab for any eye condition.

Dexamethasone

As noted earlier in this report, there are reasons for not regarding dexamethasone as the main comparator, these including;

- The size of the needle required to insert it
- Long-term AEs, cataract and raised IOP

- The dominance by ranibizumab in the recent STA
- We are not aware of any PAS for dexamethasone

However we also note that;

- The risk of cataract will not apply in those who are now pseudophakic
- Comparative effectiveness based on results at 6 months, may under-estimate the effectiveness of dexamethasone, as discussed in the ERG report on dexamethasone for RVO. It may be more effective if repeated after 4 months. This might only be done once because of needle size concerns.
- Not all people with CRVO respond sufficiently to anti-VEGFs.

So there may still be a place for the dexamethasone implant, Ozurdex.

Fluocinolone

The fluocinolone implant, Iluvien, has recently been approved by NICE for DMO in pseudophakic patients only, and only after other treatments have failed. Given its 3-year duration of action and the almost inevitability of cataract formation over that time period, we have not considered it as a comparator in CRVO.

6.6 Mortality and visual impairment

In section 5.2.6, we noted that the manufacturer had used a mortality multiplier of 1.54 for blindness, based on the Christ 2008 study,[54] but that no additional weighting had been added for associated cardiovascular risk factors.

Mortality can be associated with CRVO in two ways. Firstly, CRVO is associated with cardiovascular risk factors. So people who develop CRVO may be at higher risk of CVD than the general population.

The Eye Disease Case Control Study [68] reported risk factors for CRVO. The risk was increased in the presence of diabetes, hypertension and glaucoma, and with low physical activity. Cardiovascular risk factors were particularly associated with ischaemic CRVO. Hypertension doubled the risk of CRVO, as did diabetes requiring glucose lowering drugs, oral or insulin. Moderate alcohol intake and physical activity reduced the risk.

Secondly, visual impairment (VI) may increase the risk of death through increases in accidents such as falls. Legood and colleagues[69] reviewed studies on falls amongst people with visual impairment but did not subdivide according to unilateral or bilateral VI. They estimated that visual impairment increased the risk of hip fracture by 30 to 90%. However they also noted a shortage of high quality

evidence. Coleman and her colleagues[70] reported an increased risk of falls in women with VI but had small numbers with no data on RVO. So the findings of these studies may not apply to people with CRVO who have unilateral vision loss.

Christ and her colleagues[54] from the USA divided people from a large population based sample from the American National Health Interview Survey (NHIS) into 3 groups: blind both eyes; some VI - blind or visually impaired in one eye (as in CRVO); no VI. They adjusted for chronic non-ocular conditions (not specified) and found that some VI was associated with a 13% rise in mortality. Severe VI is associated with a 28% increase, and the hazard ratios for severe VI and some VI are 1.54 and 1.23 respectively. The 1.54 ratio is appropriate for people with both eyes falling into HS5, as outlined in section 5.2.6.

Lee et al[71] also used data from NHIS but divided visual impairment into more groups, with their group 4 being most relevant to CRVO. They reported increases in mortality of 14% in men and 35% in women after adjustment for health status with the increase mostly in cardiovascular diseases. They do note that self-reported health status has not been validated by comparison with physician diagnosis.

Xu and colleagues [72] from the Beijing Eye Study provide data on mortality associated with RVO, in over 4000 people. Nearly all had BRVO (only in in 14 had CRVO – quite different from the UK ratio). Only a short summary was available. Xu et al do not give figures for CRVO separately and numbers were too small anyway. They attribute increased mortality in people with RVO to associated cardiovascular factors.

Cugati and colleagues[73] combine data from the Blue Mountains and Beaver Dam studies to look at cerebrovascular and cardiovascular mortality amongst people who have had RVO. Mortality from cardiovascular disease was doubled in those aged 43 to 69, but not in older age groups. 71 of 96 people with RVO had BRVO, so the hazard ratio of 2.2 in the CRVO group has very wide confidence limits of 0.3 to 16.

The most useful study is by Tsaloumas and colleagues[74] from the West Midlands of England. They followed up a cohort of 588 patients who had had RVO and achieved a 93% follow-up. 48% had CRVO which perhaps suggests selective referral to an expert centre. Over 9 years of follow-up, 17% died. Hypertension, diabetes and hyperlipidaemia were common in those with RVO. Two-thirds of those who died did so from cardiovascular disease. The relative risk of mortality was 1.6 very similar to the 1.54 used in the Bayer modelling.

So it could perhaps have been argued that the weighting for mortality should take into account the two causes of increased mortality associated with CRVO. However, the sensitivity analysis in table 43 shows that increasing the mortality weighting has little effect on the ICER.

Had we applied a CRVO mortality multiplier of 1.60 as estimated by Tsaloumas and colleagues, it would have reduced the modelled patient benefits for both comparisons (ranibizumab and dexamethasone) by around 13%, with a parallel worsening in the ICERs for the comparisons where aflibercept is not dominant. But the overall conclusions would not be affected.

6.7 Research needs.

6.7.1. CRVO is most often due to thrombosis in the central retinal vein. There have been a few trials of drugs to dissolve the clot and re-open the vein, but these treatments do not seem to have come into widespread use.

This may be because the evidence is somewhat sparse. Antithrombotics, such as low-molecular weight heparin (LMWH), and fibrinolytics have been found to preserve or improve visual acuity in RVO with no associated MO. Two systematic reviews[75, 76] identifying the same three RCTs in recent onset (≤30 days) BRVO or CRVO found that LMWH improved VA compared with aspirin and that the associated benefit was larger in CRVO; only one of the three RCTs included people solely with CRVO. One review[76] also included an RCT comparing ticlopidine with placebo and two RCTs assessing intravenous fibrinolytic therapy followed by warfarin or aspirin with either haemodilution or no treatment. The authors of the reviews conclude that no definitive recommendations can be made on clinical effectiveness of LMWH in CRVO given the limited evidence available. Further trials may be justified.

6.7.2. Head to head trials of ranibizumab, bevacizumab and aflibercept are required.

6.7.3. The anti-VEGF drugs are a major advance in the management of MO, but only about 60% of patients get an improvement of 15 or more letters. We therefore need more effective treatments for the rest, and also research into how to predict response.

If after three injections VA is worsening, then options include trying another anti-VEGF agent, or a steroid. So there may be a role for dexamethasone when anti-VEGFs fail.

If there is neither improvement nor worsening (i.e. VA remains within 5 letters of baseline), it may mean that treatment has prevented deterioration, and that it is reasonable to continue with treatment if fluid is present on OCT. (Fluid being more useful than change in CRT.)

6.7.4. Is there any place for laser treatment in CRVO?

The consensus, for example as expressed by the RCO, is that laser photocoagulation is not beneficial for treating MO in CRVO. The Retinal Vein Occlusion Study showed no benefit of laser in macular oedema secondary to CRVO. However we note a small Chinese trial suggesting that grid laser, especially combined with anti-VEGF (bevacizumab was used), was beneficial in reducing CRT.

Whether laser treatment has a place once the retina has dried, to reduce the need for further treatment, is not known.

6.7.5. Treatment and monitoring

The regimen of an initial six injections at monthly intervals, as used in the trials, may be more than is required with aflibercept. Further research into reduced frequency regimens, as mentioned in the SmPC, is required. Research into reduced frequency could be accompanied by studies of the optimum frequency of monitoring.

6.8 Aflibercept for AMD: implications for CRVO

NICE recently appraised aflibercept for AMD, with the main comparator being ranibizumab. While AMD is an entirely different condition from CRVO, there are some similarities, since in both, anti-VEGF agents are used because VEGF levels are raised. We therefore consider what lessons may be drawn from the AMD appraisal for the CRVO one.

Selected points from NICE guidance TA 294.

- NICE has approved aflibercept for treating wet AMD
- The recommended dose is 2mg monthly for 3 doses, then one injection every 2 months for rest of first year, then as required. This implies 7 injections at months 0, 1, 2, 4, 6, 8, 10. Since wet AMD is more aggressive than CRVO, one implication is that seven injections is enough, and possibly more than enough, for CRVO in the first year.
- The main clinical evidence came from the VIEW trial in which there was a direct comparison with ranibizumab. The result showed similar effectiveness, reported as non-inferiority.
- No differences in adverse effect were seen between aflibercept and ranibizumab in an indirect NMA (done to compare aflibercept with ranibizumab in the PRN regimen).

- The costing of aflibercept administration assumed 45%/55% split between administration as outpatients and as day cases. This increased costs, more for ranibizumab because of the more frequent administration.
- The drivers in cost-effectiveness were: drug costs; frequency of injections; frequency of monitoring visits; discount rates; proportions losing or gaining visual acuity; and numbers having monitoring and treatment on the same visit ("one-stop") or on separate visits ("two-stop").
- The base case analysis used EQ-5D data from the VIEW trial. Utilities from the Czoski-Murray study were used in a scenario analysis.
- The appraisal committee (AC) heard from clinical specialists that very few hospital trusts were able to provide the optimal treatment and monitoring frequency of treatment with ranibizumab or bevacizumab, and that the number of injections given was less than used in the trials. The AC accepted that aflibercept could be given less frequently, this reducing the burden on hospital clinics.
- The AC noted that the frequency of AEs with aflibercept in the VIEW trial was low, and "The Committee concluded that aflibercept was safe and well-tolerated in patients with wet AMD".
- The ERG had argued for an average cost per outpatient treatment visit of £129. (NB there is a separate cost code for OP visits that have treatment included.) A cost of £51 for OCT was considered too low.

6.9 Conclusion

Some uncertainties remain, but aflibercept is a very useful addition to the therapeutic options in macular oedema after CRVO.

7. REFERENCES

1. The Central Vein Occlusion Study Group. Natural history and clinical management of central retinal vein occlusion. The Central Vein Occlusion Study Group. *Arch Ophthalmol*. 1997;**115**(4):486-91.

2. Klein R, Klein BE, Lee KE, Cruickshanks KJ, Gangnon RE. Changes in visual acuity in a population over a 15-year period: the Beaver Dam Eye Study. *Am J Ophthalmol*. 2006;**142**(4):539-49.

3. The Royal College of Ophthalmologists. Interim Guidelines for Management of Retinal Vein Occlusion. 2010 [cited 04/10/2013]; Available from: http://www.rcophth.ac.uk/core/core_picker/download.asp?id=728&filetitle=Interim+Guidelines+for+Management+of+Retinal+Vein+Occlusion+2010.

4. Hayreh SS, Podhajsky PA, Zimmerman MB. Natural history of visual outcome in central retinal vein occlusion. *Ophthalmology*. 2011;**118**(1):119-33.

5. McIntosh RL, Rogers SL, Lim L, Cheung N, Wang JJ, Mitchell P, *et al.* Natural history of central retinal vein occlusion: an evidence-based systematic review. *Ophthalmology*. 2010;**117**(6):1113-23.

6. Hayreh SS. Classification of central retinal vein occlusion. *Ophthalmology*. 1983;**90**(5):458-74.

7. National Institute for Health and Clinical Excellence. Dexamethasone intravitreal implant for the treatment of macular oedema secondary to retinal vein occlusion: NICE technology appraisal guidance 229. 2011 [cited 04/10/2013]; Available from: http://guidance.nice.org.uk/TA229/Guidance/pdf/English.

8. National Institute for Health and Care Excellence. Ranibizumab for treating visual impairment caused by macular oedema secondary to retinal vein occlusion: NICE technology appraisal guidance 283. 2013 [cited 04/10/2013]; Available from: http://guidance.nice.org.uk/TA283/Guidance/pdf/English.

9. Papadopoulos N, Martin J, Ruan Q, Rafique A, Rosconi M, Shi E, *et al.* Binding and neutralization of vascular endothelial growth factor (VEGF) and related ligands by VEGF Trap, ranibizumab and bevacizumab. *Angiogenesis*. 2012;**15**(2):171-85.

10. National Institute for Health and Care Excellence. Aflibercept solution for injection for treating wet-age related macular degeneration: NICE technology appraisal guidance 294. 2013 [cited 04/10/2013]; Available from: http://guidance.nice.org.uk/TA294.

11. European Medicines Agency. Eylea (Aflibercept): Assessment report for an extension of indication. 2013 [cited 26/09/2013]; Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/002392/WC500148631.pdf.

12. Edwards SJB, S.; Trevor,N.; Lois,N.; Nherera,L.; Hamilton,V. Ranibizumab for the treatment of macular oedema caused by retinal vein occlusion (RVO): A Single Technology Appraisal. BMJ-TAG, London. 2011 [cited 26/09/2013]; Available from: http://www.nice.org.uk/nicemedia/live/13040/57240/57240.pdf.

13. Epstein D, Algvere P, Von WG, Seregard S, Kvanta A. Long-term benefit from bevacizumab for macular edema in central retinal vein occlusion: 12-month results of a prospective study. *Acta Ophthalmologica*. 2012;**90**:48.

14. Epstein DL, Algvere PV, Von WG, Seregard S, Kvanta A. Benefit from bevacizumab for macular edema in central retinal vein occlusion: twelve-month results of a prospective, randomized study. *Ophthalmology*. 2012;**119**(12):2587-91.

15. Epstein DL, Algvere PV, Von WG, Seregard S, Kvanta A. Bevacizumab for macular edema in central retinal vein occlusion: a prospective, randomized, double-masked clinical study. *Ophthalmology*. 2012;**119**(6):1184-9.

16. Wittstrom E, Holmberg H, Hvarfner C, Andreasson S. Clinical and electrophysiologic outcome in patients with neovascular glaucoma treated with and without bevacizumab. *Eur J Ophthalmol*. 2012;**22**(4):563-74.

17. Cummins ES, D.; Royle,P.; Johnston,R.; Ho,V.; Briscoe,S.; Lois,N.; Waugh,N. Fluocinolone acetonide intravitreal implant for the treatment of chronic diabetic macular oedema: A Single Technology Appraisal. Warwick Evidence. 2012 [cited 20/09/2013]; Available from: http://www.nice.org.uk/nicemedia/live/13304/60438/60438.pdf.

18. Boyer D, Heier J, Brown DM, Clark WL, Vitti R, Berliner AJ, *et al.* Vascular endothelial growth factor Trap-Eye for macular edema secondary to central retinal vein occlusion: six-month results of the phase 3 COPERNICUS study. *Ophthalmology*. 2012;**119**(5):1024-32.

19. Brown DM, Heier JS, Clark WL, Boyer DS, Vitti R, Berliner AJ, *et al.* Intravitreal Aflibercept Injection for Macular Edema Secondary to Central Retinal Vein Occlusion: 1-Year Results From the Phase 3 COPERNICUS Study. *American Journal of Ophthalmology*. 2013;**155**(3):429-37.

20. Holz FG, Roider J, Ogura Y, Korobelnik JF, Simader C, Groetzbach G, *et al.* VEGF Trap-Eye for macular oedema secondary to central retinal vein occlusion: 6-month results of the phase III GALILEO study. *British Journal of Ophthalmology*. 2013;**97**(3):278-84.

21. Gillies M. Intravitreal vegf trap-eye in central retinal vein occlusion: Results of the phase 3 copernicus and galileo studies. *Clinical and Experimental Ophthalmology*. 2012;**40**:44.

22. Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, *et al.* The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *Bmj*. 2011;**343**:d5928.

23. World Health Organization. International Classification of Diseases (ICD) - 10. 2010 [cited 04/10/2013]; Available from: http://www.who.int/classifications/icd/en/.

24. Brown DM, Campochiaro PA, Singh RP, Li Z, Gray S, Saroj N, *et al.* Ranibizumab for macular edema following central retinal vein occlusion: six-month primary end point results of a phase III study. *Ophthalmology*. 2010;**117**(6):1124-33.

25. Campochiaro PA, Brown DM, Awh CC, Lee SY, Gray S, Saroj N, *et al.* Sustained benefits from ranibizumab for macular edema following central retinal vein occlusion: twelve-month outcomes of a phase III study. *Ophthalmology*. 2011;**118**(10):2041-9.

26. Deramo VA, Cox TA, Syed AB, Lee PP, Fekrat S. Vision-related quality of life in people with central retinal vein occlusion using the 25-item National Eye Institute Visual Function Questionnaire. *ArchOphthalmol*. 2003;**121**(9):1297-302.

27. European Medicines Agency. Eylea. Assessment report. 2012 [cited 10/10/2013]; Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002392/WC500135744.pdf.

28. Haller JA, Bandello F, Belfort R, Jr., Blumenkranz MS, Gillies M, Heier J, *et al.* Randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with macular edema due to retinal vein occlusion. *Ophthalmology*. 2010;**117**(6):1134-46.

29. Haller JA, Bandello F, Belfort R, Jr., Blumenkranz MS, Gillies M, Heier J, *et al.* Dexamethasone intravitreal implant in patients with macular edema related to branch or central retinal vein occlusion twelve-month study results. *Ophthalmology*. 2011;**118**(12):2453-60.

30. Yeh WS, Haller JA, Lanzetta P, Kuppermann BD, Wong TY, Mitchell P, *et al.* Effect of the duration of macular edema on clinical outcomes in retinal vein occlusion treated with dexamethasone intravitreal implant. *Ophthalmology*. 2012;**119**(6):1190-8.

31. Wroblewski JJ, Wells JA, III, Adamis AP, Buggage RR, Cunningham ET, Jr., Goldbaum M, *et al.* Pegaptanib sodium for macular edema secondary to central retinal vein occlusion. *Archives of Ophthalmology*. 2009;**127**(4):374-80.

32. Heier JS, Campochiaro PA, Yau L, Li Z, Saroj N, Rubio RG, *et al.* Ranibizumab for macular edema due to retinal vein occlusions: long-term follow-up in the HORIZON trial. *Ophthalmology*. 2012;**119**(4):802-9.

33. Bhavsar AR, Ip MS, Glassman AR, Groups DatSS. The risk of endophthalmitis following intravitreal triamcinolone injection in the DRCRnet and SCORE clinical trials. *American Journal of Ophthalmology*. 2007;**144**(3):454-6.

34. Blodi BA, Domalpally A, Scott IU, Ip MS, Oden NL, Elledge J, *et al.* Standard Care vs Corticosteroid for Retinal Vein Occlusion (SCORE) Study system for evaluation of stereoscopic color fundus photographs and fluorescein angiograms: SCORE Study Report 9. *Archives of Ophthalmology*. 2010;**128**(9):1140-5.

35. Chan CK, Ip MS, VanVeldhuisen PC, Oden NL, Scott IU, Tolentino MJ, *et al.* SCORE Study report #11: incidences of neovascular events in eyes with retinal vein occlusion. *Ophthalmology*. 2011;**118**(7):1364-72.

36. Ip M, Oden N, VanVeldhuisen P, Scott I, Blodi B. The Standard Care vs. Corticosteroid for Retinal Vein Occlusion Study: Design and Baseline Characteristics. *American Academy of Ophthalmology*. 2008:260.

37. Ip MS, Oden NL, Scott IU, VanVeldhuisen PC, Blodi BA, Figueroa M, *et al.* SCORE Study report 3: study design and baseline characteristics. *Ophthalmology*. 2009;**116**(9):1770-7.

38. Ip MS, Scott IU, VanVeldhuisen PC, Oden NL, Blodi BA, Fisher M, *et al.* A randomized trial comparing the efficacy and safety of intravitreal triamcinolone with observation to treat vision loss associated with macular edema secondary to central retinal vein occlusion: the Standard Care vs

Corticosteroid for Retinal Vein Occlusion (SCORE) study report 5. *Archives of Ophthalmology*. 2009;**127**(9):1101-14.

39. Myers D, Blodi B, Ip M, Scott I, Warren K. Reading Center Evaluation of OCT Images From Patients Enrolled in the Standard Care vs. Corticosteroid for Retinal Vein Occlusion (SCORE) Study. *Iovs*. 2006;**47**:ARVO.

40. Oden NL, Veldhuisen PC, Scott IU, Ip MS, Blodi BA. Temporal Variability of OCT in Retinal Vein Occlusion Participants in the SCORE Study. *Iovs*. 2007;**48**:ARVO.

41. Scott IU, Blodi BA, Ip MS, VanVeldhuisen PC, Oden NL, Chan CK, *et al.* SCORE Study Report 2: Interobserver agreement between investigator and reading center classification of retinal vein occlusion type. *Ophthalmology*. 2009;**116**(4):756-61.

42. Scott IU, Oden NL, VanVeldhuisen PC, Ip MS, Blodi BA, Antoszyk AN, *et al.* SCORE Study Report 7: incidence of intravitreal silicone oil droplets associated with staked-on vs luer cone syringe design. *American Journal of Ophthalmology*. 2009;**148**(5):725-32.

43. Scott IU, VanVeldhuisen PC, Oden NL, Ip MS, Blodi BA, Hartnett ME, *et al.* Baseline predictors of visual acuity and retinal thickness outcomes in patients with retinal vein occlusion: Standard Care Versus COrticosteroid for REtinal Vein Occlusion Study report 10. *Ophthalmology*. 2011;**118**(2):345-52.

44. Scott IU, VanVeldhuisen PC, Oden NL, Ip MS, Blodi BA, Jumper JM, *et al.* SCORE Study report 1: baseline associations between central retinal thickness and visual acuity in patients with retinal vein occlusion. *Ophthalmology*. 2009;**116**(3):504-12.

45. Scott IU, VanVeldhuisen PC, Oden NL, Ip MS, Domalpally A, Doft BH, *et al.* Baseline Characteristics and Response to Treatment of Participants With Hemiretinal Compared With Branch Retinal or Central Retinal Vein Occlusion in the Standard Care vs COrticosteroid for REtinal Vein Occlusion (SCORE) Study: SCORE Study Report 14. *Archives of Ophthalmology*. 2012;**130**(12):1517-24.

46. Warren K, Blodi BA, Oden N, Veldhuisen P, Scott IU, Ip M. Reading Center Evaluation of Baseline Retinal Images in the Standard Care vs. Corticosteroid for Retinal Vein Occlusion (SCORE) Study. *Iovs*. 2008:ARVO.

47. Aggermann T, Brunner S, Krebs I, Haas P, Womastek I, Brannath W, *et al.* A prospective, randomised, multicenter trial for surgical treatment of central retinal vein occlusion: results of the

Radial Optic Neurotomy for Central Vein Occlusion (ROVO) study group. *Graefes ArchClinExpOphthalmol*. 2013;**251**(4):1065-72.

48. Ocular Surgery News. New anti-VEGF shows good results in poor responders to previous anti-VEGF therapy. 2013.

49. Kinge B, Stordahl PB, Forsaa V, Fossen K, Haugstad M, Helgesen OH, *et al.* Efficacy of ranibizumab in patients with macular edema secondary to central retinal vein occlusion: results from the sham-controlled ROCC study. *AmJOphthalmol*. 2010;**150**(3):310-4.

50. Donegan S, Williamson P, Gamble C, Tudur-Smith C. Indirect comparisons: a review of reporting and methodological quality. *PloS one*. 2010;**5**(11):e11054.

51. Czoski-Murray C, Carlton J, Brazier J, Young T, Papo NL, Kang HK. Valuing condition-specific health states using simulation contact lenses. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research*. 2009;**12**(5):793-9.

52. Chakravarthy U, Harding SP, Rogers CA, Downes SM, Lotery AJ, Wordsworth S, *et al.* Ranibizumab versus bevacizumab to treat neovascular age-related macular degeneration: one-year findings from the IVAN randomized trial. *Ophthalmology*. 2012;**119**(7):1399-411.

53. Klein R, Klein BE, Linton KL, De Mets DL. The Beaver Dam Eye Study: visual acuity. *Ophthalmology*. 1991;**98**(8):1310-5.

54. Christ SL, Lee DJ, Lam BL, Zheng DD, Arheart KL. Assessment of the effect of visual impairment on mortality through multiple health pathways: structural equation modeling. *Investigative ophthalmology & visual science*. 2008;**49**(8):3318-23.

55. Brown GC, Brown MM, Brown HC, Kindermann S, Sharma S. A value-based medicine comparison of interventions for subfoveal neovascular macular degeneration. *Ophthalmology*. 2007;**114**(6):1170-8.

56. Vaahtoranta-Lehtonen H, Tuulonen A, Aronen P, Sintonen H, Suoranta L, Kovanen N, *et al.* Cost effectiveness and cost utility of an organized screening programme for glaucoma. *Acta ophthalmologica Scandinavica*. 2007;**85**(5):508-18.

57. Brown GC. Vision and quality-of-life. *Transactions of the American Ophthalmological Society*. 1999;**97**:473-511.

58. McCrone PD, S.; Patel,A.; Knapp,M.; Lawton-Smith,S. Paying the price: The cost of mental health care in England to 2026. 2008.

59. Meads C, Hyde C. What is the cost of blindness? *The British journal of ophthalmology*. 2003;**87**(10):1201-4.

60. Grunwald JE, Daniel E, Huang J, Ying GS, Maguire MG, Toth CA, *et al.* Risk of Geographic Atrophy in the Comparison of Age-related Macular Degeneration Treatments Trials. *Ophthalmology*. 2013.

61. Bakall B, Folk JC, Boldt HC, Sohn EH, Stone EM, Russell SR, *et al.* Aflibercept therapy for exudative age-related macular degeneration resistant to bevacizumab and ranibizumab. *Am J Ophthalmol*. 2013;**156**(1):15-22.e1.

62. Stewart MW, Rosenfeld PJ. Predicted biological activity of intravitreal VEGF Trap. *The British journal of ophthalmology*. 2008;**92**(5):667-8.

63. Poku ER, J.; Everson-Hock,E.; Essat,M.; Wong,R.; Pandor,A.; Wailoo,A. . Bevacizumab in eye conditions: issues related to quality, use, efficacy and safety. Report by the Decision Support Unit. 2012.

64. Zehetner C, Kirchmair R, Huber S, Kralinger MT, Kieselbach GF. Plasma levels of vascular endothelial growth factor before and after intravitreal injection of bevacizumab, ranibizumab and pegaptanib in patients with age-related macular degeneration, and in patients with diabetic macular oedema. *The British journal of ophthalmology*. 2013;**97**(4):454-9.

65. Schmucker C, Loke YK, Ehlken C, Agostini HT, Hansen LL, Antes G, *et al.* Intravitreal bevacizumab (Avastin) versus ranibizumab (Lucentis) for the treatment of age-related macular degeneration: a safety review. *The British journal of ophthalmology*. 2011;**95**(3):308-17.

66. Chakravarthy U, Harding SP, Rogers CA, Downes SM, Lotery AJ, Culliford LA, *et al.* Alternative treatments to inhibit VEGF in age-related choroidal neovascularisation: 2-year findings of the IVAN randomised controlled trial. *Lancet*. 2013.

67. Ford JA, Elders A, Shyangdan D, Royle P, Waugh N. The relative clinical effectiveness of ranibizumab and bevacizumab in diabetic macular oedema: an indirect comparison in a systematic review. *BMJ*. 2012;**345**:e5182.

68. The Eye Disease Case-Control Study Group. Risk factors for central retinal vein occlusion. The Eye Disease Case-Control Study Group. *Arch Ophthalmol*. 1996;**114**(5):545-54.

69. Legood R, Scuffham P, Cryer C. Are we blind to injuries in the visually impaired? A review of the literature. *Injury prevention : journal of the International Society for Child and Adolescent Injury Prevention*. 2002;**8**(2):155-60.

70. Coleman AL, Stone K, Ewing SK, Nevitt M, Cummings S, Cauley JA, *et al.* Higher risk of multiple falls among elderly women who lose visual acuity. *Ophthalmology*. 2004;**111**(5):857-62.

71. Lee DJ, Gomez-Marin O, Lam BL, Zheng DD. Visual acuity impairment and mortality in US adults. *Arch Ophthalmol*. 2002;**120**(11):1544-50.

72. Xu L, Liu WW, Wang YX, Yang H, Jonas JB. Retinal vein occlusions and mortality: the Beijing Eye Study. *Am J Ophthalmol*. 2007;**144**(6):972-3.

73. Cugati S, Wang JJ, Knudtson MD, Rochtchina E, Klein R, Klein BE, *et al.* Retinal vein occlusion and vascular mortality: pooled data analysis of 2 population-based cohorts. *Ophthalmology*. 2007;**114**(3):520-4.

74. Tsaloumas MD, Kirwan J, Vinall H, O'Leary MB, Prior P, Kritzinger EE, *et al.* Nine year follow-up study of morbidity and mortality in retinal vein occlusion. *Eye (Lond).* 2000;**14**(Pt 6):821-7.

75. Lazo-Langner A, Hawel J, Ageno W, Kovacs MJ. Low molecular weight heparin for the treatment of retinal vein occlusion: a systematic review and meta-analysis of randomized trials. *Haematologica*. 2010;**95**(9):1587-93.

76. Squizzato A, Manfredi E, Bozzato S, Dentali F, Ageno W. Antithrombotic and fibrinolytic drugs for retinal vein occlusion: a systematic review and a call for action. *ThrombHaemost*. 2010;**103**(2):271-6.

8. APPENDICES

Appendix 1. Bayer's NMA results

Table 71. Odds ratio - Patients gaining ≥15 letters of BCVA from baseline at 6 months

Treatments	Fixed Effects			Random Effects		
	Odds Ratio	lCr.Int.	uCr.Int.	Odds Ratio	lCr.Int.	uCr.Int.
Dexamethasone 0.7mg vs. Aflibercept 2mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ranibizumab 0.5mg vs. aflibercept 2mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
sd	n.a.			0.67	0.03	1.90

lCr.Int – lower credible interval; uCr.Int – upper credible interval; sd – between study standard deviation; totresdev – total residual deviance; DIC – deviance information criterion

Table 72. Odds Ratios - Patients losing >15 letters of BCVA from baseline at 6 months

Treatments	Fixed Effects			Random Effects		
	Odds Ratio	lCr.Int.	uCr.Int.	Odds Ratio	lCr.Int.	uCr.Int.
Ranibizumab 0.5mg vs. aflibercept 2mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
sd				1.18	0.15	1.96

lCr.Int – lower credible interval; uCr.Int – upper credible interval; sd – between study standard deviation; totresdev – total residual deviance; DIC – deviance information criterion

Table 73. Mean Change in BCVA/number of letters read from baseline at 6 months (ROCC excluded)

Treatments	Fixed Effects			Random Effects		
	Mean Change	lCr.Int.	uCr.Int.	Mean Change	lCr.Int.	uCr.Int.
Aflibercept 2mg vs. dexamethasone 0.7mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Aflibercept 2mg vs. ranibizumab 0.5mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
sd	n.a.			3.00	0.25	4.90

lCr.Int – lower credible interval; uCr.Int – upper credible interval; sd – between study standard deviation; totresdev – total residual deviance; DIC – deviance information criterion