Single Technology Appraisal (STA)

Aflibercept solution for injection for the treatment of macular oedema caused by central retinal vein occlusion [ID578]

Section A: Clarification on effectiveness data

Priority question A1. In the trials, non-responders have been defined as those discontinuing prematurely and receiving less than 5 injections. Please clarify:

1. How many patients did not respond to the treatment in the two trials?
2. How non-response was defined. Table 1, on page 13 of the submission states "No improvement in visual and anatomic outcomes over the course of the first three injections". Please explain what is meant by "no improvement" Was this less than 5 letters?
3. Is it correct to assume that a stopping rule is applied at week 12 after three injections at weeks 0, 4 and 8? And if so, is it correct to assume that patients who stop receiving treatment at 12 weeks are listed under "lack of efficacy" in Figures 4 and 5, on pages 48 and 49 of the submission?

This question relates to two distinct issues; discontinuation in the pivotal trials (Q1/3), as shown in Figure 4 and 5, and recommendations by the European Medicines Agency (EMA) in the Summary of Product Characteristics (SmPC) on continuation of aflibercept treatment, as stated in Table 1 (Q2). This may be explored by looking at the subgroup analysis of those in the pivotal trials gaining less than 5 letters at week 12.

1. The numbers of those in the COPERNICUS and GALILEO trials discontinuing prior to 24 weeks is shown in Figure 4 and 5. In the pivotal clinical trials (COPERNICUS/GALILEO), the protocol defined six initial monthly injections of aflibercept 2mg or sham from Week 0 through to Week 20. Treatment failure/lack of efficacy was only reported as a reason for discontinuation in the sham arm.

In this time period, subjects may have been removed from study by the investigator or the sponsor if one or more of the following occurred:

• Non-compliance with protocol by the subject.
• Adverse event (decision to be removed from study made by either the investigator or subject).
• Decision by the investigator or sponsor that termination is in the subject's best medical interest or administrative decision for a reason other than that of an adverse event.
• Request for withdrawal by the subject for reasons other than an intolerable adverse event.
• Withdrawal of informed consent.
• Loss to follow-up as determined by the subject's failure to respond to at least 2 telephone calls and a certified letter sent to the subject's last known address.

The definition of response, as described in Question A1, in the trials was for analysis purposes. The primary efficacy analysis was conducted on the FAS population. The full analysis set (FAS) included all randomized subjects who received any study treatment (aflibercept or sham injection) and have at least one post-baseline assessment. In COPERNICUS, in the primary endpoint analysis, patients who discontinued prematurely (prior to week 24) and had fewer than 5 injections were evaluated as non-responders. In GALILEO, in primary analyses, patients who discontinued prior to week 24 were also considered as non-responders.

Holz, 2013, notes from GALILEO: "*The sham group had a higher percentage of patients discontinuing study primarily due to AEs and lack of efficacy; this had no major impact on the analysis of the primary endpoint (with discontinued patients before week 24 judged as non-responders), as similar results were obtained after imputing the missing values with the LOCF approach, using observed cases, or excluding patients who discontinued prior to week 24 and received fewer than five injections."*

2. In the SmPC for aflibercept (September 2013), the EMA has stated: "*If there is no improvement in visual and anatomic outcomes over the course of the first three injections, continued treatment is not recommended."*

The European Assessment Report (EPAR) for aflibercept explains the reasoning of the EMA that led to this wording in the SmPC: "*Verification of the clinical response at 3-month time-point was therefore required by CHMP. In this way, non-responders will not continue receiving treatment after an initial, futile 3-month course. If the clinician decides to continue treatment, the patient should receive monthly injections until visual and anatomic outcomes are stable for three monthly assessments. This will reduce the probability of under treating patients who would still benefit from monthly injections (including the 15% who still gain benefit after 3 months). When stability is reached, treatment may be discontinued or continued with longer intervals. In case of deterioration, treatment should be resumed.*

The final agreed wording for section 4.2 is considered relevant for clinical practice, allowing discontinuation of treatment in patients who would not benefit or have reached stabilization, and an extension of the treatment interval for patients who are stable and still under treatment. The CHMP considered that the revised posology fits well with the current clinical practice and allows adaptation of treatment for all patients, hence avoiding as much as possible, over or under treatments."

3. *As discussed in the previous responses,* in the pivotal clinical trials (COPERNICUS/GALILEO), the protocol defined six initial monthly injections of aflibercept 2mg or sham from Week 0 through to Week 20. The numbers of those in the COPERNICUS and GALILEO trials discontinuing prior to 24 weeks is shown in Figure 4 and 5 and the reasons allowed for this in the protocol are listed above. Treatment failure/lack of efficacy was only reported as a reason for discontinuation in the sham arm.

Although not specifically defined in the SmPC, five letter changes are generally regarded as the minimum relevant BCVA change. An analysis of the subgroup of patients in the COPERNICUS and GALILEO trials that had gained less than 5 letters at week 12, was conducted. The analysis of visual gain of this subgroup of 'non-responders' after three injections in the COPERNICUS and GALILEO trials confirmed that patients regarded as being 'non-responders' did not gain BCVA despite intensive on-going treatment.

See figures below (academic in confidence):

At the request of the EMA, an analysis of after how many injections patients' visual acuity stabilised. Of the patients considered 'responders, approximately [redacted]% reached stability after three injections and approximately [redacted]% never reached stability. Please see figure provided below (academic in confidence):

Priority question A2. Figures 6 and 7, on pages 52 and 53 of the submission, show the percentages of patients gaining 15 or more letters over time. In COPERNICUS, it appears that the plateau was reached at approximately 8 weeks, with only about a 2% increase between 8 and 12 weeks, while in GALILEO the plateau was reached after 12 weeks, with about a 10% rise between weeks 8 and 12. Please clarify:

1. Why there was a difference between the trials in the time taken to reach the plateau?
2. How many patients who gained fewer than 5 letters by week 8 later went on to gain more than 10 letters?

1. No specific reason is known to explain this difference between studies. We believe that it was just an inherent variability in the study populations, possibly reflecting the differences in trial design.

2. An additional subgroup data analysis for those gaining fewer than 5 letters by week 8 was conducted in terms of mean change (analysis by 10 letter gain was not conducted):

[redacted]

Table 14.5 / 2: Summary statistics for ETDRS letter score and changes from baseline by visit and by futility subgroup based on a futility limit of 5 letters at week 8, LOCF (FAS, VTE 2Q4)

futility status: futile

Planned treatment Number	Visit	Value at Visit								Change from Baseline							
		n	Mean	SD	Min	Q1	Median	Q3	Max	n	Mean	SD	Min	Q1	Median	Q3	Max
VTE 2Q4 + PRN (N=31)	BASELINE	[redacted]															
	WEEK 4																
	WEEK 8																
	WEEK 12																
	WEEK 16																
	WEEK 20																
	WEEK 24																
	WEEK 28																
	WEEK 32																
	WEEK 36																
	WEEK 40																
	WEEK 44																
	WEEK 48																
	WEEK 52																
	WEEK 76																
	WEEK 76/100																

[redacted]

Table 14.5 / 2: Summary statistics for ETDRS letter score and changes from baseline by visit and by futility subgroup based on a futility limit of 5 letters at week 8, LOCF (FAS, VTE 2Q4) (cont.)

futility status: non-futile

Planned treatment Number	Visit	Value at Visit								Change from Baseline							
		n	Mean	SD	Min	Q1	Median	Q3	Max	n	Mean	SD	Min	Q1	Median	Q3	Max
VTE 2Q4 + PRN (N=186)	BASELINE	[redacted]															
	WEEK 4	[redacted]								[redacted]							
	WEEK 8	[redacted]								[redacted]							
	WEEK 12	[redacted]								[redacted]							
	WEEK 16	[redacted]								[redacted]							
	WEEK 20	[redacted]								[redacted]							
	WEEK 24	[redacted]								[redacted]							
	WEEK 28	[redacted]								[redacted]							
	WEEK 32	[redacted]								[redacted]							
	WEEK 36	[redacted]								[redacted]							
	WEEK 40	[redacted]								[redacted]							
	WEEK 44	[redacted]								[redacted]							
	WEEK 48	[redacted]								[redacted]							
	WEEK 52	[redacted]								[redacted]							
	WEEK 76	[redacted]								[redacted]							
	WEEK 76/100	[redacted]								[redacted]							

[redacted]

Priority question A3. In Table 9, on page 46 of the submission, there are references to 'LOCF, observed cases' and 'pure LOCF. Please clarify what is meant by the two terms.

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).

Priority question A4. Please verify the figures in Tables 35 and 36 on page 104 of the submission? It is understood that table 36 was supposed to report relative risk (RR) but it appears that the figures are actually for odds ratios (ORs), as they are identical to those in table 35. If the figures have inadvertently been duplicated from table 35, please provide the correct figures.

Please see below the table reporting the RR for patients losing >15 letters that should replace the existing table 36 in the submission. Please note that the interpretation of the results remains the same.

Table 36. 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						
sd				1.18	0.15	1.96
totresdev	9.50	5.87	18.20	5.79	1.35	15.20
Data Points	6					
DIC	37.66			34.94		

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

Priority question A5. Were patients asked at the end of the trials what treatment they thought they had received?

No they were not.

Priority question A6. It is noted(see page 79 of the submission) that there was a slight decline in Visual Acuity in patients receiving aflibercept once they went on to PRN aflibercept, which could be 12-weekly as in COPERNICUS. Please advise what the minimum monitoring interval should be in routine care.

There is a difference between the frequency of assessment conducted in the COPERNICUS and GALILEO trials and monitoring frequency stipulated in the SmPC. Whereas the clinical trials mandated 4-weekly assessments in the *pro re nata* phase, no such requirement for monthly monitoring was made by the EMA in the SmPC for aflibercept. Clinicians monitor at injections visits until stability and then are given flexibility, according to the SmPC, with regard to the minimum monitoring interval during the treatment extension period:

> *"…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.

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." (Eylea SmPC)

The SmPC for aflibercept does not mandate monthly monitoring of visual acuity. Monthly monitoring of visual acuity is required according to the SmPC for ranibizumab. The SmPC for aflibercept allows for treatment extension after stability is reached and, therefore, monitoring is expected to be less frequent than monthly in real life clinical practice.

Monitoring for aflibercept was also conservatively estimated in the economic model. Due to the early timing of this NICE submission, a final SmPC and posology from the EMA was not available at the time of submission. Therefore, the physician survey used for the economic model was conducted in the absence of a final SmPC posology and relied heavily on an interpretation of the clinical trial data, which included 4-weekly monitoring.

Updated estimation of monitoring frequency - aflibercept:

Based on the analysis of those gaining less than 5 letters ('non-responders') in the COPERNICUS and GALILEO trials ([redacted]), it is assumed that these patients would stop treatment after 3 injections according to the SmPC and, therefore, would attend 4 visits in the first year. For 'responders', assuming a visit at the same time as a treatment injection, these patients would have a minimum of 7.5 visits in the first year (see QA10). Overall, combining these estimates for all patients, this therefore indicates a minimum of 7 monitoring visits in the first year, although monitoring according to the SmPC would be determined by the treating physician based on the individual patient's response and may be more frequent than the schedule of injections.

Priority question A7. Please clarify or correct the figures in Table 24, on page 81 of the submission. In GALILEO, these figures report that [redacted]% of patients in the aflibercept arm received no aflibercept. The mean frequency in the aflibercept arm is given as 1.3, with a maximum of [redacted] injections, which should apply only to injections between weeks 52 and 76.

The GALILEO data relate only to weeks 52 to 76. The COPERNICUS data relates to baseline to week 100. This presentation is due to differences in reporting of the two trials.

Priority question A8. Tables 21 and 22 (on pages 79 and 80 of the submission) report the changes in letters differently. The ERG has converted the table into an easier format, please see below. Please confirm that the table below contains the correct figures for COPERNICUS, and please complete the table with the equivalent figures for GALILEO.

	COPERNICUS		GALILEO	
	sham	aflib	sham	aflib
Change by 24 weeks (number of letters)				
Gain 15 or more	9	66	15	65
Gain 10-14	7	21	6	13
Gain 5-9	13	10	See response below	

Gain 0-4	9	10		
Loss 1-4	6	2	[redacted]	[redacted]
Loss 5-9	7	3		
Loss 10-14	2	0	[redacted]	[redacted]
Loss15 or more	20	2		

The GALILEO reported summaries of the data in terms of >=10 letters gain and <0 letters loss whereas the COPERNICUS data also reported summaries of the data in terms of >= 5 letters and >= 0 letters gain. The presentation in the submission is due to differences in reporting of the two trials, one sponsored by Regeneron and one sponsored by Bayer.

Please clarify why 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 [redacted]% (ERG calculation) and [redacted]% in GALILEO (table 22, page 80 of the submission)?

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. Nevertheless, sham patients who did worse in COPERNICUS were allowed active treatment after 24 weeks.

Priority question A9. Please check the figures in brackets in line 4, paragraph 5 on page 81 of the submission. Line 4 states "number of active injections was higher in sham group (1.7) than in aflibercept group (1.7 injections)". Should the first 1.7 relating to the sham group be 1.3?

Yes this is correct, as described in Table 24.

Priority question A10. Please comment on the number of injections expected in routine care, compared with the number in the protocol-driven trials. It is noted that on page 131 of the submission, states that the draft SmPC may allow less frequent injections than in the trials. For example, might aflibercept be given at weeks 0, 4, 8, and then at 8 weekly intervals as required, as in age-related macular degeneration (AMD)? That would result in 5 injections in the first 24 weeks rather than the 6 injections reported in Table 4, on page 34 of the submission.

As noted above, there is a difference between the treatment regimen in the COPERNICUS and GALILEO trials and that stipulated in the SmPC. Whereas the clinical trial mandated 6 initial monthly injections, no such requirement was made by the EMA in the SmPC (see QA1). The posology recommends treatment to stability, at which point clinicians are then given flexibility with regard to extending treatment intervals in the following periods:

> *"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…" (Eylea SmPC)*

The number of injections was conservatively estimated in the economic model. Due to the early timing of this NICE submission, a final SmPC and posology from the EMA was not available at submission. The economic model used data from the clinical trials and a physician survey to estimate frequency. The survey was conducted in the absence of a final SmPC posology and relied heavily on an interpretation of the clinical trial data, which included the 6 initial monthly doses. Frequency according to the SmPC may, therefore, be less frequent than that used in the model.

Updated treatment frequency estimation - aflibercept:

Based on the SmPC posology and an analysis of the data, the estimated number of injections with aflibercept in the first year is 7 injections:

- Data from the COPERNICUS and GALILEO trials showed that approximately [redacted] of patients may be considered 'non-responders', assuming that is defined as a gain of less than 5 letters. According to the SmPC, these patients would receive 3 injections in clinical practice.
- As discussed in QA1, of the remaining ([redacted]) patients considered 'responders', approximately [redacted] reached stability after three injections and approximately [redacted] never reached stability. Please see figure provided below ([redacted]):

- Of those that may be considered responders [redacted] of the total population)achieved stability after 3 initial monthly injections, [redacted] after 4 injections, [redacted] after 5 injections, [redacted] after 6 injections and [redacted] continuing to receive monthly injections but not achieving target.
- Assuming that 2.6 injections are required over a 6 month period once stability is achieved, as was the case in the pivotal trials, and applying this to the remaining maintenance period, patients receive an average of 7.49 injections in the first year.
- Combining these figures results in an estimated 6.9 injections in the first year.

% patients	Initial monthly doses to stability	Maintenance period	Total
[redacted]	3	9*2.6/6= 3.9	6.9
[redacted]	4	8*2.6/6= 3.47	7.47
[redacted]	5	7*2.6/6= 3.03	8.03
[redacted]	6	6*2.6/6= 2.6	8.6
[redacted]	12	NA	12

Non-priority question A11. Please comment on why some patients who were randomised to the sham treatment arms of the trials discontinued because of adverse events (see figures 4 and 5, on pages 48 and 49 of the submission) but none of the patients randomised to the aflibercept arms of the trials did so? Please comment on the relationship between adverse events and lack of efficacy. Adverse events do not include lack of efficacy – there is a separate entry for that. Also, there are no cases of lack of efficacy at all in the aflibercept arms.

No specific reason is known to explain this difference between treatment arms. We believe that it was just an inherent variability in the trial data. In addition, there is no further detail available in the clinical study reports on these reasons for discontinuation prior to 24 weeks. According to the study protocol, patient received 6 initial monthly doses of aflibercept or sham between Week 0 and Week 20. According to the protocol, subjects may have been removed from study by the investigator or the sponsor if one or more of the following occurred:

• Noncompliance with protocol by the subject.

• Adverse event (decision to be removed from study made by either the investigator or subject).
• Decision by the investigator or sponsor that termination is in the subject's best medical interest or administrative decision for a reason other than that of an adverse event.
• Request for withdrawal by the subject for reasons other than an intolerable adverse event.
• Withdrawal of informed consent.
• Loss to follow-up as determined by the subject's failure to respond to at least 2 telephone calls and a certified letter sent to the subject's last known address.

Non-priority question A12. Please comment on the differences between the COPERNICUS and GALILEO trials in relation to change in Best Corrected Visual Acuity in the sham arms. In COPERNICUS, there was very little difference in BCVA in the sham perfused and sham non-perfused groups (see Figure 11, page 66 of the submission). However in GALILEO (see Figure 12, page 66 of the submission), there was a large difference in BCVA change between perfused and non-perfused in the sham arm.

This is already discussed in the context of Question A8. More patients in COPERNICUS had disease duration longer than 2 months and also had a slightly worse BCVA at baseline compared to GALILEO. This may be a chance difference in study populations, or may have been driven by the differences in study design, as discussed in the response to Question 8.

We feel the important point here is that non-perfused patients achieved very poor outcomes in both studies if not treated. This highlights the importance of including non-perfused patients in both studies.

The breakdown between perfused and non-perfused sham arms simply shows that the 'better' sham arm performance in GALILEO was driven mainly by perfused patients doing well. Perfused patients in GALILEO treated with sham did better than perfused patients in COPERNICUS, but this may reflect the fact that the GALILEO population seemed to have overall slightly less severe disease than COPERNICUS.

As stated in our response to Q8, 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 in GALILEO and COPERNICUS to work as well in non-perfused patients as in perfused patients.

Non-priority question A13. Please advise if any patients were excluded from GALILEO and/or COPERNICUS because of more severe ischaemia.

No, as long as they met inclusion and exclusion criteria they were allowed into the study.

Non-priority question A14. The section on Subgroup analyses for Central Retinal Thickness, on page 68 of the submission, reports changes in each trial, but gives no actual data for subgroups by baseline CRT. Please advise if any subgroup analysis by bands of baseline CRT was carried out and if so, please provide details. Did improvements in VA vary according to baseline CRT, for both the aflibercept and sham treatment arms?

This paragraph relates to the analysis of the outcome 'Mean change in CRT from baseline'. As for the other outcomes specified on page 47 of the submission, an analysis of pre-specified subgroups (gender, age, race, renal function, hepatic impairment) was conducted for this outcome. CRT was not, in itself, a pre-defined subgroup analysis.

Non-priority question A15. In COPERNICUS, after 24 weeks almost all (57 of the 60 who reached week 24) patients who had been randomised to receive a sham treatment crossed over to receive aflibercept. They received a mean of 6.4 injections of aflibercept by week 100. Table 21 on page 79 of the submission shows that by week 52, 30% of those patients who had crossed over to receive PRN aflibercept group gained 15 or more letters, and 47% gained 10 or more. These figures compare with the 58% and 76% in the aflibercept group between weeks 0 and 24. Please provide a comment as to why those crossing over to aflibercept from the in sham group did less well once they received aflibercept.

This supports the concept that early treatment is appropriate for CRVO to avoid unnecessary decline in vision and poorer outcomes with delayed treatment.

Interim clinical guidelines on the management of Retinal Vein Occlusion from the Royal College of Ophthalmologists (2010) indicate earlier treatment for macula oedema secondary to CRVO:

> *"…the longer the duration of macular oedema, the more the structural damage at the fovea so it is justifiable that early treatment be initiated."*

Non-priority question A16. Please provide clarification on how the figure of 6 injections was derived. Would monthly treatment given at weeks 0, 4, 8, 12, 16, 20 and 24 not represent 7 treatments? Or is the 24 week injection not counted at this stage? If so, then there would be 4 not 5 with a switch to 8-weekly after the first three.

Initial monthly injections were given at week 0, 4, 8, 12, 16 and 20, representing 6 initial monthly treatments. Starting with Week 24 through Week 48, subjects in this arm were evaluated monthly and received aflibercept 2 mg as needed (PRN) or a sham treatment according to protocol retreatment criteria.

Section B: Clarification on cost-effectiveness data

Quality of Life

Priority 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 EQ5D. 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?

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 B1 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.

Priority question B2. Please provide the mean EQ-5D values from the European population of the GALILEO study evaluated using the UK social tariff, the sample standard deviations of these and the numbers of observations these apply to, pooled between the study arms across the health states of the model. Please supply this separately for baseline, week 24, week 52, week 76 and early termination as in the table below (one table for each time point):

The table below presents the mean EQ5D values from the European population of the GALILEO study evaluated using the UK social tariff, the sample standard deviations (SD) of these and the numbers of observations (n) these apply to, pooled between the study arms across the health states (HS) of the model. These values are unadjusted in line with the values used in the submission.

Table B2. Unadjusted EQ5D values by HS from the European subset of the GALILEO population for each time point

			Fellow eye				
Baseline	HS	Measure	HS1: >=80	HS2: 79-65	HS3: 64-50	HS4: 49-35	HS5: <35
Study eye	HS1: >=80	mean	[redacted]				
		SD					
		n					
	HS2: 79-65	mean					
		SD					
		n					
	HS3: 64-50	mean					
		SD					
		n					

	HS4: 49-35	mean	[redacted]
		SD	
		n	
	HS5: <35	mean	
		SD	
		n	

Source: GALILEO European dataset, observed case analyses

			Fellow eye				
Week 24			HS1: >=80	HS2: 79-65	HS3: 64-50	HS4: 49-35	HS5: <35
Study eye	HS1: >=80	mean	[redacted]				
		SD					
		n					
	HS2: 79-65	mean					
		SD					
		n					
	HS3: 64-50	mean					
		SD					
		n					
	HS4: 49-35	mean					
		SD					
		n					
	HS5: <35	mean					
		SD					
		n					

Source: GALILEO European dataset, observed case analyses

			Fellow eye				
Week 52			HS1: >=80	HS2: 79-65	HS3: 64-50	HS4: 49-35	HS5: <35
Study eye	HS1: >=80	mean	[redacted]				
		SD					
		n					
	HS2: 79-65	mean					
		SD					
		n					
	HS3: 64-50	mean					
		SD					
		n					
	HS4: 49-35	mean					
		SD					

		n	[redacted]
	HS5: <35	mean	
		SD	
		n	
Source: GALILEO European dataset, observed case analyses			

			Fellow eye				
Week 76			HS1: >=80	HS2: 79-65	HS3: 64-50	HS4: 49-35	HS5: <35
Study eye	HS1: >=80	mean	[redacted]				
		SD					
		n					
	HS2: 79-65	mean					
		SD					
		n					
	HS3: 64-50	mean					
		SD					
		n					
	HS4: 49-35	mean					
		SD					
		n					
	HS5: <35	mean					
		SD					
		n					
Source: GALILEO European dataset, observed case analyses							

Please note the values in Table B2 above do not match HS inputs used on the submission as for these we analysed the data based on the patients' WSE and across timepoints.

Priority question B3. Please tabulate the LogMAR midpoints for each health state that were used for the calculation of the Czoski-Murray utilities.

Table B3 presents the LogMAR midpoints for each HS that were used for the calculation of the Czoski-Murray utilities used in the scenario analysis presented in the submission.
The ETDRS score was translated into the LogMAR mid point using a method suggested by (Gregori et al., 2010, Retina 30(7)). This paper introduces a formula which links the ETDRS score and Snellen fraction (presented below the table), this formula was used to calculate the Snellen fraction from the ETDRS mid-point. The minimum angle of resolution (MAR) can then simply be calculated by taking the inverse of the Snellen fraction.

Table B3. LogMAR midpoints for HS utility values derived from Czoski-Murray et al. 2009

Health state	ETDRS (mid-point)	Snellen Fraction	MAR	Log MAR
legally blind (<35)	35	0.10	10.00	1.00
midpoint of 35-49	42	0.14	7.24	0.86

midpoint of 50-64	57	0.28	3.63	0.56
midpoint of 65-79	72	0.55	1.82	0.26
best vision (80+)	85	1.00	1.00	0.00

Snellen fraction: 10^((x – 85)/50)

where x = ETDRS mid-point

MAR: 1/y

where y = Snellen fraction

Resource use

Priority question B4. Please provide the number of doses and number of patients remaining on trial within the aflibercept arm, separately for GALILEO and COPERNICUS by 4 weekly cycles for weeks 0-52 as in the table below. If possible, please provide the data separately for the COPERNICUS subset of patients who did not cross over at week 24 and were treated with aflibercept throughout during weeks 0-52.

Table B4 below presents, for each 4-weekly cycle, the number of doses and number of patients on active treatment, separately for GALILEO and COPERNICUS.

Table B4. Number of Patients with active Injections and number of injections

From start of week to end of week	0 0	1 4	5 8	9 12	13 16	17 20	21 24	25 28	29 32	33 36	37 40	41 44	45 48
GALILEO Doses Patients on trial	[redacted]												
COPERNICUS Doses Patients on trial	[redacted]												

Source: GALILEO and COPERNICUS FAS LOCF dataset

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.

Priority question B5. Please provide the summary data by year for the responses to the resource use questionnaire “What is the average number of monitoring visits per year for a typical CRVO patient”.

Table B5 below presents the number of monitoring visits needed for patients treated with aflibercept and ranibizumab based on the Physician survey.

Table B5. Number of monitoring visits based on Physician survey

	Year 1 (week 0-24)	Year 1 (week 24-52)	Year 1 (Total)	Year 2	Year 3	Year 4	Year 5
Aflibercept	3.3	3.5	6.8	4.8	3.8	3.2	2.4
Ranibizumab	4.2	4.4	8.6	5.8	4.4	3.8	2.8

Source: Physician survey

Please note that in the base-case analysis, the week 24-25 results from the Physician survey only were used in the CE model. The frequency of monitoring over the first 6 months

of treatment was assumed to be aligned with the frequency of injections during the 6-month loading period. The total number of monitoring visits used in the model for Year 1 (see Table 91 in submission) was higher (aflibercept: 9.25; ranibizumab: 9.90) than the number of monitoring visits for Year 1 that would have been derived using inputs from the Physician survey only (aflibercept: 6.8; ranibizumab: 8.6) .

Furthermore, the additional number of visits assumed for a ranibizumab patient compared with an aflibercept patient would have been greater (8.6-6.8=1.8) when using Physician survey data only than when using the approach followed in the base-case (9.90-9.25=0.65). This shows that the base-case number of monitoring visits used in the submission was conservative.

Model implementation

Priority question B6. The meaning of the following statement on page 156 of the submission is unclear: "applying both the RR of improving and the RR of worsening could have led to overestimating the treatment effect" is unclear. Please explain what you mean by this statement.

In the model, applying both the RR of improving and the RR of worsening could have led to overestimating the treatment effect as:

- each transition probability matrix used in the model consists of 25 possible transitions, 10 of which correspond to transitions to health states (HS) with better vision;
- the treatment effect of ranibizumab was estimated by applying the relative risk (RR) for gaining 15 letters according to these 10 probabilities;
- the interrelated nature of the transition probability matrix structure means that if the probability of transitioning to a better health state is increased, then the probabilities of remaining in the same HS or of moving to a HS with worse vision must also decrease.

Therefore, by applying the RR of losing 15 letters in addition to the RR of gaining 15 letters, we believe we would be double counting the effectiveness of aflibercept.

Priority question B7. The SE_Transitions worksheet cells A8:G54 contain the patient numbers at the 4 weekly time points to 24 weeks. These sum to 201, 209, 203, 205, 206, 203. Please explain this variation, in particular the initial 4 week matrix having the lowest number of patients?

The values used in "SE_Transitions" worksheet cells (A8:G54) were taken from observed cases as opposed to LOCF. Consequently, there is variation between the patient numbers at different points in time (visits). The data included in the cost-effectiveness model represented the most recent data available at the time of submission. Updated FAS observed data (based on a more recent cut of data) show a more predictable variation pattern with n = 217 at week 4, n = 209 at week 8, n = 203 at week 12, n = 205 at week 16, n = 206 at week 20 and n = 203 at week 24.

When considering updated FAS LOCF data, the number of patients at baseline remains constant throughout the first 24 weeks of treatment (n = 217 at week 4, 8, 12, 16, 20 and 24). Please therefore note that for subsequent answers in this document (B8-B20), where additional data are requested, LOCF data will be presented.

Please however note that observed data only were used to derive the transition probabilities applied in the submitted model.

Priority question B8. For the SE_Transitions worksheet cells A8:G54, with the exception of the week 12-16 matrix, the number of patients entering the various health states rarely corresponds with the relevant number given in that state in column A. For instance, between week 0 and week 4, the sum of C5:C9 suggests 31 patients are modelled as moving into the best health state. But this is given as 34 patients in cell A13, which corresponds with the sum of C13:G13. The sum of the absolute discrepancies from this source can be greater than the differences between the total sums of patients within the relevant matrices; e.g. week 0-4 totals 201 while week 4-8 totals 209, but the sum of the absolute discrepancies between the transitions in weeks 0-4 and the patient number totals at the start of weeks 4-8 is 10. Please provide an explanation for these discrepancies?

Please note that some of the inconsistencies flagged up in question B8 relate to the use of observed values in the CE model and as explained in answer to question B7 above.

In each table in cells A8:G54 of in sheet “SE_Transitions worksheet”, the values need to be added horizontally. Taking for example the table at the top (A8:G14), with transitions for the period baseline to week 4:
- the value in cell A11 is equal to the sum of the values in (C11:G11).
- the value in cell A11 reflects the total number of patients with BCVA range "79-65 letters" in the study eye (SE) for which there were observations both at baseline and at week 4.
- the values in (C11:G11) reflect the number of patients which BCVA in the SE improves (C11), remains the same (D11) or deteriorates (E11-G11) over this 4-week period.
To our knowledge, all cells in columns (C:G) sum up to the value in cell A of the corresponding row.

Cells (C5:C9) do not relate to the cells discussed in this question (A8:G54). We believe there is a cell mismatch in this question. We have attempted to reword this question using the cells we believe are the ones that were referred to and have provided an answer.

By the end of the first four weeks with observations (equivalent to the 1st model cycle), a total of 31 patients (sum(C10:C14)) have a BCVA >80 letters in their SE. However, the table below (A16:G22), summarises observed data for patients with data available at both the week 4 and 8 time-point (i.e. 2nd model cycle), and indicates that at the beginning of the cycle (i.e. week 4), 34 patient (cell A18) have a BCVA >80 letters. This data mismatch can also be observed for the other BCVA ranges across these 2 cycles. This reflects the fact that the total number of patients, as per the observed cases from the FAS dataset, is different for week 0-4 (n=201) and for week 4-8 (n=209). This inconsistency is explained further in answer to question B7 above.

As described above, for the BCVA range ">80 letters", 3 patients (31-34=-3) were “lost” i.e. 3 fewer patients had values attributed between week 0-4 and week 4-8. Following the same approach, the following discrepancies can be observed for the other BCVA rates

- "79-65 letters": 88-91=-3
- "64-50 letters": 53-54 = -1
- "49-35 letters": 18-17 = +1
- "<35 letters": 11-13 = -2

The sum of the discrepancies observed across the 5 BCVA ranges is -8, not 10; this is in line with the discrepancy between the number of patients in week 0-4 (n=201) and in week 4-8 (n=209) as 201-209 = -8.

Priority question B9. Please explain how drop-outs and patients lost to follow up have been handled within the SE_Transitions worksheet cells A8:G54. Is it correct to assume that by

definition, LOCF values are on the principal diagonal of each block of patient transitions? Please provide the numbers of patients within each row that have LOCF.

The dataset used to derive the transition probabilities applied in the CE model are only based on observed data; any drop-outs are therefore excluded from the computation of subsequent transition matrices.

No LOCF data have been implemented into the dataset used to calculate the transition probabilities used in the submitted model, therefore we are not able to populate the below table with LOCF.

Table B9 below presents the number of patients entering each HS at each point in time based on the observed data that were used in the submitted model.

Table B9. Number of patients entering each HS at each time point (observed data)

Start of week	0		5		9		13		17		21	
End of week	4		8		12		16		20		24	
HS start of week	N	LOCF	N	LOCF	N	LOCF	N	LOCF	N	LOCF	N	LOCF
1	0	n=?	34	n=?	48	n=?	56	n=?	72	n=?	69	n=?
2	47	n=?	91	n=?	87	n=?	81	n=?	72	n=?	73	n=?
3	81	n=?	54	n=?	42	n=?	45	n=?	40	n=?	39	n=?
4	40	n=?	17	n=?	15	n=?	10	n=?	12	n=?	14	n=?
5	33	n=?	13	n=?	11	n=?	13	n=?	10	n=?	8	n=?

Priority question B10. The 6 month rate of raised intraocular pressure (IOP) is adjusted to be a monthly rate of incidence. Costs are applied to this monthly rate.

1. The cost of hospital care for raised IOP is divided by 6. Please explain why this adjustment to the cost of hospital care is required given that it is applied to a monthly rate of incidence?
2. Similarly, the cost of medication for raised IOP is divided by 13. Please explain why this adjustment to the cost of medication is required given that it is applied to a monthly rate of incidence?
3. Are the medication costs in the Data_Inputs worksheet cells AD221:AD233 annual medication costs per incident event?

Please see individual responses below:

1. The cost calculation in cells (AH246:AH251) in the "Data inputs" sheet gives the average of the cost per patient experiencing the adverse event over 6 months. Therefore, these costs are divided by 6 in order to get the monthly cost and these are then applied to the monthly rate of incidence. The approach used to calculate these costs is in line with previous submissions in the RVO area.

2. The cost calculation in cells (AG221:AG225) in the "Data inputs" sheet gives the average per patient cost of experiencing the adverse event over 12 months (i.e. 13 model cycles of 4 weeks each). The costs are divided by 13 to convert the yearly cost to a per cycle cost in order to apply these to the monthly rate of incidence. The approach used to calculate these costs is in line with previous submissions in the RVO area.

3. The costs in cells (AD221:AD225) and (AD229:AD233) are the average medication costs per patient per incident event over the first 6 months and over the second half of the year respectively; they are not annual costs.

Priority question B11. Please provide the data source for the days of treatment in the Data_Inputs worksheet cells AB221:AB233?

The days of treatment were taken from "Table 111: Incidence and cost of pharmacological treatment for increased IOP" on page 169 of the Allergan manufacturer submission report for the treatment of RVO with dexamethasone: "National Institute for Health and Care Excellence. - Dexamethasone intravitreal implant for the treatment of macular oedema secondary to retinal vein occlusion, September 2010". This report is available following the link: http://www.nice.org.uk/nicemedia/live/13037/52863/52863.pdf. The reference in the submission incorrectly refers to the technology appraisal.

Priority question B12. Please explain why, for the scenario analysis that includes adverse events (AEs) it appears that the 43% rate of IOP treatment of the physician survey as per table 86 (page 205 of the submission) is applied within the modelling, but the 68% removal rate for cataracts of the physician survey is not applied within the modelling?

The 68% removal rate for cataracts of the physician survey should be applied in the AE scenario analyses. However this change had only a very small impact on the results of these analyses:
- Aflibercept vs. ranibizumab in the scenario analyses with AEs included the ICER increased from [redacted] per QALY;
- Aflibercept vs. dexamethasone the ICER increased from £[redacted] per QALY to £[redacted] per QALY.

Priority question B13. Within the markov worksheets, the disutilities from adverse events of columns GX:HA are added to the quality of life values for each health state within the calculations of columns BK:CI. Cell BK6 is divided by 13 to give the total number of QALYs. Is the implicit assumption within this that the duration of the quality of life (QoL) impact of an incident adverse event is 4 weeks?

Yes. No data were available regarding the duration of the AEs considered in the CE model. As a result, an assumption was made that the impact of these AEs would last for 4 weeks. Given the severity of the majority of AEs, this is on balance considered to be a conservative assumption.

Priority question B14. Please clarify the location of the ongoing costs of blindness within the model? The Markov_Aflibercept worksheet column GV appears to allow for the first month of incident blindness, though the incidence may be incorrectly calculated and searching the Markov_Aflibercept worksheet for cVisionLoss2 does not result in any matches.

There are no ongoing costs of blindness in the model. This was an overly conservative approach. The cost of blindness was applied as a one-off cost to incident patients entering the model blindness health state (HS), in which patients can read <35 letters in either eye.

"Incident" or "new" cases of blindness were derived by comparing the percentage of patients in the blindness HS at t0 and t1, and only accruing cases when the percentage in t1 was greater than in t0. For the first model cycle (~1 month), it was assumed that the incident blind cases were the same as the proportion of patients in the blindness HS in this same cycle. Given the current approach to modelling approach, the input "cVisionLoss 2" would not be used in the base-case analysis. However, this input should be linked to the model engine.

Non-priority question B15. Please provide the corollary of the adverse events rates of table 96 on page 220 of the submission for weeks 24 to 52.

Table B15 below provides, as much as possible, AE rates for week 24-52 separately for each treatment. Given data limitations, the following rates were provided for each treatment:

- for aflibercept, week 24-52 AE rates are presented that were derived from pooled 52-week COPERNICUS and GALILEO CSR;
- for ranibizumab and dexamethasone, the AE rates presented were estimated for the period from baseline to week 52 only as the (publicly available) sources indicated in Table 96 of the submission do not provide rates for the period week 24-52 specifically.

B15. Adverse events rates for week 24-52

Treatment arm	AE rate	Reference
Aflibercept		
Cataracts	[redacted]%	Pooled 1year COPERNICUS and GALILEO CSR (Week 24- Week 52)
IOP	10.10%	
Retinal tear	[redacted]%	
Ranibizumab		
Cataracts	7.00%	Ranibizumab in RVO; NICE manufacturer submission - Table B34 Frequency of adverse events at 12 months (CRUISE)
IOP	NR	
Retinal tear	1.60%	
Dexamethasone		
Cataracts	1.8%*	Haller *et al*. 2011
IOP	32.8% **	
Retinal tear	NR	

* This rate relates to the group of patients that were retreated with dexamethasone 0.7mg at week 24
** 32.8% of patients in the dexamethasone 0.7/0.7 (retreated) group had at least a 10-mmHg in IOP from baseline at some point in the 52-week study.

Non-priority question B16. For the assessment of the mean change from baseline in ETDRS letters (FAS) by treatment arm, please provide patient numbers that had LOCF for both GALILEO and COPERNICUS at week 24 and week 52.

Please note that results for this trial endpoint (mean change from baseline in ETDRS letters) have not been used in the CE model used in the submission. Furthermore, FAS LOCF data were not used in the CE analysis.

For trial endpoint "mean change from baseline in ETDRS letters", for the "FAS;LOCF dataset", the number of patients (n) was the following:

COPERNICUS

Week 24 and 52: aflibercept (VTE 2Q4): n = 114; sham: n = 73

GALILEO
Week 24 and 52: aflibercept (VTE 2Q4): n = 103; sham: n = 68.

Non-priority question B17. Please provide the numbers of patients at baseline pooled between the arms but separately for GALILEO and COPERNICUS, distributed across the 25 health states of the model as in the table below (one table for each trial):

The distribution of patients across the 25 HS at baseline is not known; for modelling purpose, an assumption was used to derive this distribution as reported and described in Section 7.3.2 of the submission.

The separate SE and FE distributions across the five visual acuity HS categories are known at baseline, however the two-eye distribution is not known. To derive the baseline distribution of patients across the 25 HS, each SE visual acuity category is broken down into five two-eye visual acuity categories by applying the distribution of the FEs across the five visual acuity states to each SE visual acuity category.

The baseline distribution of patients across the 25 model health states has been calculated in the same way as described above for the COPERNICUS and GALILEO trials separately (presented in tables B16a and B16b respectively). Please note that the data available for these calculations was LOCF data from an updated analysis, therefore the sum of patient numbers does not exactly match with the current pooled baseline distribution used in the cost-effectiveness model.

Table B16a. Baseline distribution of patients across 25 model health states in COPERNICUS

			Study eye				
			1	**2**	**3**	**4**	**5**
Fellow eye	>=80	**1**	[redacted]				
	65-79	**2**					
	50-64	**3**					
	35-49	**4**					
	<35	**5**					

Table B16b. Baseline distribution of patients across 25 model health states in GALILEO

			Study eye				
			1	**2**	**3**	**4**	**5**
Fellow eye	>=80	**1**	[redacted]				
	65-79	**2**					
	50-64	**3**					
	35-49	**4**					
	<35	**5**					

Quality of life

Non-priority question B18. Please provide the mean EQ-5D values from all patients in the GALILEO study evaluated using the UK social tariff, the sample standard deviations of these and the numbers of observations these apply to, pooled between the study arms across the health states of the model. Please supply this separately for baseline, week 24, week 52, week 76 and early termination as in the table below (one table for each time point):

The table below presents the EQ-5D values from all patients in the GALILEO study, the sample standard deviations (SD) of these and the numbers of observations (n) these apply

to, pooled between the study arms across the health states of the model for the different time points.

Table B18. Unadjusted EQ5D values by HS from whole GALILEO population for each time point

			Health State FE				
			HS1: >=80	HS2: 79-65	HS3: 64-50	HS4: 49-35	HS5: <35
Baseline	**HS**	Measure	[redacted]				
Health state SE	HS1: >=80	mean					
		SD					
		n					
	HS2: 79-65	mean					
		SD					
		n					
	HS3: 64-50	mean					
		SD					
		n					
	HS4: 49-35	mean					
		SD					
		n					
	HS5: <35	mean					
		SD					
		n					
Source: GALILEO whole dataset, observed case analyses							
Week 24	HS	Measure	Health State FE				
			HS1: >=80	HS2: 79-65	HS3: 64-50	HS4: 49-35	HS5: <35
Health state SE	HS1: >=80	mean	[redacted]				
		SD					
		n					
	HS2: 79-65	mean					
		SD					
		n					
	HS3: 64-50	mean					
		SD					
		n					
	HS4: 49-35	mean					
		SD					
		n					
	HS5: <35	mean					
		SD					
		n					
Source: GALILEO whole dataset, observed case analyses							
Week 52	HS	Measure	Health State FE				
			HS1: >=80	HS2: 79-65	HS3: 64-50	HS4: 49-35	HS5: <35
Health state SE	HS1: >=80	mean	[redacted]				
		SD					
		n					
	HS2: 79-65	mean					
		SD					
		n					
	HS3: 64-50	mean					
		SD					

		n	[redacted]
	HS4: 49-35	mean	
		SD	
		n	
	HS5: <35	mean	
		SD	
		n	

Source: GALILEO whole dataset, observed case analyses

Week 76	HS	Measure	Health State FE				
			HS1: >=80	HS2: 79-65	HS3: 64-50	HS4: 49-35	HS5: <35
Health state SE	HS1: >=80		[redacted]				
	HS2: 79-65						
	HS3: 64-50						
	HS4: 49-35						
	HS5: <35						

Source: Whole GALILEO dataset, observed case analyses

Non-priority question B19. Please provide the rationale for the quality of life literature review not including Brown "Vision and Quality-of-Life." Transactions of the American Ophthalmological Society. 1999. 97:473-511.

The paper Brown "Vision and Quality-of-Life." Transactions of the American Ophthalmological Society. 1999. 97:473-511 was not identified by the systematic quality of life value search as it was outside the timeframe of the search (between January the 1st, 2001 and March the 11th, 2013) defined on page 171 of the submission.

There is currently no NICE guidance about the time period over which quality of life search should be conducted. This timeframe was deemed reasonable to identify:

- papers reporting values that could be used in the model to capture the impact on the quality of life of a patient/person currently treated for CRVO. Older papers were deemed outdated as they would reflect quality of life of patients that lived at a time when clinical practice was very different.

- the paper by Czoski-Murray 2009 that was deemed the most relevant by NICE for the appraisal of ranibizumab for the treatment of RVO.

It should be noted that the economic model uses directly measured EQ-5D data from the GALILEO trial as this is the preferred instrument according to the NICE methods of techonolgy appraisal. The Czoski-Murray was used for sensitivity analysis only.

Model implementation

Non-priority question B20. Please provide the corollary of the SE_Transitions worksheet cells A8:G54 but as a single TPM for baseline to 24 weeks.

Table B20 below presents the study eye transitions as a single transition probability matrix from baseline to week 24.

Table B20. Transition probability matrix from baseline to week 24, pooled COPERNICUS and GALILEO

		Week 24						
n(row)	**Baseline**	HS		>=80	65-79	50-64	35-49	<35
217	53	65-79	n	[redacted]				
			Prob.(SE)					
			95% CI					
	85	50-64	n					
			Prob.(SE)					
			95% CI					
	42	35-49	n					
			Prob.(SE)					
			95% CI					
	37	<35	n					
			Prob.(SE)					
			95% CI					

Source: Transition Probabilities for Study Eye (LOCF); Pooled COPERNICUS and GALILEO (Full Analysis Set)

Non-priority question B21. Please provide the corollary of the SE_Transitions worksheet cells A8:G54 for just the COPERNICUS trial.

Table B21 below presents the weekly transition probabilities for the SE using the COPERNICUS dataset only.

Table 21. Weekly transition probabilities of the study eye, COPERNICUS only

			Week 4					
N	n(row)	Baseline		>=80	65-79	50-64	35-49	<35
114	18	65-79	n	7	10	1		
			Prob.(SE)	[redacted]				
			95% CI					
	53	50-64	n					
			Prob.(SE)					
			95% CI					
	23	35-49	n					
			Prob.(SE)					
			95% CI					

	20	<35	n	[redacted]				
			Prob.(SE)					
			95% CI					
Source: COPERNICUS, FAS, LOCF								
			Week 8					
N	n(row)	Week 4		>=80	65-79	50-64	35-49	<35
114	12	>=80	n	[redacted]				
			Prob.(SE)					
			95% CI					
	51	65-79	n					
			Prob.(SE)					
			95% CI					
	36	50-64	n					
			Prob.(SE)					
			95% CI					
	11	35-49	n					
			Prob.(SE)					
			95% CI					
	4	<35	n					
			Prob.(SE)					
			95% CI					
Source: COPERNICUS, FAS, LOCF								
			Week 12					
N	n(row)	Week 8		>=80	65-79	50-64	35-49	<35
114	19	>=80	n	[redacted]				
			Prob.(SE)					
			95% CI					
	52	65-79	n					
			Prob.(SE)					
			95% CI					
	30	50-64	n					
			Prob.(SE)					
			95% CI					
	7	35-49	n					
			Prob.(SE)					
			95% CI					
	6	<35	n					
			Prob.(SE)					
			95% CI					
Source: COPERNICUS, FAS, LOCF, weekly tps								
			Week 16					
N	n(row)	Week 12		>=80	65-79	50-64	35-49	<35

114	25	>=80	n	[redacted]
			Prob.(SE)	
			95% CI	
	47	65-79	n	
			Prob.(SE)	
			95% CI	
	31	50-64	n	
			Prob.(SE)	
			95% CI	
	4	35-49	n	
			Prob.(SE)	
			95% CI	
	7	<35	n	
			Prob.(SE)	
			95% CI	

Source: COPERNICUS, FAS, LOCF

				Week 20				
N	n(row)	Week 16		>=80	65-79	50-64	35-49	<35
114	31	>=80	n	[redacted]				
			Prob.(SE)					
			95% CI					
	41	65-79	n					
			Prob.(SE)					
			95% CI					
	32	50-64	n					
			Prob.(SE)					
			95% CI					
	5	35-49	n					
			Prob.(SE)					
			95% CI					
	5	<35	n					
			Prob.(SE)					
			95% CI					

Source: COPERNICUS, FAS, LOCF

				Week 24				
N	n(row)	Week 20		>=80	65-79	50-64	35-49	<35
114	31	>=80	n	[redacted]				
			Prob.(SE)					
			95% CI					
	37	65-79	n					
			Prob.(SE)					
			95% CI					

	33	50-64	n	[redacted]
			Prob.(SE)	
			95% CI	
	10	35-49	n	
			Prob.(SE)	
			95% CI	
	3	<35	n	
			Prob.(SE)	
			95% CI	
Source: COPERNICUS, FAS, LOCF				

Section C - Clarification on other topics:

Question C1 Please check the data that is marked as AiC and lift confidentiality marking where appropriate? Some marked data are in published papers in the public domain. In other cases, the marking seems inconsistent Examples include:

1. Table 21, on page xx of the submission, the data for weeks 52 week data for aflibercept gains of more than 15 letters is marked but the sham group is not.

2. Table 22, ten or more letter gains by week 24 are marked for aflibercept but not for sham.

3. Table 17, the week 100 columns for COPERNICUS are marked, but the data can be worked out from the other, unmarked columns

4. p. 48, top two boxes (screened & excluded) - numbers are in Brown et al. 2013 437.e4

5. p. 53 GALILEO n/% gaining 15 or more letters at 52 weeks - is published in: Gillies, M. Intravitreal vegf trap-eye in central retinal vein occlusion: Results of the phase 3 copernicus and galileo studies. Clinical and Experimental Ophthalmology 40, 44. 2012.

6. GALILEO subgroup analysis for primary efficacy endpoint <2 mo vs >=2 mo since diagnosis - also given in Holz et al. 2013

7. GALILEO BCVA gain at 52 weeks - is published in: Gillies, M. Intravitreal vegf trap-eye in central retinal vein occlusion: Results of the phase 3 copernicus and galileo studies. Clinical and Experimental Ophthalmology 40, 44. 2012.

8. Same for CRT at 52 weeks in GALILEO

For questions 1-8, this confidentiality marking has now been removed. An updated marked submission will be provided shortly.