Bayer response to NICE clarification letter for the single technology appraisal of aflibercept solution for injection for the treatment of neovascular wet AMD

Section A: Clarification on effectiveness data

A1: priority question
Page 45: Please clarify if the follow-up period of each of the two VIEW trials adopted the same blinding approach as outlined in Table B5. If not, please clarify what blinding approach was taken for both trials.

That is correct except it should be noted that sham injections were not administered in the second year of the study. As described in the submission, patients were masked to treatment. Otherwise, the study drug was performed by an unmasked physician who did not have any role in the study beyond the receipt, tracking, preparation, destruction and administration of study drug, as well as assessing safety at 30-60 minutes post IVT injection. A separate masked physician was assigned to 1) assess AEs and 2) supervise the masked assessment of efficacy.

A2: priority question
Page 72: Please provide the patient numbers (N per column) for the 'per protocol set' in Tables B11 and B12.

Please see Table 15 for the numbers of patients in each arm in the per protocol set.

A3: priority question
Page 72: For Tables B11 and B12 please provide the patient numbers (N per column) for which 52 week primary outcome data were a) observed and b) obtained through LOCF.

VIEW 1 CSR
([redacted]):

VIEW 2 CSR
([redacted]):

A4: priority question
Pages 130-131 (section 6.7.6): please clarify which Table/Figure in the Kleijnen report (reference 59) provides each of the results quoted in the text, for example:

a. Results for outcome of maintained vision do not correspond with Table 16 in reference 59.
b. Results for improved vision and change in BCVA do not correspond with Table 14 in reference 59.

The results in the submission are correct. The correct reference, the Kleijnen report from November 2012, has been attached with this clarification to replace the previous reference 59 from July 2012(1).

A5: priority question
Please clarify to what extent the probabilities of losing letters were incorporated into the Kleijnen systematic review (reference 59). If this was not considered, please provide the rationale for this.

Losing vision was included in the first stage of searching in the systematic review.
The most relevant outcomes were prioritised for the second stage of the systematic review. The proportion losing vision is, by default, the remaining proportion of those neither gaining or maintaining vision. As discussed in the submission, the mixed treatment comparison is limited by the differences between trials in terms of baseline characteristics, retreatment criteria and number of injections, as well as the differences between the trial regimens and those specified in the marketing authorisations for aflibercept and ranibizumab.

The vast majority of patients in the VIEW studies (>95%) maintained vision (i.e. a loss of less than 15 letters) with anti-VEGF treatment at the primary analysis point at 52 weeks(2). This was also reflected in the CATT study where over 94% maintained vision at 52 weeks.

Data from the VIEW studies on proportion of patients losing vision (>=15 letters and >=30 letters) is included in the responses to clarification questions A7 and A8. In the CATT study, the only other study included in the indirect comparison at 24 months, the proportion of patients losing 15 letters and over from baseline was 6% (n=284) in the ranibizumab monthly arm and 5% (n=285) in the ranibizumab as needed arm at 52 weeks. This was 6.7% (n=134) and 7.2% (n=264) at 2 years, from baseline, for each of the previously mentioned arms respectively. The proportion losing 15 letters and over was 9.2% at 2 years in patients who were switched from monthly to ranibizumab as needed after a year (n=130)(3;4).

In practice, those who do not respond to treatment will discontinue treatment according to Royal College Guidelines on the management of wet AMD 2009(5;6):

Criteria for continuation of treatment
After the three loading doses, ranibizumab should be continued at 4 weekly intervals and pegaptanib at 6 weekly intervals if:

- *There is persistent evidence of lesion activity*

- *The lesion continues to respond to repeated treatment*
- *There are no contra-indications (see below) to continuing treatment.*

Consider discontinuing treatment permanently if there is:

- *1. A **hypersensitivity** reaction to ranibizumab is established or suspected. A change to pegaptanib or PDT is recommended.*
- *2. Reduction of BCVA in the treated eye to **less than 15 letters (absolute) on 2 consecutive visits** in the treated eye, attributable to AMD in the absence of other pathology*
- *3. Reduction in BCVA of **30 letters or more compared to either baseline and/or best recorded level since baseline** as this may indicate either poor treatment effect or adverse event or both*
- *4. There is evidence of deterioration of the **lesion morphology** despite optimum treatment. Such evidence includes progressive increase in lesion size confirmed with FFA, worsening of OCT indicators of CNV disease activity or other evidence of disease activity in the form of significant new haemorrhage or exudates despite optimum therapy over a 3 consecutive visits.*

A6: priority question

Please provide the proportions of patients were treated in their best seeing eye at baseline in VIEW1, VIEW2 and VIEW1+VIEW2 pooled (3 separate estimates). Please also clarify whether these calculations depend upon a minimum clinically significant difference between the two eyes. If so, please define this minimum clinically significant difference between the two eyes along with the relevant reference, and please also present the proportions of patients treated in their best seeing eye at baseline in VIEW1, VIEW2 and VIEW1+VIEW2 pooled when this minimum clinically significant difference is not applied within the calculation.

The protocol for the VIEW 1 study (same as VIEW 2) indicated that: *Only one eye will be designated as the study eye. For subjects who meet eligibility criteria in both eyes, the eye with the worse VA will be selected as the study eye. If both eyes have equal VA, the eye with the clearest lens and ocular media and least amount of subfoveal scar or geographic atrophy will be selected. If there is no objective basis for selecting the study eye, factors such as ocular dominance, other ocular pathology and subject preference should be considered in making the selection. Ophthalmic eligibility criteria apply to the study eye only unless otherwise specified.*

A6: Proportion of subjects with better or worse BCVA at baseline in study eye compared to fellow eye (Safety Analysis Set)

	R 0.5 mg Q4 N=595 (100%)	VTE 0.5 mg Q4 N=601 (100%)	VTE 2.0 mg Q4 N=613 (100%)	**VTE 2.0 mg Q8 N=610 (100%)**
VIEW 1	304 (51.1%)	304 (50.6%)	304 (49.6%)	303 (49.7%)
- of these: % study eye = better VA at baseline visit compared to fellow eye	[redacted]			
% study eye = worse VA at baseline visit compared to fellow eye				
% study eye has same VA as the fellow eye at baseline				
can not be judged				
VIEW 2	291 (48.9%)	297 (49.4%)	309 (50.4%)	307 (50.3%)
- of these: % study eye = better VA at baseline visit compared to fellow eye	[redacted]			
% study eye = worse VA at baseline visit compared to fellow eye				
% study eye has same VA as the fellow eye at baseline				
can not be judged				
Pooled	595 (100.0%)	601 (100.0%)	613 (100.0%)	610 (100.0%)
- of these: % study eye = better VA at baseline visit compared to fellow eye	[redacted]			
% study eye = worse VA at baseline visit compared to fellow eye				
% study eye has same VA as the fellow eye at baseline				
can not be judged				

A7: priority question

Please present the following effectiveness data for the treated eye for both the Aflibercept 2mg Q8 arm and the Ranibizumab arm on the basis of LOCF, for VIEW1, VIEW2 and VIEW1+VIEW2 pooled (**in 6 separate Tables**). The numbers gaining and losing letters should be relative to the original baseline values in month 0 (i.e. for the follow-up period not relative to the start of the follow-up period but to the original baseline).

This information is available in the attached tables from the respective VIEW 1 and VIEW 2 clinical study reports. These studies were reported separately and only a more limited summary report is available for integrated data. It should be noted that the VIEW studies included an exploratory phase up to 96 weeks not 24 months.

A8: priority question

Please present the following effectiveness data for the treated eye for both the Aflibercept2mg Q8 arm and the Ranibizumab arm on the basis of the observed data, for VIEW1, VIEW2 and VIEW1+VIEW2 pooled (**in 6 separate Tables**). The numbers gaining and losing letters should be relative to the original baseline (i.e. for the follow-up period not relative to the start of the follow-up period but to the original baseline).

This information is available in the attached tables from the respective VIEW 1 and VIEW 2 clinical study reports. These studies were reported separately and only a more limited summary report is available for integrated data.

A9: priority question

Please present the following effectiveness data for the treated eye for both the Aflibercept2mg Q8 arm and the Ranibizumab arm on the basis of LOCF for VIEW1, VIEW2 and VIEW1+VIEW2 pooled (**in 6 separate Tables**).

Proportion of subjects within VA levels by visit from baseline to week 96, LOCF (Safety Analysis Set)

Study identifier: VIEW 1

	R 0.5 mg Q4 (N=304)	VTE 0.5 mg Q4 (N=304)	VTE 2.0 mg Q4 (N=304)	**VTE 2.0 mg Q8 (N=303)**
Visual acuity in treated study eye	[redacted]			
No VI, >80 Letters				
SCREENING				
BASELINE				
WEEK 1				
WEEK 4				
WEEK 8				
WEEK 12				
WEEK 16				
WEEK 20				
WEEK 24				
WEEK 28				
WEEK 32				
WEEK 36				
WEEK 40				
WEEK 44				
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WEEK 52				
WEEK 56				
WEEK 60				
WEEK 64				
WEEK 68				
WEEK 72				
WEEK 76				
WEEK 80				
WEEK 84				
WEEK 88				
WEEK 92				
WEEK 96				
Mild VI, 80-66 Letters				
SCREENING				
BASELINE				
WEEK 1				
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WEEK 80				
WEEK 84				
WEEK 88				
WEEK 92				
WEEK 96				
Moderate VI, 65-51 Letters				
SCREENING				
BASELINE				
WEEK 1				
WEEK 4				
WEEK 8				
WEEK 12				
WEEK 16				
WEEK 20				
WEEK 24				
WEEK 28				
WEEK 32				
WEEK 36				

Proportion of subjects within VA levels by visit from baseline to week 96, LOCF (Safety Analysis Set)

Study identifier: VIEW 1

	R 0.5 mg Q4 (N=304)	VTE 0.5 mg Q4 (N=304)	VTE 2.0 mg Q4 (N=304)	**VTE 2.0 mg Q8 (N=303)**
WEEK 40	[redacted]			
WEEK 44				
WEEK 48				
WEEK 52				
WEEK 56				
WEEK 60				
WEEK 64				
WEEK 68				
WEEK 72				
WEEK 76				
WEEK 80				
WEEK 84				
WEEK 88				
WEEK 92				
WEEK 96				
Severe VI, 50-36 Letters				
SCREENING				
BASELINE				
WEEK 1				
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WEEK 96				
Blind, <36 Letters				
SCREENING				
BASELINE				
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WEEK 72				
WEEK 76				
WEEK 80				
WEEK 84				
WEEK 88				
WEEK 92				

Proportion of subjects within VA levels by visit from baseline to week 96, LOCF (Safety Analysis Set)

Study identifier: VIEW 1

	R 0.5 mg Q4 (N=304)	VTE 0.5 mg Q4 (N=304)	VTE 2.0 mg Q4 (N=304)	**VTE 2.0 mg Q8 (N=303)**
WEEK 96	[redacted]			

Proportion of subjects within VA levels by visit from baseline to week 96, LOCF (Safety Analysis Set) (cont.)

Study identifier: VIEW 2

	R 0.5 mg Q4 (N=291)	VTE 0.5 mg Q4 (N=296)	VTE 2.0 mg Q4 (N=309)	**VTE 2.0 mg Q8 (N=306)**
Visual acuity in treated study eye	[redacted]			
No VI, >80 Letters				
SCREENING				
BASELINE				
WEEK 1				
WEEK 4				
WEEK 8				
WEEK 12				
WEEK 16				
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Mild VI, 80-66 Letters				
SCREENING				
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WEEK 68				
WEEK 72				
WEEK 76				
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WEEK 84				
WEEK 88				
WEEK 92				
WEEK 96				
Moderate VI, 65-51 Letters				
SCREENING				
BASELINE				
WEEK 1				
WEEK 4				
WEEK 8				

Proportion of subjects within VA levels by visit from baseline to week 96, LOCF (Safety Analysis Set) (cont.)

Study identifier: VIEW 2

	R 0.5 mg Q4 (N=291)	VTE 0.5 mg Q4 (N=296)	VTE 2.0 mg Q4 (N=309)	**VTE 2.0 mg Q8 (N=306)**
WEEK 12	[redacted]			
WEEK 16				
WEEK 20				
WEEK 24				
WEEK 28				
WEEK 32				
WEEK 36				
WEEK 40				
WEEK 44				
WEEK 48				
WEEK 52				
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WEEK 96				
Severe VI, 50-36 Letters				
SCREENING				
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Blind, <36 Letters				
SCREENING				
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WEEK 44				
WEEK 48				
WEEK 52				
WEEK 56				

Proportion of subjects within VA levels by visit from baseline to week 96, LOCF (Safety Analysis Set) (cont.)

Study identifier: VIEW 2

	R 0.5 mg Q4 (N=291)	VTE 0.5 mg Q4 (N=296)	VTE 2.0 mg Q4 (N=309)	**VTE 2.0 mg Q8 (N=306)**
WEEK 60	[redacted]			
WEEK 64				
WEEK 68				
WEEK 72				
WEEK 76				
WEEK 80				
WEEK 84				
WEEK 88				
WEEK 92				
WEEK 96				

Proportion of subjects within VA levels by visit from baseline to week 96, LOCF (Safety Analysis Set) (cont.)

Study identifier: Pooled

	R 0.5 mg Q4 (N=595)	VTE 0.5 mg Q4 (N=600)	VTE 2.0 mg Q4 (N=613)	**VTE 2.0 mg Q8 (N=609)**
Visual acuity in treated study eye	[redacted]			
No VI, >80 Letters				
SCREENING				
BASELINE				
WEEK 1				
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Mild VI, 80-66 Letters				
SCREENING				
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WEEK 64				
WEEK 68				
WEEK 72				
WEEK 76				
WEEK 80				

Proportion of subjects within VA levels by visit from baseline to week 96, LOCF (Safety Analysis Set) (cont.)

Study identifier: Pooled

	R 0.5 mg Q4 (N=595)	VTE 0.5 mg Q4 (N=600)	VTE 2.0 mg Q4 (N=613)	**VTE 2.0 mg Q8 (N=609)**
WEEK 84	[redacted]			
WEEK 88				
WEEK 92				
WEEK 96				
Moderate VI, 65-51 Letters				
SCREENING				
BASELINE				
WEEK 1				
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Severe VI, 50-36 Letters				
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WEEK 92				
WEEK 96				
Blind, <36 Letters				
SCREENING				
BASELINE				
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WEEK 16				
WEEK 20				

Proportion of subjects within VA levels by visit from baseline to week 96, LOCF (Safety Analysis Set) (cont.)

Study identifier: Pooled

	R 0.5 mg Q4 (N=595)	VTE 0.5 mg Q4 (N=600)	VTE 2.0 mg Q4 (N=613)	**VTE 2.0 mg Q8 (N=609)**
WEEK 24	[redacted]			
WEEK 28				
WEEK 32				
WEEK 36				
WEEK 40				
WEEK 44				
WEEK 48				
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WEEK 84				
WEEK 88				
WEEK 92				
WEEK 96				

A10: priority question

Please present the following effectiveness data for the treated eye for both the Aflibercept2mg Q8 arm and the Ranibizumab arm on the basis of the observed data for VIEW1, VIEW2 and VIEW1+VIEW2 pooled (**in 6 separate Tables**).

Proportion of subjects within VA levels by visit from baseline to week 96, observed values (Safety Analysis Set)

Study identifier: VIEW 1

	R 0.5 mg Q4 (N=304)	VTE 0.5 mg Q4 (N=304)	VTE 2.0 mg Q4 (N=304)	VTE 2.0 mg Q8 (N=303)
Visual acuity in treated study eye	[redacted]			
No VI, >80 Letters				
SCREENING				
BASELINE				
WEEK 1				
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WEEK 96				
Mild VI, 80-66 Letters				
SCREENING				
BASELINE				
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WEEK 92				
WEEK 96				
Moderate VI, 65-51 Letters				
SCREENING				
BASELINE				
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WEEK 20				
WEEK 24				
WEEK 28				

Proportion of subjects within VA levels by visit from baseline to week 96, observed values (Safety Analysis Set)

Study identifier: VIEW 1

	R 0.5 mg Q4 (N=304)	VTE 0.5 mg Q4 (N=304)	VTE 2.0 mg Q4 (N=304)	VTE 2.0 mg Q8 (N=303)
WEEK 32	[redacted]			
WEEK 36				
WEEK 40				
WEEK 44				
WEEK 48				
WEEK 52				
WEEK 56				
WEEK 60				
WEEK 64				
WEEK 68				
WEEK 72				
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Severe VI, 50-36 Letters				
SCREENING				
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WEEK 88				
WEEK 92				
WEEK 96				
Blind, <36 Letters				
SCREENING				
BASELINE				
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WEEK 48				
WEEK 52				
WEEK 56				
WEEK 60				
WEEK 64				
WEEK 68				
WEEK 72				
WEEK 76				

Proportion of subjects within VA levels by visit from baseline to week 96, observed values (Safety Analysis Set)

Study identifier: VIEW 1

	R 0.5 mg Q4 (N=304)	VTE 0.5 mg Q4 (N=304)	VTE 2.0 mg Q4 (N=304)	VTE 2.0 mg Q8 (N=303)
WEEK 80	[redacted]			
WEEK 84				
WEEK 88				
WEEK 92				
WEEK 96				

Proportion of subjects within VA levels by visit from baseline to week 96, observed values (Safety Analysis Set) (cont.)

study identifier: VIEW 2

	R 0.5 mg Q4 (N=291)	VTE 0.5 mg Q4 (N=296)	VTE 2.0 mg Q4 (N=309)	VTE 2.0 mg Q8 (N=306)
Visual acuity in treated study eye	[redacted]			
No VI, >80 Letters				
SCREENING				
BASELINE				
WEEK 1				
WEEK 4				
WEEK 8				
WEEK 12				
WEEK 16				
WEEK 20				
WEEK 24				
WEEK 28				
WEEK 32				
WEEK 36				
WEEK 40				
WEEK 44				
WEEK 48				
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WEEK 60				
WEEK 64				
WEEK 68				
WEEK 72				
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WEEK 80				
WEEK 84				
WEEK 88				
WEEK 92				
WEEK 96				
Mild VI, 80-66 Letters				
SCREENING				
BASELINE				
WEEK 1				
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WEEK 20				
WEEK 24				
WEEK 28				
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WEEK 48				
WEEK 52				
WEEK 56				
WEEK 60				
WEEK 64				
WEEK 68				
WEEK 72				
WEEK 76				
WEEK 80				
WEEK 84				
WEEK 88				
WEEK 92				

Proportion of subjects within VA levels by visit from baseline to week 96, observed values (Safety Analysis Set) (cont.)

study identifier: VIEW 2

	R 0.5 mg Q4 (N=291)	VTE 0.5 mg Q4 (N=296)	VTE 2.0 mg Q4 (N=309)	VTE 2.0 mg Q8 (N=306)
WEEK 96	[redacted]			
Moderate VI, 65-51 Letters				
SCREENING				
BASELINE				
WEEK 1				
WEEK 4				
WEEK 8				
WEEK 12				
WEEK 16				
WEEK 20				
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WEEK 72				
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WEEK 92				
WEEK 96				
Severe VI, 50-36 Letters				
SCREENING				
BASELINE				
WEEK 1				
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WEEK 72				
WEEK 76				
WEEK 80				
WEEK 84				
WEEK 88				
WEEK 92				
WEEK 96				
Blind, <36 Letters				
SCREENING				
BASELINE				
WEEK 1				
WEEK 4				
WEEK 8				
WEEK 12				
WEEK 16				
WEEK 20				
WEEK 24				

Proportion of subjects within VA levels by visit from baseline to week 96, observed values (Safety Analysis Set) (cont.)

study identifier: VIEW 2

	R 0.5 mg Q4 (N=291)	VTE 0.5 mg Q4 (N=296)	VTE 2.0 mg Q4 (N=309)	VTE 2.0 mg Q8 (N=306)
WEEK 28	[redacted]			
WEEK 32				
WEEK 36				
WEEK 40				
WEEK 44				
WEEK 48				
WEEK 52				
WEEK 56				
WEEK 60				
WEEK 64				
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WEEK 88				
WEEK 92				
WEEK 96				

Proportion of subjects within VA levels by visit from baseline to week 96, observed values (Safety Analysis Set) (cont.)

Study identifier: Pooled

	R 0.5 mg Q4 (N=595)	VTE 0.5 mg Q4 (N=600)	VTE 2.0 mg Q4 (N=613)	VTE 2.0 mg Q8 (N=609)
Visual acuity in treated study eye	[redacted]			
No VI, >80 Letters				
SCREENING				
BASELINE				
WEEK 1				
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 56				
WEEK 60				
WEEK 64				
WEEK 68				
WEEK 72				
WEEK 76				
WEEK 80				
WEEK 84				
WEEK 88				
WEEK 92				
WEEK 96				
Mild VI, 80-66 Letters				
SCREENING				
BASELINE				
WEEK 1				
WEEK 4				
WEEK 8				
WEEK 12				
WEEK 16				
WEEK 20				
WEEK 24				
WEEK 28				
WEEK 32				
WEEK 36				

Proportion of subjects within VA levels by visit from baseline to week 96, observed values (Safety Analysis Set) (cont.)

Study identifier: Pooled

	R 0.5 mg Q4 (N=595)	VTE 0.5 mg Q4 (N=600)	VTE 2.0 mg Q4 (N=613)	VTE 2.0 mg Q8 (N=609)
WEEK 40	[redacted]			
WEEK 44				
WEEK 48				
WEEK 52				
WEEK 56				
WEEK 60				
WEEK 64				
WEEK 68				
WEEK 72				
WEEK 76				
WEEK 80				
WEEK 84				
WEEK 88				
WEEK 92				
WEEK 96				
Moderate VI, 65-51 Letters				
SCREENING				
BASELINE				
WEEK 1				
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 56				
WEEK 60				
WEEK 64				
WEEK 68				
WEEK 72				
WEEK 76				
WEEK 80				
WEEK 84				
WEEK 88				
WEEK 92				
WEEK 96				
Severe VI, 50-36 Letters				
SCREENING				
BASELINE				
WEEK 1				
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 56				
WEEK 60				
WEEK 64				
WEEK 68				
WEEK 72				
WEEK 76				
WEEK 80				
WEEK 84				

Proportion of subjects within VA levels by visit from baseline to week 96, observed values (Safety Analysis Set) (cont.)

Study identifier: Pooled

	R 0.5 mg Q4 (N=595)	VTE 0.5 mg Q4 (N=600)	VTE 2.0 mg Q4 (N=613)	VTE 2.0 mg Q8 (N=609)
WEEK 88	[redacted]			
WEEK 92				
WEEK 96				
Blind, <36 Letters				
SCREENING				
BASELINE				
WEEK 1				
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 56				
WEEK 60				
WEEK 64				
WEEK 68				
WEEK 72				
WEEK 76				
WEEK 80				
WEEK 84				
WEEK 88				
WEEK 92				
WEEK 96				

A11: priority question

Page 190: Please clarify whether the relative risk of 0.99 for the maintenance of vision for months 12 to 24 given in Table B39 is derived from the 1.01 24 month indirect analysis of Table 15 of the Kleijnen systematic review coupled with the 1.02 12 month indirect analysis of Table 10 of the Kleijnen systematic review: i.e. 0.99*1.02=1.01? If not, please clarify how the relative risk of 0.99 for the maintenance of vision for months 12 to 24 given in Table B39 was derived.

The relative risk of 0.99 is taken from Table 14 of the systematic review report. The results in the submission are correct. The correct reference from November 2012 has now been attached.

A12: priority question

Page 190: Please clarify whether the relative risk of 0.88 for the improvement of vision for months 12 to 24 given in Table B39 is derived from the 1.05 24 month indirect analysis of Table 15 of the Kleijnen systematic review coupled with the 1.19 12 month indirect analysis of Table 10 of the Kleijnen systematic review: i.e. 0.88*1.19=1.05? If not, please clarify how the relative risk of 0.88 for the improvement of vision for months 12 to 24 given in Table B39 was derived.

The relative risk of 0.88 is taken from Table 14 of the systematic review report. The results in the submission are correct. The correct reference from November 2012 has now been attached.

A13: priority question

Please present the following relative risks for aflibercept versus ranibizumab on the basis of LOCF for VIEW1, VIEW2 and VIEW1+VIEW2 pooled (**in 3 separate Tables**).

VIEW data – Aflibercept 2mg Q8 vs. Ranibizumab (Full analysis set)

VIEW 1

	Gain30+	Gain15+	Gain15-30	Gain0+	Stay±15	Lose15-30	Lose15+	Lose30+
Months 0-12								
Months 0-24								
Months 12-24								

NR= Not reported

VIEW 2

	Gain30+	Gain15+	Gain15-30	Gain0+	Stay±15	Lose15-30	Lose15+	Lose30+
Months 0-12								
Months 0-24								
Months 12-24								

VIEW 1 and 2

	Gain30+	Gain15+	Gain15-30	Gain0+	Stay±15	Lose15-30	Lose15+	Lose30+
Months 0-12								
Months 0-24								
Months 12-24								

Greyed out boxes indicate data not available from clinical trial reports. Given data from the VIEW studies is only available for up to 96 weeks, this data has been used.

A14

Page 49: It states that in VIEW 1 and VIEW 2 RCTs eligible patients were those that had "subfoveal CNV" but the definition of subfoveal CNV was "presence of subfoveal neovascularisation, including juxtafoveal lesions that affect the fovea". Please clarify whether there may not have been "CNV" under the fovea but only that part of the lesion was under the fovea for some patients [for instance, Pigment Epithelial Detachment (PED)]. Please also clarify whether the number of "juxtafoveal " lesions was equally distributed among treatment groups?

Analysis of baseline characteristics was conducted in terms of visual acuity letter score, retinal thickness, area of CNV, lesion type and total lesion size.

The protocol for the VIEW 1 study (same as VIEW 2) indicated that: *Subjects eligible for this study must have subfoveal CNV secondary to AMD. "Subfoveal" CNV shall be defined as the presence of subfoveal neovascularization, documented by FA, or presence of a lesion*

that is juxtafoveal in location angiographically but affects the fovea. The reading centre will confirm subject eligibility based on angiographic criteria prior to randomization.

The protocol for the VIEW 1 study (same as VIEW 2) included patients with a*ctive primary subfoveal CNV lesions secondary to AMD, including juxtafoveal lesions that affect the fovea as evidenced by FA in the study eye. The CNV must be at least 50% of total lesion size. The protocol excluded those with total lesion size > 12 disc areas (30.5 mm2, including blood, scars and neovascularization) as assessed by FA in the study eye; subretinal hemorrhage that is either 50% or more of the total lesion area, or if the blood is under the fovea and is 1 or more disc areas in size in the study eye. (If the blood is under the fovea, then the fovea must be surrounded 270 degrees by visible CNV.); Scar or fibrosis, making up > 50% of total lesion in the study eye; Scar, fibrosis, or atrophy involving the centre of the fovea; Presence of retinal pigment epithelial tears or rips involving the macula in the study eye; History of any vitreous hemorrhage within 4 weeks prior to Visit 1 in the study eye; and Presence of other causes of CNV, including pathologic myopia (spherical equivalent of – 8 diopters or more negative, or axial length of 25 mm or more), ocular histoplasmosis syndrome, angioid streaks, choroidal rupture, or multifocal choroiditis in the study eye.*

A15

Page 49 and pages 50-52: It states that eligible patients were those with “CNV”. Please clarify whether other phenotypes of neovascular AMD [retinal angiomatous prolifearion (RAP) and idiopathic polypoidal choroidal vasculopathy (IPCV)] were not included in the VIEW 1 VIEW 2 RCTs? If they were included, please provide the proportion of individuals with different phenotypes in each of the treatment groups in VIEW 1 and VIEW 2.

Analysis of baseline characteristics was conducted in terms of visual acuity letter score, retinal thickness, area of CNV, lesion type and total lesion size.

As specified by the selection criteria for the VIEW studies, patients with RAP or PCV were not excluded. Active primary subfoveal CNV lesions secondary to AMD, including juxtafoveal lesions that affect the fovea as evidenced by FA in the study eye, was the main criterion to randomize patients with CNV according to the final judgment by the reading centre.

With regard to RAP: following rule and definition was applied by the reading centre:

[redacted]

[redacted]

A16
Pages 51-52: In VIEW 1 most patients were white and non Hispanic (96.6%). In VIEW2, most patients were white (72.8%) but 20% were Asian. Please clarify if there are any separate data with regards to the Asian group?

Race and ethnicity was included in the pre-specified subgroup efficacy analyses. However, it should be noted that whilst the VIEW 2 study included Indian centres, the term 'Asian' in the context of the VIEW 2 demographics included, for example, people of Japanese and Korean Asian origin. Therefore, the 'Asian' population in the VIEW 2 study was not wholly representative of the British Asian population. Moreover, primary and secondary efficacy results in all evaluable subgroups were consistent with the overall population.

A17
Page 73: Please clarify what comparisons 4 to 15 for superiority testing using secondary endpoints were.

The protocol for the VIEW 1(same as VIEW 2) study indicated that:

Secondary: If all three VEGF Trap-Eye groups are shown to be non-inferior to ranibizumab on the primary endpoint, additional comparisons of those non-inferior VEGF Trap-Eye groups to ranibizumab will be made with respect to secondary endpoints. The secondary analysis will be conducted in the FAS and will test for superiority of VEGF Trap-Eye over ranibizumab. A conditional sequence of statistical hypothesis tests will control for multiplicity for secondary endpoint analyses. The following sequence of analyses will be performed.

1. VEGF Trap-Eye 2Q4 will be compared to ranibizumab relative to subjects mean change in BCVA as measured by ETDRS letter score from baseline to Week 52.

2. VEGF Trap-Eye 2Q4 will be compared to ranibizumab relative to the proportions of subjects who gain 15 or more letters of vision from baseline to Week 52.

3. VEGF Trap-Eye 2Q4 will be compared to ranibizumab relative to subjects mean change in total NEI-VFQ-25 score from baseline to Week 52.

4. VEGF Trap-Eye 0.5Q4 will be compared to ranibizumab relative to subjects mean change in BCVA as measured by ETDRS letter score from baseline to Week 52.

5. VEGF Trap-Eye 0.5Q4 will be compared to ranibizumab relative to the proportions of subjects who gain 15 or more letters of vision from baseline to Week 52.

6. VEGF Trap-Eye 0.5Q4 will be compared to ranibizumab relative to subjects mean change in total NEI-VFQ-25 score from baseline to Week 52.

7. VEGF Trap-Eye 2Q8 will be compared to ranibizumab relative to subjects mean change in BCVA as measured by ETDRS letter score from baseline to Week 52.

8. VEGF Trap-Eye 2Q8 will be compared to ranibizumab relative to the proportions of subjects who gain 15 or more letters of vision from baseline to Week 52.

9. VEGF Trap-Eye 2Q8 will be compared to ranibizumab relative to subjects mean change in total NEI-VFQ-25 score from baseline to Week 52.

10. VEGF Trap-Eye 2Q4 will be compared to ranibizumab relative to subjects mean change in CNV area from baseline to Week 52

11. VEGF Trap-Eye 0.5Q4 will be compared to ranibizumab relative to subjects mean change in CNV area from baseline to Week 52

12. VEGF Trap-Eye 2Q8 will be compared to ranibizumab relative to subjects mean change in CNV area from baseline to Week 52

As mentioned above, the primary analysis is conducted in the PPS population and the secondary analyses are conducted in the FAS. Additional analyses of the primary endpoint will be performed on the FAS following the intent-to-treat (ITT) principle with last observation carried forward to support the PPS analysis.

[redacted]

For secondary and exploratory analyses, for continuous measures, the following descriptive statistics will be reported: mean, median, minimum, maximum, standard deviation. For ordinal or categorical variables, frequencies and proportions will be reported.

[redacted]

A18
Page 87: Please clarify whether Figure 6 is for the per-protocol set (PPS) or full analysis set (FAS).

This figure is taken from the Heier 2012 publication(2) of the VIEW 52 week data and corresponds to the per protocol set.

A19
Page 89: Please present separate figures for the mean change in visual acuity at the end of 96 weeks (Figure B7) for VIEW1 and for VIEW2. Please also clarify if Figure B7 is for the PPS or FAS.

This data is presented in the submission in Table B16. Change from baseline at 96 weeks was analysed in terms of the full analysis set (FAS).

VIEW 1 CSR:

[redacted]

VIEW 2 CSR :

[redacted]

A20

Page 114: It states that "VIEW 1 and VIEW 2 were of nearly identical design". Please clarify what were the differences in study design between these two trials? ('nearly identical' does not mean 'identical').

Both VIEW 1 and VIEW 2 were randomized, double-masked, and active-controlled studies with almost identical inclusion/exclusion criteria. The primary and secondary efficacy endpoints were identical in the two protocols. There were no differences in terms of the main contents of the study protocols that would prevent the integration of the data. The two studies were executed in different geographical locations.

The two protocols were also similar in terms of the regular visit assessments, their re-treatment criteria for Year 2, and their statistical considerations (and, therefore, had identical statistical analysis plans). Subjects in both studies were assessed with identical protocol deviation methods for exclusion from the per protocol set. The fluorescein angiography reading centre was the same for both VIEW 1 and VIEW 2 and the optical coherence tomography (OCT) centres were similar in terms of the methodology used for the analysis of the OCT images. The safety measurements in both studies were tightly controlled to ensure subject safety.

The following few differences between the VIEW 1 and VIEW 2 protocols did not affect the results obtained from the integrated analysis:

- *A few additional pharmacokinetics, pharmacogenetic and safety analyses were performed in subgroups of subjects in the VIEW 2 study*
- *Minor differences in coding and adjustments in the protocol safety assessments in VIEW 1*
- *Minor wording differences in the inclusion and exclusion criteria between the two trials*
- *The VIEW 2 study included the EQ5D whereas the VIEW 1 study did not.*

A21

Page 122: It states that the IVAN trial was not included in the network meta-analysis because the outcomes were combined for the as needed (PRN) and fixed dosing regimens. Please clarify whether data from the monthly regime and those from the PRN are available separately.

As stated, the interim analysis of IVAN(7) did not provide separate data for ranibizumab PRN and ranibizumab monthly. This was requested from the authors but was not available given this analysis was planned for completion of the study.

A22

Page 125: Some trials included only "occult" CNV, such as MARINA. Please clarify why the ranibizumab arm of the ANCHOR trial (which included predominantly classic CNV) was not considered in the network meta-analysis?

ANCHOR and MARINA were included at Stage 1 of the systematic review. The ANCHOR study was not included in the indirect comparison as it did not compare monthly ranibizumab to as needed (pro re nata - PRN) and included sham photodynamic therapy (PDT) in the ranibizumab arms of the study. Sham PDT differs from placebo in terms of patient experience. This meant that it was over two steps away from aflibercept in the network and met the exclusion criteria defined in the protocol.

A23

Pages 129-130: Please clarify what the purpose of the normal adjustment in the analysis of continuous outcomes was and why it was required.

As described in the report, the methods of indirect comparison were based on the Cochrane Handbook, Bucher et al 1997(8) and Wells et al 2009(9). The text also states that As the normal distribution gives slightly deviating values based on chance, these values were corrected using the following formula "adjusted outcome = (xq-meqq) sdq/sdqq+ meanq" (where xq = new mean based on normal distribution, meqq = adjustment for mean, sdq = new sd based on normal distribution, sdqq = adjustment for sd, meanq = original mean outcome).*

The Puhan method: you assume a normal distribution of the outcomes, by sampling from this distribution a data set can be generated which is comparable to the original data set of individual values. Assume that in a treatment arm N persons are included with a specific mean and standard deviation. Drawing N values from a normal distribution with these parameters will result in a sample with a mean and standard deviation. By chance these parameters will be somewhat different from the original parameters. That is why an adjustment is necessary to generate a population with a mean and a sd that is exactly the same. This is done by transforming the sampled values X` into X=(X`- μ` +μ)* σ/σ`.

A24

Please present the baseline distributions of the BCVA of the treated eye across the model health states for VIEW1, VIEW2 and VIEW1+VIEW2 pooled (**in 3 separate tables**). Please also present for each health state the proportion of untreated eyes that had wet AMD at baseline.

Please note that this data is limited by the definition of wet AMD in the fellow eye and how this was reported, given that outcomes in the VIEW studies were measured in terms of the study eye.

Question A24a: Combinations of VA levels at baseline in the two eye model (Safety Analysis Set)

Study identifier: VIEW 1
Treatment group: **Ranibizumab**

Visual acuity at baseline in treated study eye	missing (N=1)	No VI, >80 Letters (N=0)	Mild VI, 80-66 Letters (N=66)	Moderate VI, 65-51 Letters (N=144)	Severe VI, 50-36 Letters (N=51)	Blind, <36 Letters (N=42)
No wet AMD in fellow eye	[redacted]					
Visual acuity at baseline in fellow eye						
missing						
No VI, >80 Letters						
Mild VI, 80-66 Letters						
Moderate VI, 65-51 Letters						
Severe VI, 50-36 Letters						
Blind, <36 Letters						
Wet AMD in fellow eye						
Visual acuity at baseline in fellow eye						
missing						
No VI, >80 Letters						
Mild VI, 80-66 Letters						
Moderate VI, 65-51 Letters						
Severe VI, 50-36 Letters						
Blind, <36 Letters						
Total						
Visual acuity at baseline in fellow eye						
missing						
No VI, >80 Letters						
Mild VI, 80-66 Letters						
Moderate VI, 65-51 Letters						
Severe VI, 50-36 Letters						
Blind, <36 Letters						

A24: Combinations of VA levels at baseline in the two eye model (Safety Analysis Set) (cont.)

Study identifier: VIEW 1
Treatment group: **Aflibercept 2.0 mg Q8**

Visual acuity at baseline in treated study eye	missing (N=0)	No VI, >80 Letters (N=1)	Mild VI, 80-66 Letters (N=72)	Moderate VI, 65-51 Letters (N=138)	Severe VI, 50-36 Letters (N=66)	Blind, <36 Letters (N=26)
No wet AMD in fellow eye	[redacted]					
Visual acuity at baseline in fellow eye						
missing						
No VI, >80 Letters						
Mild VI, 80-66 Letters						
Moderate VI, 65-51 Letters						
Severe VI, 50-36 Letters						
Blind, <36 Letters						
Wet AMD in fellow eye						
Visual acuity at baseline in fellow eye						
missing						
No VI, >80 Letters						
Mild VI, 80-66 Letters						
Moderate VI, 65-51 Letters						
Severe VI, 50-36 Letters						
Blind, <36 Letters						
Total						
Visual acuity at baseline in fellow eye						
missing						
No VI, >80 Letters						
Mild VI, 80-66 Letters						
Moderate VI, 65-51 Letters						
Severe VI, 50-36 Letters						
Blind, <36 Letters						

A24: Combinations of VA levels at baseline in the two eye model (Safety Analysis Set) (cont.)

Study identifier: VIEW 2
Treatment group: **Ranibizumab**

Visual acuity at baseline in treated study eye	missing (N=0)	No VI, >80 Letters (N=1)	Mild VI, 80-66 Letters (N=57)	Moderate VI, 65-51 Letters (N=137)	Severe VI, 50-36 Letters (N=58)	Blind, <36 Letters (N=38)
No wet AMD in fellow eye	[redacted]					
Visual acuity at baseline in fellow eye						
missing						
No VI, >80 Letters						
Mild VI, 80-66 Letters						
Moderate VI, 65-51 Letters						
Severe VI, 50-36 Letters						
Blind, <36 Letters						
Wet AMD in fellow eye						
Visual acuity at baseline in fellow eye						
missing						
No VI, >80 Letters						
Mild VI, 80-66 Letters						
Moderate VI, 65-51 Letters						
Severe VI, 50-36 Letters						
Blind, <36 Letters						
Total						
Visual acuity at baseline in fellow eye						
missing						
No VI, >80 Letters						
Mild VI, 80-66 Letters						
Moderate VI, 65-51 Letters						
Severe VI, 50-36 Letters						
Blind, <36 Letters						

A24: Combinations of VA levels at baseline in the two eye model (Safety Analysis Set) (cont.)

study identifier: VIEW 2
Treatment group: **Aflibercept 2.0 mg Q8**

Visual acuity at baseline in treated study eye	missing (N=1)	No VI, >80 Letters (N=0)	Mild VI, 80-66 Letters (N=54)	Moderate VI, 65-51 Letters (N=115)	Severe VI, 50-36 Letters (N=87)	Blind, <36 Letters (N=50)
No wet AMD in fellow eye	[redacted]					
Visual acuity at baseline in fellow eye						
missing						
No VI, >80 Letters						
Mild VI, 80-66 Letters						
Moderate VI, 65-51 Letters						
Severe VI, 50-36 Letters						
Blind, <36 Letters						
Wet AMD in fellow eye						
Visual acuity at baseline in fellow eye						
missing						
No VI, >80 Letters						
Mild VI, 80-66 Letters						
Moderate VI, 65-51 Letters						
Severe VI, 50-36 Letters						
Blind, <36 Letters						
Total						
Visual acuity at baseline in fellow eye						
missing						
No VI, >80 Letters						
Mild VI, 80-66 Letters						
Moderate VI, 65-51 Letters						
Severe VI, 50-36 Letters						
Blind, <36 Letters						

A24: Combinations of VA levels at baseline in the two eye model (Safety Analysis Set) (cont.)

Study identifier: Pooled
Treatment group: **Ranibizumab**

Visual acuity at baseline in treated study eye	missing (N=1)	No VI, >80 Letters (N=1)	Mild VI, 80-66 Letters (N=123)	Moderate VI, 65-51 Letters (N=281)	Severe VI, 50-36 Letters (N=109)	Blind, <36 Letters (N=80)
No wet AMD in fellow eye	[redacted]					
Visual acuity at baseline in fellow eye						
missing						
No VI, >80 Letters						
Mild VI, 80-66 Letters						
Moderate VI, 65-51 Letters						
Severe VI, 50-36 Letters						
Blind, <36 Letters						
Wet AMD in fellow eye						
Visual acuity at baseline in fellow eye						
missing						
No VI, >80 Letters						
Mild VI, 80-66 Letters						
Moderate VI, 65-51 Letters						
Severe VI, 50-36 Letters						
Blind, <36 Letters						
Total						
Visual acuity at baseline in fellow eye						
missing						
No VI, >80 Letters						
Mild VI, 80-66 Letters						
Moderate VI, 65-51 Letters						
Severe VI, 50-36 Letters						
Blind, <36 Letters						

A24: Combinations of VA levels at baseline in the two eye model (Safety Analysis Set) (cont.)

Study identifier: Pooled
Treatment group: **Aflibercept 2.0 mg Q8**

Visual acuity at baseline in treated study eye	missing (N=1)	No VI, >80 Letters (N=1)	Mild VI, 80-66 Letters (N=126)	Moderate VI, 65-51 Letters (N=253)	Severe VI, 50-36 Letters (N=153)	Blind, <36 Letters (N=76)
No wet AMD in fellow eye						
Visual acuity at baseline in fellow eye	[redacted]					
missing						
No VI, >80 Letters						
Mild VI, 80-66 Letters						
Moderate VI, 65-51 Letters						
Severe VI, 50-36 Letters						
Blind, <36 Letters						
Wet AMD in fellow eye						
Visual acuity at baseline in fellow eye						
missing						
No VI, >80 Letters						
Mild VI, 80-66 Letters						
Moderate VI, 65-51 Letters						
Severe VI, 50-36 Letters						
Blind, <36 Letters						
Total						
Visual acuity at baseline in fellow eye						
missing						
No VI, >80 Letters						
Mild VI, 80-66 Letters						
Moderate VI, 65-51 Letters						
Severe VI, 50-36 Letters						
Blind, <36 Letters						

A25

Please clarify if any indirect treatment comparison (ITC) of the year 1 discontinuation rate, the year 2 discontinuation rate and the 2 year discontinuation rate was undertaken in the Kleijnen systematic review. If not, please clarify the reasons for this not being part of the systematic review given its possible centrality to the cost effectiveness results.

The indirect comparison did not include discontinuation rates. As stated in the submission and report for the indirect comparison and systematic review, the results of any of the indirect comparisons should be treated with caution due to differences in retreatment criteria,

numbers of injections and baseline criteria. This is even more so in terms of discontinuations rates.

It is not appropriate to compare discontinuation rates from two or more different studies, such as VIEW and CATT. There may be a variety of reasons why dropout rates differ between separate studies.

- *There may be a difference between patients and investigators being willing to remain in a study if they are aware they are having one of the two 'standard' treatments available (e.g. ranibizumab or bevacizumab in the CATT study in the US) compared to a situation where they have a 1 in 4 chance of being on an experimental treatment (as in the VIEW studies)*
- *Different protocols with different monitoring requirements may make life easier or harder for patients*
- *Inclusion/exclusion criteria or criteria for remaining on study may differ between protocols*

It would be more appropriate to compare the dropout rates between ranibizumab and aflibercept within the VIEW studies, as here we can be certain that the patients will be well balanced in terms of background characteristics, withdrawal criteria, intensity of protocol investigations and availability/cost of alternative treatments, if not on the study.

Considering the dropout rates in the Heier et al publication of the VIEW studies(2) (see the 2 flowcharts in 'Figure 1'), there are only small differences between aflibercept and ranibizumab withdrawal in VIEW 2 (10.7% vs. 8.9%), and the rates in VIEW 1 are almost identical (7.1% vs. 7.2%). The withdrawal due to adverse events (AE) for aflibercept was slightly higher in terms of percentage in VIEW 2, but identical to ranibizumab in VIEW 1, suggesting any difference may have been down to other environmental factors or chance and not a true difference between treatments. These facts would also support the view that any difference in withdrawal rates between aflibercept in VIEW and ranibizumab as needed in CATT is down to study-related factors rather than drug-related factors.

In the context of the NHS, where the only difference between the experience of ranibizumab and aflibercept patients should be slightly more monitoring visits/trips to hospital for the former, it is difficult to think of a reason why dropout rates should differ, based on the head-to-head experience in the VIEW studies.

In addition, the available studies do not mirror exactly the dosing regimens specified in the summary of product characteristics (SmPCs)(10;11) for aflibercept and ranibizumab and therefore, the discontinuation rates in trials may not fully represent those expected in practice. For example, the SmPC for aflibercept does not require monthly monitoring whereas patients in the VIEW studies had monthly visits for masking and study assessment purposes.

A wider review of the literature (summary attached with this response) was conducted for discontinuation rates but this also found insufficient evidence to use in the model. Hence, expert opinion was the best available evidence used.

A26

Page 190: Please clarify whether the relative risks reported in Table B39 suggest that there is a greater probability of gaining letters in year 1 from aflibercept, but a greater probability of gaining letters in year 2 from Ranibizumab. Please also clarify whether this has implications for extrapolation of effect (with the year 2 figure being potentially more relevant for extrapolation).

As stated in the indirect comparison and systematic review, the results of any of the comparisons should be treated with caution given the differences between trials in terms of baseline characteristics, retreatment criteria and numbers of injections. In addition, as discussed in the submission, the applicability of the evidence is also limited by the differences in the dosing regimens specified in the trials and those specified in the marketing authorisations for aflibercept and ranibizumab.

Given the absence of robust comparative evidence for years 3-5, a conservative assumption of identical efficacy between ranibizumab and aflibercept has been made.

A27
Please present the following relative risks on the basis of observed data for VIEW1, VIEW2 and VIEW1+VIEW2 pooled (**in 3 separate Tables**).

VIEW data – Aflibercept 2mg Q8 vs. Ranibizumab (Full analysis set)

VIEW 1

	Gain30+	Gain15+	Gain15-30	Gain0+	Stay±15	Lose15-30	Lose15+	Lose30+
Months 0-12	[redacted]							
Months 0-24								
Months 12-24								

VIEW 2

	Gain30+	Gain15+	Gain15-30	Gain0+	Stay±15	Lose15-30	Lose15+	Lose30+
Months 0-12	[redacted]							
Months 0-24								
Months 12-24								

VIEW 1 and 2

	Gain30+	Gain15+	Gain15-30	Gain0+	Stay±15	Lose15-30	Lose15+	Lose30+
Months 0-12	[redacted]							
Months 0-24								
Months 12-24								

Please note data from the VIEW studies is only available for up to 96 weeks.

Appendix 15, Reference Pack –Systematic review

A28: priority question
Page 58 - Please confirm which forest plot corresponds to which outcome and comparison (there are no titles for these plots).

An updated report from November 2012 has been attached.

A29: priority question
Figure 16, 24m direct analysis – Please clarify why the numerical results are labelled as 'odds ratio' in the analysis but the plots refer to 'risk ratios'.

This should read risk ratios to match that written in the text.

A30
Appendix 2-4: Please provide the STATA code used for the frequentist network meta-analysis.

These are attached.

A31
Please provide the Excel file used to undertake the Bucher analysis.

These are attached.

Section B: Clarification on cost-effectiveness data

Quality of life data

B1: priority question
Page 200: Please clarify whether the quality of life values reported in Table B42 are derived using the UK population norms for the EQ-5D. If not, please present the equivalent quality of life values for the same health states based on the UK social tariff weights for the EQ-5D.

The utility values reported in table B42 were derived using the UK population valuations applied to the EQ-5D data from the VIEW 2 trial (see reference 104 and 105 of the submission document). As described in the text, the Dolan 1996(12) and Kind 1998(13) UK population tariffs were used.

B2: priority question
Page 200: The model structure is defined in terms of the combined BCVA of both eyes. The utilities listed in Table B42 appear to adopt counting fingers rather than the blind categorisation of the model. Please complete the following table of health state classifications for single eyes adopted within the model and within the utility study, and clarify any differences between the model and the VIEW2 EQ-5D utility analysis.

Table B42 is mislabelled. The visual acuity level described as counting fingers should be recorded as blind. The definition of blind used in the model is having a visual acuity of <36 EDTRS letters. There is no visual acuity level for counting fingers.

Please see below for the corrected table

Table B42: Summary of quality-of-life values for cost-effectiveness analysis

Vision acuity in both eyes	Utility (EQ-5D)	SD	Reference in submission	Justification
None/None	[redacted]	[redacted]	7.4.3	VIEW protocol
None/Mild	[redacted]	[redacted]		
None/Moderate	[redacted]	[redacted]		
None/Severe	[redacted]	[redacted]		
None/Blind	[redacted]	[redacted]		
Mild/Mild	[redacted]	[redacted]		
Mild/Moderate	[redacted]	[redacted]		
Mild/Severe	[redacted]	[redacted]		
Mild/Blind	[redacted]	[redacted]		
Moderate/Moderate	[redacted]	[redacted]		
Moderate/Severe	[redacted]	[redacted]		
Moderate/Blind	[redacted]	[redacted]		
Severe/Blind	[redacted]	[redacted]		
Severe/Severe	[redacted]	[redacted]		
Blind /Blind	[redacted]	[redacted]		

B3: priority question
Page 200: Please clarify whether the ETDRS letters used to define health states in the model differ from the ETDRS letters for the VIEW2 EQ-5D utility analysis. If so, please present a separate table (based on Table B42) using the ETDRS health states of the model and the UK population norms.

The same definition of ETDRS letters were used for both the model health states and the utility analysis.

B4
Page 200: Please clarify whether the EQ-5D results from VIEW2 as presented in Table B42 are derived from all EQ-5D data points pooled across baseline, week 52 and week 96 and pooled across the 4 arms of VIEW2. If not, please summarise which data points have been included and which have been excluded and the reasons for this.

The EQ-5D scores are for both eyes, all treatment groups combined, and at all stated time points.

B5

Please present the following VIEW2 EQ-5D patient numbers at baseline, week 52 and week 96 (**in 3 separate Tables**).

EQ5D 5a scores by visual impairment category in both eyes, all treatment groups combined, baseline

Baseline				
Vision Impairment, both eyes	**EQ5D Average**	**SD**	**N**	**Missing**
None/None	[redacted]			
None/Mild				
None/Moderate				
None/Severe				
None/Counting Fingers				
Mild/Mild				
Mild/Moderate				
Mild/Severe				
Mild/Counting Fingers				
Moderate/Moderate				
Moderate/Severe				
Moderate/Counting Fingers				
Severe/Severe				
Severe/Counting Fingers				
Counting Fingers/Counting Fingers				

EQ5D 5b scores by visual impairment category in both eyes, all treatment groups combined, Year 1

Year 1				
Vision Impairment, both eyes	**EQ5D Average**	**SD**	**N**	**Missing**
None/None	[redacted]			
None/Mild				
None/Moderate				
None/Severe				
None/Counting Fingers				
Mild/Mild				
Mild/Moderate				
Mild/Severe				
Mild/Counting Fingers				
Moderate/Moderate				
Moderate/Severe				
Moderate/Counting Fingers				
Severe/Severe				
Severe/Counting Fingers				
Counting Fingers/Counting Fingers				

Table 5c: EQ5D scores by visual impairment category in both eyes, all treatment groups combined, Year 2

Year 2				
Vision Impairment, both eyes	EQ5D Average	SD	N	Missing
None/None	[redacted]			
None/Mild				
None/Moderate				
None/Severe				
None/Counting Fingers				
Mild/Mild				
Mild/Moderate				
Mild/Severe				
Mild/Counting Fingers				
Moderate/Moderate				
Moderate/Severe				
Moderate/Counting Fingers				
Severe/Counting Fingers				
Severe/Severe				
Counting Fingers/Counting Fingers				

Please note that missing data refers to participants missing both VA and EQ5D scores. There were no single missing values of the 5 dimensions of the EQ-5D at a visit. In the case that the EQ-5D was asked at a visit, all 5 questions of the EQ-5D were answered by the subject. Missing values at a visit were not imputed or extrapolated (e.g. LOCF). Unfortunately, it was not possible to define discontinuers within the datasets used to calculate EQ5D scores. As the VIEW datasets have one observation per visit, it was possible to combine the VA data with the EQ5D data at a given visit and output the number with a missing EQ5D score (given that they are included in the VA dataset). However, there was not a variable that defined discontinuation and the analysis considered each visit at a time (not per patient longitudinally), so it was not possible to report numbers discontinued alongside this analysis. Since each patient can switch VA state between visits, it is not possible to subtract the observations from the previous visit. Therefore, we have attached the EQ5D tables from the clinical study reports for VIEW 2 at 52 weeks and 96 weeks to show missing visits.

B6

Page 200: Please present a separate table (based on Table B42) for the subset of patients falling into either regions 7 or region 8 of VIEW2, applying the UK population norms for the EQ-5D, along with the relevant patient numbers at baseline, week 52 and week 96.

Regions 7 and 8 include Australia, Belgium, Israel, Sweden, The Netherlands, UK, France, Italy, Portugal and Spain. Only a small number of patients were included from the UK and this group is not representative of the UK. Patients with wet AMD are treated differently across Europe, for example, in the UK ophthalmologists are hospital based but may be office based in other countries.

B7
Page 221: Please clarify how the Czoski-Murray utility values presented in Table B54 were applied within the modelling framework using the health states described in Table B42 (based on the following table).

	NVI	*Mild*	*Moderate*	*Severe*	*Blind*
NVI	*0.71*				
Mild	*0.61*	*0.69*			
Moderate	*0.61*	*0.59*	*0.62*		
Severe	*0.61*	*0.59*	*0.52*	*0.51*	
Blind	*0.61*	*0.59*	*0.52*	*0.41*	*0.31*

Resource use data

B8: priority question
Please provide the following dosing information for both the Aflibercept 2mg Q8 arm and the Ranibizumab arm for VIEW2, VIEW1 and VIEW1+VIEW2 pooled (**in 6 separate Tables**).

View 1: Study medication: Number of injections baseline to week 96/100 by visit (Safety Analysis Set)

Analysis Timepoint Number		R 0.5Q4 N=304 (100%)	VTE 2Q8 N=303 (100%)
WEEK 0, DAY 1	n on treatment	[redacted]	[redacted]
	n doses		
WEEK 4	n on treatment		
	n doses		
WEEK 8	n on treatment		
	n doses		
WEEK 12	n on treatment		
	n doses		
WEEK 16	n on treatment		
	n doses		
WEEK 20	n on treatment		
	n doses		
WEEK 24	n on treatment		
	n doses		
WEEK 28	n on treatment		
	n doses		

Analysis Timepoint Number		R 0.5Q4 N=304 (100%)	VTE 2Q8 N=303 (100%)
WEEK 32	n on treatment	[redacted]	[redacted]
	n doses		
WEEK 36	n on treatment		
	n doses		
WEEK 40	n on treatment		
	n doses		
WEEK 44	n on treatment		
	n doses		
WEEK 48	n on treatment		
	n doses		
WEEK 52	n on treatment		
	n doses		
WEEK 56	n on treatment		
	n doses		
WEEK 60	n on treatment		
	n doses		
WEEK 64	n on treatment		
	n doses		
WEEK 68	n on treatment		
	n doses		
WEEK 72	n on treatment		
	n doses		
WEEK 76	n on treatment		
	n doses		
WEEK 80	n on treatment		
	n doses		
WEEK 84	n on treatment		
	n doses		

Analysis Timepoint Number		R 0.5Q4 N=304 (100%)	VTE 2Q8 N=303 (100%)
WEEK 88	n on treatment	[redacted]	
	n doses		
WEEK 92	n on treatment		
	n doses		

View 2: Study medication: Number of injections baseline to week 96/100 by visit (Safety Analysis Set)

Analysis Timepoint Number		R 0.5Q4 N=291 (100%)	VTE 2Q8 N=307 (100%)
WEEK 0, DAY 1	n on treatment	[redacted]	[redacted]
	n doses		
WEEK 4	n on treatment		
	n doses		
WEEK 8	n on treatment		
	n doses		
WEEK 12	n on treatment		
	n doses		
WEEK 16	n on treatment		
	n doses		
WEEK 20	n on treatment		
	n doses		
WEEK 24	n on treatment		
	n doses		
WEEK 28	n on treatment		
	n doses		
WEEK 32	n on treatment		
	n doses		
WEEK 36	n on treatment		
	n doses		
WEEK 40	n on treatment		
	n doses		
WEEK 44	n on treatment		
	n doses		
WEEK 48	n on treatment		
	n doses		
WEEK 52	n on treatment		
	n doses		

Analysis Timepoint Number		R 0.5Q4 N=291 (100%)	VTE 2Q8 N=307 (100%)
WEEK 56	n on treatment	[redacted]	
	n doses		
WEEK 60	n on treatment		
	n doses		
WEEK 64	n on treatment		
	n doses		
WEEK 68	n on treatment		
	n doses		
WEEK 72	n on treatment		
	n doses		
WEEK 76	n on treatment		
	n doses		
WEEK 80	n on treatment		
	n doses		
WEEK 84	n on treatment		
	n doses		
WEEK 88	n on treatment		
	n doses		
WEEK 92	n on treatment		
	n doses		

Pool: Study medication: Number of injections baseline to week 96/100 by visit (Safety Analysis Set)

Analysis Timepoint Number		R 0.5Q4 N=595 (100%)	VTE 2Q8 N=610 (100%)
WEEK 0, DAY 1	n on treatment	[redacted]	
	n doses		
WEEK 4	n on treatment		
	n doses		
WEEK 8	n on treatment		
	n doses		

Analysis Timepoint Number		R 0.5Q4 N=595 (100%)	VTE 2Q8 N=610 (100%)
WEEK 12	n on treatment	[redacted]	[redacted]
	n doses		
WEEK 16	n on treatment		
	n doses		
WEEK 20	n on treatment		
	n doses		
WEEK 24	n on treatment		
	n doses		
WEEK 28	n on treatment		
	n doses		
WEEK 32	n on treatment		
	n doses		
WEEK 36	n on treatment		
	n doses		
WEEK 40	n on treatment		
	n doses		
WEEK 44	n on treatment		
	n doses		
WEEK 48	n on treatment		
	n doses		
WEEK 52	n on treatment		
	n doses		
WEEK 56	n on treatment		
	n doses		
WEEK 60	n on treatment		
	n doses		
WEEK 64	n on treatment		
	n doses		

Analysis Timepoint Number		R 0.5Q4 N=595 (100%)	VTE 2Q8 N=610 (100%)
WEEK 68	n on treatment	[redacted]	
	n doses		
WEEK 72	n on treatment		
	n doses		
WEEK 76	n on treatment		
	n doses		
WEEK 80	n on treatment		
	n doses		
WEEK 84	n on treatment		
	n doses		
WEEK 88	n on treatment		
	n doses		
WEEK 92	n on treatment		
	n doses		

B9

Page 206: The frequency of injections for Ranibizumab in year 1 and year 2 are reported as being taken from TA155 and the EMA report. Please provide the exact table or paragraph references for these two estimates.

The dosing regimen in the SmPC for ranibizumab for wet AMD was changed by the EMA in 2011(14). Public copies of the EMA assessment report for this amendment are not freely available via the EMA website but individual copies can be requested directly from the EMA.

The EMA assessment report(15) estimates 8.4 injections with the revised regimen on page 10 compared to 6.4 with the previous regimen in the first year. This is also similar to other publications that have estimated the number of injections needed in the first year with ranibizumab to be 8.1 and 8.4(16;17).

The NICE guidance TA155 was re-issued in May 2012 based on a report from the Decision Support Unit. This document evaluated the impact of a revised patient access scheme for ranibizumab. This document considered 8 injections in the first year and 6 injections in the second year, as was used in the original appraisal (http://www.nice.org.uk/nicemedia/live/11700/60523/60523.pdf (see page 4 and 5) and see sections 4.3.11 and 4.3.12 of the current guidance(18).

Despite the differences in the retreatment regimens in the SmPC for ranibizumab and that in the CATT study, the number of injections in the CATT study was also 5.7 in the second year under an as needed regimen which considering the EMA conclusions for the first year may be an underestimate of on label treatment with ranibizumab.

B10
Please provide a copy of the list of questions of the physician survey on resource use, along with a tabulation of the responses (e.g. x anticipated 3 Ranibizumab injections in year 3, y anticipated 4 Ranibizumab injections in year 3 etc).

This is included in Appendix 17 – physician survey report.

Model structure

B11: priority question
Please clarify whether the probability of maintaining vision within the Kleijnen systematic review was defined in the same way as in the model which appears to permit gains and losses of up to (but not including) 15 letters. If the two probabilities are not aligned, please also clarify how these differences will impact on the model outcomes?

The VIEW study defined maintained vision as losing fewer than 15 letters.

Maintaining vision in the systematic review and indirect comparison is defined as losing ≤ 15 ETDRS letters. In addition, "improved" visual acuity is defined as gaining ≥ 15 ETDRS letters. By inference patients whose vision is "not maintained" or "improved" lose 15 or more ETDRS letters.

In the model, patients who "improve" their visual acuity are defined by those patients gaining ≥ 15 ETDRS letters (same as in the systematic review); patients whose visual acuity remain the "same" are defined by those patients gaining <15 ETDRS letters or losing ≤ 15 ETDRS letters (see cell HG14 in tab "1st Eye_RbzPRN") . Finally, the visual acuity of patients "losing" vision is defined as losing >15 ETDRS letters (see cells HG17:HG2 in tab "1st Eye_RbzPRN").

In addition, in the model people who gain or lose vision can improve or decline one or two health states, equal to a gain or loss of 15 or 30 ETDRS letters.
By dividing ETDRS into bands of 15 ETDRS letters the model represents a simplification of patient experience. We note than a 15 letter change has been proposed as a clinically significant difference (see NICE TA155 section 4.2.3.1).

B12: priority question
Please present the parameter estimate(s) along with their source(s) for the development of wet AMD in the 2nd eye for:

- year 1 of the model;
- year 2 of the model;
- years 3-5 of the model; and,
- years 5+ of the model.

Development of wet AMD in the second eye was taken from Wong et al(19). The probability of developing wet AMD in the second eye during year 1 and 2 of the model is zero. From year 3 onwards, the monthly probability of developing wet AMD in the second eye is 0.0065. This probability was derived from Wong et al. 2008, by converting data reporting the proportion of patients who develop wet AMD in their second eye at 4 years (26.8%) into a monthly probability by assuming a constant rate.

B13: priority question

The ERG has identified possible serious structural errors in the modelling of second eye involvement. Two transition probability matrices (TPMs) in the economic model are presented in the 2nd eye worksheets:

- The "post treatment" TPM in cells XM70:YK94. This appears to be applicable only when both eyes have received treatment of more than two years duration and both eyes remain on treatment. This in turn appears to imply no change in the visual acuity of either eye hence no change in health state for those to whom it is applied.

The TPM in cells XM70:YK94 implements the assumption in section 7.3.2 (page 186) of the submission document "For years 3 to 5 the model assumes that patients on active treatment will remain in the same health state that they are in after 24 months". The model assumes due to the lack of alternative efficacy data that patients on treatment during the post trial period (years 3-5) will not lose any visual acuity.

- The BSC TPM in cells XM100:YK124. This appears to be applicable only when both eyes are receiving only Best supportive care (BSC).

The assumption of maintained visual acuity (section 7.3.2) is applied during years 3-5 only. From year 6 onwards all patients stop treatment and follow natural disease progression as defined by the probabilities contained in BSC TPM in cells XM100:YK124.

The ERG has identified possible major concerns around the application of these TPMs, and the probabilities within them, in the modelling of bilateral wet AMD. The ERG has also not been able to identify any other TPMs applied in the modelling of bilateral wet AMD. It would be appreciated if each of the following bullet points could be addressed individually in turn:

- Please clarify whether there is no consideration of the impact of the initial two years of treatment upon the BCVA of the 2nd eye; i.e. cells GR6:GX65 of the 1st eye worksheets appear to be applied to the annual incidences of 2nd eye involvement, with ongoing annual incidences of 2nd eye involvement occurring over the time horizon of the model and receiving this treatment effect. If this is not correct, please provide some indication of the location of these calculations and the underlying model logic, along with how it applies any treatment of the ongoing annual incidences of 2nd eye involvement over the time horizon of the model.

The assumption/simplification incorporated into the model is that the second eye cannot develop wet AMD until after year 2.

- Please clarify whether the "post treatment" TPM of no change in BCVA of either eye is applied for years 3-5, with the BSC TPM being applied from year 6 onwards. Please also clarify whether this does not apply any initial 2 years treatment effect for the 2nd eye, but also does not take into account the differential timing of the development of wet AMD in the 2nd eye. For example, those developing 2nd eye involvement at the start of year 3 appears to have the "post treatment" TPM applied for three years, those developing 2nd eye involvement at the start of year 5 appear to have it applied for one year, and those developing 2nd eye involvement at the start of year 6 do not have it applied at all. If this is correct, please provide the rationale behind this model structure.

The post treatment TPM is applied for years 3-5 and the BSC TPM is applied from year 6 onwards. Second eye involvement is not modelled until after year 2. The treatment period is fixed to years 1-5 only and the model does not adjust treatment duration based on when the second eye involvement occurred.

- Please clarify whether the treatment costs for second eye involvement are limited to years 3-5 of the model; e.g. cells SO8:SO368 are zero with the exception of cells SO34:SO68. If this is correct, please provide the rationale for this given that 2nd eye involvement can occur over the time horizon of the model and so presumably treatment costs can be incurred over the time horizon of the model.

The model limits treatment to years 1-5 of the analysis (see 7.3.2). The model assumes that wet AMD can only develop in the second eye from year 3 onwards; consequently treatment costs for the second eye are limited to years 3-5.

- The ERG has identified a possible error within the modelling of 2nd eye involvement in terms of discontinuations. Please clarify whether some patients discontinue in years 3, 4 and 5 based upon the variable *pDiscont3_VTE2q8*, with there being no discontinuations thereafter. Please also clarify whether this fails to take into account patients who develop 2nd eye involvement throughout the time horizon of the model and so may both start and discontinue treatment throughout the time horizon of the model. If this is correct, please provide the rationale behind this model structure.

The variable pDiscont3_VTE2q8 defines the monthly probability of discontinuing treatment for patients in the aflibercept arm of the model during years 3-5. Treatment is limited to the first 5 years of the model analysis and no patient is treated from year 6 onwards; therefore it is not possible to discontinue treatment after year 5. Those patients who develop wet AMD in their second eye after year 5 are not treated; however their HRQoL will be impacted as the utility value assigned to model health states reflects the impact of the visual acuity in both eyes.

- It seems possible that further issues similar to those of the previous four bullet points may arise. In light of the responses to the above four bullet points, is the manufacturer confident that "*Efficacy for the fellow eye while on treatment was calculated with the same methodology as for the "treated eye"*" [Bayer submission page 187] and that the modelling of 2nd eye involvement is tenable?

The ERG is correct that in the submitted analysis modelling of second eye treatment was simplified compared to the modelling of the first eye treatment.

To examine the extent to which this simplification impacts on the base case results, an additional scenario analysis was performed. The base case analysis was run firstly with no patients developing wet AMD in their second eye and then with the monthly probability of developing wet AMD in the second eye three times that of the base case value.

No second eye with wet AMD

Treatment	Costs	QALYs gained	Incremental Cost	Incremental QALYs	ICER
Aflibercept 2q8	£21,582.15	8.04			
Ranibizumab PRN	£25,170.48	8.03	-£3,588	0.007	Dominated

Base case

Treatment	Costs	QALYs gained	Incremental Cost	Incremental QALYs	ICER

Aflibercept 2q8	*£25,009.19*	*7.77*			
Ranibizumab PRN	*£28,615.22*	*7.76*	*-£3,606*	*0.010*	*Dominated*

Base case probability of second eye developing wet AMD triples

Treatment	***Costs***	***QALYs gained***	***Incremental Cost***	***Incremental QALYs***	***ICER***
Aflibercept 2q8	*£28,145.71*	*7.56*			
Ranibizumab PRN	*£31,737.21*	*7.54*	*-£3,592*	*0.013*	*Dominated*

The results of the scenario analysis show that as the number patients who develop wet AMD in their second eye increases, total costs also increase (due to increased treatment) and total QALYs decrease (due to increased disease burden).
Incremental costs change very little and incremental QALYs increase with more treatment of the second eye.

The manufacturers' interpretation of this scenario analysis is that simplifications in the modelling of the second eye are unlikely to impact on the base case results and the findings are robust to the exclusion of this aspect of treatment.
We note that the validity of estimating utility as a function of both eyes is not challenged by these simplifications.

B14
Please provide the rationale as to why the model appears to rely upon the VIEW2 trial for many of its inputs rather than VIEW1 or the pooled VIEW1+VIEW2.

The VIEW 2 study was used because it included the EQ5D, the preferred measure for NICE utility values. Other clinical data was taken from the VIEW 2 study for the economic model in order to be consistent with the quality of life data. The VIEW 2 study is also represented the most relevant of the VIEW studies given its geographical locations included Europe and the UK.

In the clinical effectiveness section of the submission, the results of the studies have been presented together and apart to demonstrate the similarities between the results of the two studies and any occasional differences have been fully discussed.

B15
Please clarify whether patients in the single eye cohort flow who discontinue therapy after year 2 transfer to the same health state in the next period rather than have the appropriate TPM applied to them. If this is correct, what is the rationale and impact of this assumption?

Patients with wet AMD in one eye who - during years 3-5 - discontinue treatment in cycle t, transition to the same health state in the BSC arm and enter the state in cycle t+1. In this way treatment discontinuation is not explicitly linked with disease progression as the maintenance assumption (section 7.3.2) means that patients must discontinue treatment before they can progress.

A scenario analysis was performed for patients treated in one eye to investigate the impact of assuming disease progression through the loss of 15 letters of vision when treatment discontinuation occurs. In this scenario patients who discontinue treatment in years 3-5 in cycle t, enter a health state with a median value of 15 ETDRS letters less than their current health state in cycle t+1.

Base case

Treatment	Costs	QALYs gained	Incremental Cost	Incremental QALYs	ICER
Aflibercept 2q8	*£25,009.19*	*7.77*			
Ranibizumab PRN	*£28,615.22*	*7.76*	*-£3,606*	*0.010*	*Dominated*

Scenario treatment discontinuation with disease progression

Treatment	Costs	QALYs gained	Incremental Cost	Incremental QALYs	ICER
Aflibercept 2q8	*£25,244.84*	*7.74*			
Ranibizumab PRN	*£28,852.98*	*7.73*	*-£3,608*	*0.009*	*Dominated*

The results of the scenario analysis show that the assumption of disease progression with treatment discontinuation decreases the total QALYs gained through increased disease burden and also total cost through the cost associated with blindness. Incremental costs are slightly increased making aflibercept more cost saving versus ranibizumab while incremental QALYs decrease slightly. Overall aflibercept remains dominant versus ranibizumab in this scenario.

B16

Please clarify whether patients in the single eye cohort flow who exit to another health state do not have the mortality rate applied to them and that it is assumed that all deaths occur among those not changing health state. If this is correct, what is the rationale and impact of this assumption?

Mortality is applied to all patients either beginning or entering a health state at each cycle, therefore mortality is consistently applied both to patients who transition to another health state and those who remain in the same state.

B17

For the mortality data in cells C294:D344 of the *Model_Parameters* worksheet please clarify the source data underlying cells C294:C344 and the arithmetic underlying them. Please also clarify if cells D294:D344 are derived from C294:C344, and if so the arithmetic underlying this. If cells D294:D344 are not derived from C294:C344, please clarify the source data underlying cells D294:D344 and the arithmetic underlying them.

The mortality data in cells D294:D344 are derived from Scottish life tables obtained from the UK office of national statistics. One month probabilities were calculated from one year rates for males and females separately. A combined monthly probability was then calculated by taking an average between the one month probabilities for males and females. The combined monthly mortality data used in the model (cells D294:D344) therefore assumes that the population is split equally between males and females.

A scenario analysis was performed using the same methodology described above but applied to UK life tables.

Base case

Treatment	Costs	QALYs gained	Incremental Cost	Incremental QALYs	ICER
Aflibercept 2q8	*£25,009.19*	*7.77*			
Ranibizumab PRN	*£28,615.22*	*7.76*	*-£3,606*	*0.010*	*Dominated*

Scenario analysis: base case using UK life tables

Treatment	Costs	QALYs gained	Incremental Cost	Incremental QALYs	ICER
Aflibercept 2q8	£25,507.18	8.11			
Ranibizumab PRN	£29,114.73	8.10	-£3,608	0.010	Dominated

The results show that total QALY gain increases due the reduced monthly probability of death. This is in line with the difference in expected years of life for Scotland versus values reported for the UK. The expected years of life averaged across males and females are 7% higher for a 74 year old UK cohort than a 74 year old Scottish cohort. The incremental results change very little but both increase, meaning that aflibercept is slightly more cost saving and produces slightly more QALYs versus ranibizumab, when using UK life table data.

B18

It appears that Please clarify whether patients who develop 2nd eye involvement of wet AMD are all assumed to have mild visual impairment (VI) in the 2nd eye upon its development. If this is correct, what is the rationale behind this assumption?

Patients developing wet AMD in their second eye are assumed to have mild visual impairment in that eye. This assumption is based on clinical opinion. We note that patients on treatment undergo regular monitoring visits and so development of wet AMD in the second eye is more likely to be detected early.

It is assumed that patients receiving treatment for wet AMD would be regularly monitored in an ophthalmology department and that occurrence of wet AMD in the fellow eye would be diagnosed at an early stage.

B19

Please clarify if the mortality rates in the first two years of the modelling, 0.76% and 1.60%, are cumulative (i.e. the mortality rate in the 2nd year is around 0.83%)? Please also provide a reference or calculation for these figures (preferably an explicit table (or text) reference could be given for these, together with a presentation of any further underlying arithmetic that is required to calculate them).

The mortality rates in the first two years are cumulative. Please refer to the tables in cells GR7:GX65 in the 1st Eye_VEGF2q8 sheet and section 7.3.1 of the submission document.

B20

Please clarify if the discontinuation rates in the first two years of the modelling, 2.7% and 3.5%, are cumulative (i.e. the discontinuation rate in the 2nd year is 0.8%)?

Treatment discontinuation rates are not cumulative.

B21

The ERG has identified a possible error in the 1st eye cohort flow worksheets for the 1st eye mild – 2nd eye no wet AMD (NVI). In general the formulae for those exiting are applied to those “beginning” plus those “entering”. For reasons that are unclear, within the 1st eye Mild - 2nd eye no-wAMD (NVI) group the formulae apply the proportions exiting only to those “beginning”: e.g. T418=(R418-SUM(W418:Y418))*(BSC_G3lines+BSC_G6lines), though there is some variation in this between the 1st six years and thereafter and between active treatment and BSC. Please clarify whether this is the intended model structure or an error.

This had been an error. The error was found in the Markov traces for the Mild-NVI (no wet AMD) health state where transitions were in some instances being applied only to patients beginning a cycle in the health state and not to those entering it as well. The same error was present in both the aflibercept and ranibizumab model arms.

The error was fixed, with the result that the incremental costs decreased by £0.10 and the incremental QALYs decreased by 0.000009 in the base case analysis. Aflibercept remains dominant over ranibizumab.

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