Evidence Review Group's Report

Title: Faricimab for treating wet age-related macular degeneration [ID3898]

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Rider on responsibility for report
The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Please note that: *Sections highlighted in* [redacted] *are* [redacted]. *Figures that are CIC have been bordered with blue.* [redacted] is highlighted in pink.

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1 Summary of the ERG's view of the company's FTA case

The ERG considers that an FTA cost-comparison is appropriate (Table 1). There is an issue around the exclusion of brolucizumab, but were that to be included, the appraisal could still be handled as an FTA.

Table 1. FTA cost-comparison

Fast track cost comparison criteria	Criteria met	ERG view
The technology's expected licensed indication is the same as the chosen comparators	Yes	Faricimab has already been licensed by the FDA and is under review by EMA.
The chosen comparators meet NICE's criteria for FTA	Yes	Some concern: two drugs known to be effective in wet AMD are excluded – bevacizumab and brolucizumab. Bevacizumab has never been appraised by NICE for wet AMD and so it has to be excluded from a cost-comparison FTA. However, brolucizumab has been approved by NICE for wAMD and therefore it should be a comparator. The technical team of this appraisal confirmed the appropriateness of comparators (discussed in the decision problem).
It is plausible that the technology may incur similar or lower costs compared with the comparators.	Unsure	Key concern: The company's case is that faricimab may require fewer injections. If this reduces costs enough to offset the higher acquisition cost, then it is plausible that costs may be at least comparable with the comparators.

2 Executive summary

This summary provides a brief overview of the key issues identified by the evidence review group (ERG) as being potentially important for decision making. It also includes the ERG's preferred

assumptions and the resulting cost comparisons. All issues identified represent the ERG's view, not the opinion of NICE.

2.1 Overview of the ERG's key issues

Table 2: Summary of key issues

ID	Summary of issue	Report sections
Issue 1	Brolucizumab as a comparator	5.4.5
Issue 2	Aflibercept dosing frequency	4.2.4
Issue 3	Year 3+ dosing assumptions	5.4.1
Issue 4	Administration cost	5.3.2

The key differences between the company's preferred assumptions and the ERG's preferred assumptions are:

- The NMA network that should be employed.
- The number of doses for Years 3+ and in particular whether faricimab requires fewer doses than the comparators.
- The administration cost.

Additional issues are:

- Do many units still employ PRN dosing rather than TREX dosing?
- Has brolucizumab much market share of newly incident patients since being approved by NICE?

2.2 Overview of cost comparison outcomes

The company performs a cost comparison of faricimab with aflibercept and ranibizumab. Brolucizumab is included in the company NMA but the company does not present a cost comparison with brolucizumab due to the small market share reported for the start of 2021. Bevacizumab is not considered.

The company cost comparison results reported for this scrutiny report include the current faricimab PAS but exclude the aflibercept CMU tender discount and the ranibizumab PAS.

Table 3: Cost per dose

	List price	Discount	Discounted price
Faricimab	£857	[redacted]	[redacted]
Ranibizumab	£551	cPAS	cPAS
Aflibercept	£816	cPAS	cPAS
Brolucizumab	£816	n.a.	n.a.

For the cost comparison the clinical outcomes, adverse events and discontinuation rates are assumed to be the same for faricimab, aflibercept and ranibizumab.

The company cost comparison assumes that for Year 1 and Year 2 faricimab dosing will be as per the trials, while dosing for aflibercept and ranibizumab will be TREX as per the company NMA. For the remainder of the 25 year time horizon, Years 3+, the company assumes that [redacted]

while dosing for the comparator anti-VEGFs will be 4.00 as per previous NICE STAs.

During clarification the company identified an error in its Year 2 dosing frequency estimates. The company corrected estimates are presented below.

Table 4: Base case annual dosing frequencies

	Year 1	Year 2	Years 3+
Faricimab	6.79	[redacted]	[redacted]
Ranibizumab	[redacted]	[redacted]	4.00
Aflibercept	[redacted]	[redacted]	4.00

These dosing frequency estimates result in the following cost estimates, ignoring the common cost elements of diagnosis and downstream visual impairment.

Table 5: Company base case cost comparison

	Year 1	Year 2	Years 3+	Total
Faricimab	[redacted]	[redacted]	[redacted]	[redacted]
Ranibizumab	£8,534	£6,397	£25,232	£40,163
Net	[redacted]	[redacted]	[redacted]	[redacted]
Aflibercept	£9,870	£6,809	£32,538	£49,217
Net	[redacted]	[redacted]	[redacted]	[redacted]

Faricimab is estimated to [redacted] compared to ranibizumab and to [redacted] compared to aflibercept. Most of the cost savings are estimated to occur in Years 3+.

The assumptions that have the biggest effect upon the cost comparison are:

- The Years 3+ dosing frequencies. This is largely assumption and expert opinion with there being no hard data for faricimab requiring only [redacted] annual injections compared to 4.00 for both aflibercept and ranibizumab. Equalising year 3+ dosing frequencies at 4.00 causes faricimab [redacted]

- A joint scenario of equal Years 3+ dosing frequencies and halving the discontinuation rates causes faricimab [redacted]

- A joint scenario of equal Years 3+ dosing frequencies, halving the discontinuation rates and doubling the baseline prevalence and monthly incidence of fellow eye AMD causes faricimab [redacted]

2.3 The decision problem: summary of the ERG's key issues

Issue 1: Appropriateness of brolucizumab as a comparator

Report section	5.4.5
Description of issue and why the ERG has identified it as important	Brolucizumab not being included as a comparator. The price of ranibizumab differs from that which applied during the brolucizumab FTA, so the conclusions of the brolucizumab FTA with regards to ranibizumab no longer apply. The current price of brolucizumab relative to aflibercept is not known and may also have changed since the brolucizumab FTA.
What alternative approach has the ERG suggested?	Considering brolucizumab as a comparator.
What is the expected effect on the cost-effectiveness estimates?	Unknown
What additional evidence or analyses might help to resolve this key issue?	Brolucizumab price inclusive of PAS. Brolucizumab market share of newly incident nAMD patients since NICE approval of brolucizumab. This may be somewhat higher than its overall market share. The company will provide the relevant market share data by April 8th 2022. The ERG will provide an amended version of this report in the light of this.

2.4 The clinical effectiveness evidence: summary of the ERG's key issues

Issue 2: Aflibercept dosing frequency

Report section	4.2.45.4.5
Description of issue and why the ERG has identified it as important	The company assumes a higher frequency of aflibercept doses than seen in a number of aflibercept trials and real-life studies
What alternative approach has the ERG suggested?	Sensitivity analysis of different injection frequencies
What is the expected effect on the cost estimates?	Aflibercept may be less costly in some scenarios
What additional evidence or analyses might help to resolve this key issue?	Ideally, a trial of aflibercept TREX versus faricimab lasting at least three years. Since this is unlikely to happen, our sensitivity analysis above addresses the issue.

2.5 The cost-effectiveness evidence: summary of the ERG's key issues

Issue 3: Does faricimab require fewer annual doses for Years 3+?

Report section	5.4.1
Description of issue and why the ERG has identified it as important	The company assumes that faricimab will require [redacted] doses compared to 4.00 doses for its comparators during Years 3+
What alternative approach has the ERG suggested?	Equalising the Years 3+ dosing across all treatments.
What is the expected effect on the cost-effectiveness estimates?	The cost savings associated with faricimab fall.
What additional evidence or analyses might help to resolve this key issue?	Longer term faricimab dosing data. Real life UK studies show a reduction in annual doses over time for the comparators.

Issue 4: What is the administration cost?

Report section	5.3.2
Description of issue and why the ERG has identified it as important	The company includes the £102 cost of a consultant OP appointment plus an additional £126 cost of an OCT. A further £55 is added to this, derived from the difference between the costs of administration and monitoring visits in previous NICE assessments. This results in a total cost of £282. Note that the PSSRU estimates a 2021 cost per medical consultant including overheads of £123 per hour. The importance of this as an issue is proportionate to the assumed reduction in administrations with faricimab compared to the number of administrations with aflibercept and ranibizumab. If there is little to no reduction this ceases to be an issue.
What alternative approach has the ERG suggested?	Removing the £102 consultant OP element to yield an administration cost of £180, given the other cost elements. The total cost of £282 might be reducible if the consultant OP cost of £102 could be avoided. There are usually three elements to the cost of an injection visit: OCT, decision by an ophthalmologist after reviewing the OCT findings and examining the eye, and administration of the anti-VEGF drug. However the key determinant is probably the OCT so one option is for the OCT to be read by a technician grader and the result communicated to whoever would give the injection (for example a nurse or staff ophthalmologist) without involving the consultant. This approach has been trialled in diabetic macular oedema with good results

What is the expected effect on the cost-effectiveness estimates?	Cost savings are reduced to [redacted] compared to ranibizumab and [redacted] compared to aflibercept.
What additional evidence or analyses might help to resolve this key issue?	A bottom-up costing that addresses the grade of staff and time required for follow-up appointments.

2.6 Summary of ERG's preferred assumptions and resulting ICER

The ERG revises the company base case as follows:

- ERG01: Equalise dosing frequency for years 3+ for all treatments.
- ERG02: Apply the ERG reduced network NMA results. Revise the Mori et al[1] dosing frequencies in the NMA, noting that this only really affects the comparison with aflibercept and ranibizumab PRN dosing.
- ERG03: Remove the additional consultant OP element from the administration cost due to probable double counting.
- ERG04: Retain original company faricimab trial dosing and adjust for all treatments in the cost comparison model.
- ERG05: Revise faricimab year 1 dose to account for week 60 dose frequency reductions and extensions that would probably have occurred in year 1 had it not been for the trials' protocol.

Table 6: ERG preferred assumptions and resulting ICER

		Faricimab net cost versus	
Preferred assumption	**Section**	**Ranibizumab**	**Aflibercept**
Company base-case	6.1	[redacted]	[redacted]
ERG01: Common year 3+ dosing	5.4.1	[redacted]	[redacted]
ERG02: ERG NMA	4.3	[redacted]	[redacted]
ERG03: Administration cost	5.3.2	[redacted]	[redacted]
ERG04: Retaining Yr2 dosing	5.4.2	[redacted]	[redacted]
ERG05: FARI Yr 1 dose adj.	5.5.1	[redacted]	[redacted]
Cumulative: ERG01 – ERG05		[redacted]	[redacted]

3 Critique of the decision problem in the company's submission

3.1 Population

The population matches the NICE final scope "Adults with choroidal neovascularisation secondary to age-related macular degeneration"

3.2 Intervention

The intervention matches the NICE final scope "Faricimab"

Faricimab is an immunoglobulin antibody that inhibits two pathways in the retina. One is the vascular endothelial growth factor (VEGF) one, so faricimab is another drug in the "anti-VEGF" group. It also inhibits the angiopoietin-2 (Ang-2) pathway so is regarded by Roche as having a dual action. However the specific contribution of inhibiting the Ang-2 pathway has not yet been quantified. Faricimab is given by injection into the eye (intravitreal injections). It appears to have a longer duration of action than some other anti-VEGF drugs and the hope is that this will mean it can have equivalent benefit on wet AMD but require fewer injections.

3.3 Comparator

NICE final scope included the following comparators:

- Aflibercept, approved for nAMD in TA 294[2]
- Ranibizumab, approved for nAMD TA 155[3]
- Brolucizumab. Approved for nAMD TA 672[4]
- Bevacizumab (does not currently have a marketing authorisation in the UK for this indication)
- Best supportive care

The company submission included two anti-VEGF comparators: Aflibercept and Ranibizumab. NICE Fast Track appraisal guidance notes for ERG states that the choice of comparator should 1) adequately represent the NICE recommended treatment as a whole, and 2) have a significant market share.

A 2019 statement from the MHRA[5] supports off-label use of bevacizumab by 12 NHS Clinical Commissioning Groups which have implemented a policy of using diluted and repackaged bevacizumab as a low-cost alternative to aflibercept and ranibizumab. The MHRA concluded that splitting of the cancer dose of bevacizumab into multiple doses for intravitreal use does not exceed what is allowed for off-label use of a drug as the medicines regulatory regime "does not legislate how medicines are to be prescribed and used by healthcare professionals once they have been placed on the market."

Brolucizumab was excluded by the company because of because of infrequent use in clinical practice. However, that is based on use in January to April 2021, and NICE approved brolucizumab in February 2021 (TA 672). Therefore the usage in first quarter of 2021 was bound to be low. After NICE issued guidance, trusts will have to add it to their formularies and pharmacies will have to order it. New drugs may also need to be approved by a hospital or board formulary committee. All of which takes time. The company could have argued that because of concerns about serious adverse effects with brolucizumab including intraocular inflammation, retinal vasculitis and occlusion (Baumal), that it would not be used as a first-line treatment. The technical team for this appraisal confirmed the appropriateness of excluding Brolucizumab. Additionally, the brolucizumab appraisal[4] concluded similar effects to Ranibizumab and Aflibercept.
The ERG clinical advisor validated the clinical use of comparators:

- Aflibercept 65% (company estimates 73%)
- Ranibizumab 33% (company estimates 24%)
- Brolucizumab 0.5% (company estimates 0.4%)
- Avastin 1.5% (not listed in the submission)

Bevacizumab (excluded by the company) use may be more than the 2% suggested by NICE. We note from the brolucizumab appraisal ERG report, that use is more than assumed by Roche – 3% and possibly increasing in the wake of the court decision. Bevacizumab has been shown to be effective in wet AMD, including in the UK IVAN trial[6] funded by the HTA Programme. However, since it has not been recommended by NICE for wet AMD, it cannot be included in an FTA.
The ranibizumab prolonged delivery system, the port delivery system Susvimo, is not included by NICE as a comparator. It is produced by Genentech a Roche subsidiary. It has been approved by the FDA. It lasts for six months so injections (or implantations?) could be reduced to two a year. The key trial is called Archway. Another trial called Portal is underway in wet AMD. EMA is said to be assessing Susvimo. We note that the port delivery system in included in the NMA. However since it because it has not been approved by NICE, it cannot be included in a cost-comparison FTA.

The anti-VEGF drugs can be given in different ways, with such as fixed doses, PRN (as required), or treat and extend (TREX). See Appendix 1 for explanation.
The company and the ERG do not consider best supportive care to be a valid comparator because patients should be offered established anti-VEFG technologies (as stated in table 1 in the company submission).
The case for faricimab in the company submission rests heavily on frequency of injections, so the ERG regards the key comparator to be aflibercept.

3.4 Outcome

NICE final scope included the following outcomes:

- Visual acuity (the affected eye)
- Overall visual function
- Central subfield foveal thickness (CSFT)
- Adverse effects of treatment
- Health-related quality of life

The company submission included the final scope outcomes and BCVA outcomes.

3.5 Marketing authorization

The FDA has approved faricimab for neovascular AMD (nAMD) and diabetic macular oedema. The approval specifies regimens up to 48 weeks but not beyond that. The ERG notes the FDA request to collect data on corneal abrasion although this was not an issue in the trial.

The European Medicines Agency is assessing an application for a marketing authorization for faricimab to treat wet AMD and DME.[7]

4 Summary of the ERG's critique of clinical effectiveness evidence submitted

4.1 Literature search

The company's search (reported in CS Appendix D.1.1) used an appropriate selection of both bibliographic databases and other sources such as trials registries, websites, conference proceedings and reference list checking. The search strategies for MEDLINE, Embase and Cochrane databases include terms reflecting the population in the scope (wet AMD) and terms for all the named drug interventions and comparators listed in the eligibility criteria (CS Appendix D.1.1, Table 1). Both thesaurus (MeSH/Emtree) and free text terms are used, and general terms for anti-VEGF drugs are included. The search was designed to identify randomized controlled trials (RCTs) only and used an appropriate, sensitive RCT filter for the Medline and Embase searches.

Unfortunately, the company's search strategies used in the supplementary searches of conference proceedings, HTA agencies, clinical trials registries, government/international bodies and additional sources (CS Appendix D.1.1, Tables 9-13) are not reported. This means the searches are neither transparent nor reproducible. The process of selecting reviews for reference checking and details of reviews which were reference-checked are also not reported.

Further sources that could have been searched to ensure comprehensiveness are the INAHTA HTA database (a more up-to-date source than CRD, which is no longer updated), and the International Clinical Trials Registry Platform from WHO, as recommended in the Cochrane Handbook.[8]. The

ERG has searched the INAHTA HTA database (https://database.inahta.org/ accessed 23/02/2022) but found no entries for faricimab.

Whilst there are some limitations to the search strategies and, in particular, the reporting of supplementary searches, the ERG considers it unlikely that any studies useful for the NMA would have been missed, due to the use of a range of sources and search techniques.

4.2 Clinical evidence

The clinical effectiveness evidence was presented in the company submission in the form of:

1) a systematic literature review which primarily focused on the direct comparative evidence between faricimab and aflibercept from the TENAYA/LUCERNE trial;[9]

2) a network meta-analysis which was conducted to assess the comparative effectiveness of faricimab versus aflibercept and ranibizumab. The NMA was conducted as there was no randomised phase III trial data directly comparing faricimab with ranibizumab at the time of submission.

The clinical evidence focussed on findings from two faricimab trials, TENAYA and LUCERNE (CS doc B, section B.3.3 and the CSRs provided to the ERG). The TENAYA and LUCERNE trials were in effect identical except for study sites. The submission provides pooled data from these studies. The ERG regards them as one large trial.

4.2.1 Study design

Phase III, multi-centre, randomised, active-comparator controlled, double-masked, parallel-group ongoing trials (112-week studies). The trials aimed to evaluate the efficacy, safety, durability, and pharmacokinetics of the 6 mg dose of faricimab (intervention) administered at up to 16-week (Q16W) intervals compared with aflibercept monotherapy (comparator) every 8 weeks (Q8W) in treatment-naive patients with nAMD. The study design is presented in the company submission in document B, figure 3.

4.2.2 Study sites

TENAYA covered 163 sites and recruited an average of 4 patients per site (included UK cites). LUCERNE included 144 sites recruiting an average of 4.6 per site. There were 15 sites in the UK, 5.5% of all sites. It is not unusual for large drug trials to be split into two identical trials. The VIEW trials of aflibercept are another example. The splitting is done to meet a requirement from the FDA, which stated;

"*Generally, the agency expects that the drug maker will submit results from two well-designed clinical trials, to be sure that the findings from the first trial are not the result of chance or bias*".[10]

4.2.3 Population

Adults with treatment-naive patients with nAMD. Key inclusion criteria are reported in B.3.3.2 Summary of study methodology and patient characteristics are presented in table 6, company submission, document B. Over half the patients came from the USA and Canada. The ethnicity results are reported in an unusual way, in effect as Hispanic/Latino or not.

4.2.4 Procedure

Participants were randomised into 1:1 ratio to either:

Intervention (faricimab up to Q16W) TENYA n=334 and LUCERNE n=331: patients received 6 mg of intravitreal faricimab every 4 weeks (Q4W) up to Week 12 (four injections). All patients received a personalised treatment interval dosing regimen up to week 108.

Comparator (aflibercept up to Q8W) TENYA n=337 and LUCERENE n=327): patients received 2 mg of intravitreal aflibercept Q4W up to Week 8 (three injections), followed by 2 mg of intravitreal aflibercept Q8W up to Week 108.

A sham procedure was administered to patients in both treatment arms at study visits with no study treatment administration to maintain masking among treatment arms. Patients were not asked if they could identify Sham during the trial.

In the faricimab arm, the frequency of dosing was determined by disease activity, with shorter intervals if disease was active. The ERG regards this as a good pragmatic approach aiming at personalised care. In the aflibercept arm, the interval between doses was fixed at 8 weeks, once loading was over, rather than being adjusted according to disease activity. At the clarification stage, the ERG asked about disease activity monitoring in the aflibercept arm but the company was unable to provide this data.

Other studies have shown that intervals between aflibercept injections can be prolonged beyond 8 weeks. The ERG therefore concluded that the design of the TENAYA/LUCERNE trial did not allow the most economical use of aflibercept.

This is important because dosing frequency is the main factor in the costs of the drug regimens. The company submission assumes that there will be 8 injections of aflibercept in Year 1 and 5 injections in Year 2. These figures are higher than seen in a number of trials of aflibercept, as shown in Table 7. This table also includes data by Horner and colleagues from "real-life" NHS care in Birmingham.

Table 7. Alfibercept regimens – injections by year

Study	Number of aflibercept doses in year			
	Year 1	Year 2	Year 3	Year 4
ALTAIR[11]	6.9 (TREX)	3.7		

ARIES[12]	7 (delayed TREX)	5		
CLEAR-IT[13]	4.5 (PRN)	-		
Mori[1]	4.8 (PRN)			
Taipale[14]	7 (TREX)	4.4		
Horner[15]	7	5		
VIEW[16, 17]	7 (fixed)	3 (PRN) Khurana 4 Schmidt-Erfurth		
AZURE[18]	6 (TREX)	2 by week 76		
Arpa et al[19]	5.3	3.3	3.0	2.8
Company's assumption	8	5		

4.2.5 Outcomes

Primary outcome was BCVA change from baseline averaged over Weeks 40, 44, and 48.

Secondary outcomes included visual acuity, overall visual function, central subfield foveal thickness, adverse effects, and health related quality of life. The results of the phase III TENAYA and LUCERNE trials showed that faricimab met the primary efficacy endpoints of noninferiority to aflibercept in change in the best-corrected visual acuity (BCVA), durability, and safety for treating patients with neovascular age-related macular degeneration. Efficacy outcomes are presented in Table 8.

Table 8. Pooled efficacy outcomes of TENAYA and LUCERNE trials

Outcome	**Pooled TENAYA and LUCERNE**	
	Fari 6.0 mg n=665	**Afli 2.0 mg n=664**
BCVA change Average of week 40, 44 and 48 Adjusted mean (SE) 95% CI for adjusted mean *N*	6.2 (0.45) (5.3, 7.1) 594	5.9 (0.45) (5.0, 6.7) 591
Diff in adjmeans vs afli (SE) 95% CI	0.4 (0.64) (-0.9, 1.6)	
Average of week [redacted] Adjusted mean (SE) 95% CI *N*	[redacted]	[redacted]
Diff in adjmeans vs afli (SE) 95% CI	[redacted]	
Proportion of patients avoiding a loss of ≥15 letters in the study eye BCVA Average of week [redacted]	[redacted]	[redacted]

% CMH weighted estimate 95% CI *N*		
Diff in CMH weighted % 95% CI	[redacted]	
Average of weeks [redacted] % CMH weighted estimate 95% CI *n*	[redacted]	[redacted]
Diff in CMH weighted % 95% CI	[redacted]	
CST change Average of week 40, 44 and 48 Adjusted mean (SE) 95% CI for adjusted mean *N*	-137.0 (2.11) (-141.2, -132.9) 590	[redacted]-130.1 (2.12) (-134.2, -125.9) 584
Diff in adjmeans vs afli (SE) 95% CI	-7.0 (2.99) (-12.8, -1.1)	
Average of week [redacted] Adjusted mean (SE) 95% CI for adjusted mean *N*	[redacted]	[redacted]
Diff in adjmeans vs afli (SE) 95% CI	[redacted]	
Patient reported outcomes change (NEI VFQ-25 composite) Week 48 Adjusted mean (SE) 95% CI for adjusted mean *n*	[redacted]	[redacted]
Diff in adjmeans vs afli (SE) 95% CI	[redacted]	
CMH Cochran-Mantel-Haenszel		

4.2.6 Adverse events

Table 25 of the company submission provides data on adverse events. Serious adverse events (SAE) are reported in up to 17.7% of patients by week 60. However, SAE reporting may be regarded as hyper-sensitive because many events unrelated to the drug will be recorded. This dates back to the

early days of anti-VEGF use when there was concern that the drugs might escape from the eye into the general circulation and cause cardiovascular harm. So, all drug trials collect data on adverse events just in case an anti-VEGF drug has an effect distant from the eye. Given the age of patients with nAMD, it is inevitable that such events will occur.

It is more useful to focus on AEs in the eye, as shown in Table 25. Such events are far less common – ocular SAEs under 3%. Notably, severe intraocular inflammation (IOI) was seen in only 3 patients, one on faricimab and two on aflibercept. These results are reassuring given recent concerns about this SAE with brolucizumab, where IOI was seen in 4.4% of patients in the HAWK and HARRIER trials).[20] In a very large population-based observational study using data from two registries, both with over 10,000 patients (but with an unknown amount of overlap between registries), Khanani et al[21] report a frequency of IOI in 2.3% of patients receiving intravitreal brolucizumab.

Ocular safety data are presented in Table 27 of the company submission. Two aspects deserve comment. The first is that AEs include progression of AMD, which might be regarded more as lack of efficacy in these patients than as an AE. Secondly, no cases of corneal abrasion or corneal oedema were reported with faricimab. The ERG notes (previously discussed in the Executive Summary) that the FDA has raised "an unexpected serious risk of corneal endothelial cell loss" (FDA approval letter). The reason for this concern is not obvious.

4.2.7 Classic and occult sub-types of choroidal neovascular (CNV) AMD

The NICE decision problem mentions classic and occult wet AMD. Neovascular AMD has subtypes according to appearances after fluorescein angiography. Classic CNV appears earlier after injection of dye and has clearly defined borders. Occult CNV appears more slowly and has poorly defined borders. There is an intermediate group called minimally classic. This distinction was important in the NICE appraisal TA68 of photodynamic therapy (PDT) for wet AMD where NICE recommended PDT for classic only. It applies less in anti-VEGF treatment.

Previous guidance on anti-VEGF treatment for wet AMD has not placed any restriction on use according to classic or occult subtypes so we would not expect any such restriction on faricimab use. However, the occult type responds less well to anti-VEGF treatment. Appendix E of the company submission reports that the NMA looked at classic vs occult subgroups. The change from baseline was greater in classic – 9.1 vs 4.8 letters gained with faricimab and 7.4 vs 5.1 with aflibercept.

So if trials of the different anti-VEGF drugs had significantly different proportions of classic and occult, that might make their results less comparable.

The ERG has examined the proportions of classic and occult in the various trials of anti-VEGF drugs Details in Appendix 1. There was an unusually low proportion of minimally classic in the TENAYA/LUCERNE trial. This was also seen in the ALTAIR trial of aflibercept. In both ALTAIR and TENAYA/LUCERNE the proportion with occult was higher than in most trials. It may be that the distinction between occult and minimally classic varied amongst trials. However, the ERG does not consider that these proportions are different enough to cause concern. We note that the proportions with classic CNV were similar in TENAYA/LUCERNE and the VIEW trial of aflibercept.[16, 17]

4.2.8 Observational evidence on the long-term effect of anti-VEGF treatment

Arpa and colleagues[19] have reported long-term results of anti-VEGF treatment in a group of 103 people followed for up to 10 years, attending Moorfields Eye Hospital. Patients started anti-VEGF treatment with ranibizumab – aflibercept was not then available. The main reason for loss to follow-up was death, unsurprising in a group aged 78 at baseline. 56 patients were followed for 10 years. All started on ranibizumab but by 10 years, 84% had switched to aflibercept. Initially, patients had three loading doses in the first three months, followed by PRN treatment, but from 2015 onwards, a treat and extend regimen was used, with 2-week increments up to 12 weeks. This started at week 40 after six aflibercept injections. Patients who had three consecutive injections at 12-week intervals and had stable nAMD could be monitored at 6-weekly intervals for 6 months without injections and if disease was still inactive, could extend monitoring intervals to 3 months.

At baseline, mean BCVA was 55 letters. 25% of patients had BCVA of 70 or more letters and 18% had 35 or fewer. Mean BCVA in the initially treated eyes improved by 2.6 letters by month 12, remained stable for till month 48 and then declined by 14 letters by month 120. By month 120, 21% had BCVA of 70 or more and 41% had BCVA of 35 or fewer. Mean BCVA at the 10 year point was 43. However, 48% had BCVA of 70 or more in at least one eye. All of the better-seeing eyes had also been treated at some point. Over the 10 years, 63% required injections in both eyes. The mean total of injections per patient was 54. All eyes were treated with ranibizumab but 58% switched to aflibercept. Those who did not respond sufficiently to aflibercept could switch to ranibizumab. The average time to second eye involvement was 31 months.

By 10 years, the mean number of injections in first affected eyes was 37 (SD 24). Half of those completing follow-up were still having injections at 10 years. Eyes affected second received an average of 14 injections. The mean numbers of injections are shown in Table 9. (Note that the mean numbers sum to only 27, presumably because some stopped injections in earlier years.)

Table 9. Mean numbers of injections

Year	Mean injections
1	5.3

2	3.3
3	3.0
4	2.8
5	2.9
6	2.7
7	2.4
8	1.9
9	1.7
10	1.1

Once stable, monitoring was done in nurse or optometrist led clinics. BCVA and OCT were done at each visit.

Arpa et al note that earlier treatment (i.e. at better BCVA) delayed progression to visual loss. They recommend continued monitoring after the disease becomes inactive because activity can recur. Some deterioration in vision was due to geographic atrophy GA (indicative of advanced dry AMD). 75% of eyes had some GA at 10 years.

These data from routine care in the NHS come from one of the few long-term studies of anti-VEGF treatment. The figures from year 3 onwards are lower than the Roche assumption, based on anonymous clinical expert opinion, that 3.25 injections would be used annually.

Another long-term follow-up study by Upasani and Dhingra[22] reported 10-year results from Yorkshire. In 60 eyes followed for 10 years, the total number of injections was 32, with 6 in Year 1. All patients started with ranibizumab but about half were switched to aflibercept at a mean of 5 years, because of insufficient benefit of ranibizumab. The total number of injections by 10 years was 25 in those who stayed on ranibizumab for 10 years, and 40 in those who switched. The total numbers of visits were 10 in years 1 and 2, 8 in year 3, then 4 in years 4-6, increasing to an average of 7 in later years due to switching. In year 10, those remaining on ranibizumab had one injection, whereas those who had had a poor response on aflibercept had three. 70% of their eyes had occult CNV.

Past NICE guidance on anti-VEGF drugs for nAMD state that the best-corrected visual acuity should be between 6/12 and 6/96. This restriction was first applied in TA 155 on ranibizumab and then repeated in TA 294 for aflibercept and TA672 for brolucizumab. The ERG considers that treatment should start at a better BCVA.. Treatment of patients with better vision does not result in significant gains in VA, because they do not have much to gain. A simplistic analysis would suggest that whilst treatment may not appear cost-effective at this early stage, we should bear in mind that AMD is a progressive disease and that the aim is preservation of vision. As a large group of UK Ophthalmologist[23] says;

"Change in VA alone is not a good indicator of patients' visual function and perception of their quality of life. Instead, the maintenance of a good functional visual state that allows continued reading and driving is of greater importance. Thus, rather than the absolute gain in VA, the duration

that one can maintain good VA or reasonable visual function should be emphasised and taken into consideration when evaluating the benefits of any therapy for nAMD".

4.2.9 Other developments

A key aim in anti-VEGF treatment has been to reduce the frequency of injections required. One new development has been the Roche/Genentech implant, the port delivery system (PDS) called Susvimo, which releases 2mg of ranibizumab over a prolonged period. The Archway trial[24] (NCT03677934) compared ranibizumab by monthly injections versus the implant, in patients who had responded to three injections at monthly intervals. After two years, the implant provided as good vision as the more frequent injections. An extension study NCT03683251 (Portal) is underway. Further trials are underway in various countries using 36-week intervals for the ranibizumab PDS - NCT03683251 and NCT04657289 (Velodrome), NCT04108156 (Pagoda) and. NCT04853251 (Belvedere) is looking at the effectiveness of the port delivery system in patients previously treated with. and who responded to, other anti-VEGF drugs. NCT05126966 (Diagrid) is comparing the ranibizumab PDS with aflibercept TREX in Dubai.

Another development is high dose (8mg) aflibercept, compared with the standard 2mg dose in the CANDELA trial, NCT04126317. Two further trials comparing 8mg and 2mg doses are underway, NCT04423718 (PULSAR) and NCT04429503 (PHOTON). One aim is to see if the larger dose can be given at longer intervals.

4.3 Network meta-analysis

The NMA was undertaken for several clinical outcomes and adverse events. These demonstrated that faricimab has similar clinical effectiveness and adverse event profiles compared with various dosing regimens for aflibercept and ranibuzumab.

To assess whether or not the transitivity assumption of the NMA was violated, the ERG made a qualitative comparison of the distribution of all reported trial-related factors (design, follow-up duration), study population, inclusion/exclusion criteria and population baseline characteristics (from clarification question A20) as potential effect modifiers across several key trials. The selected trials played an important role in indirectly connecting faricimab with aflibercept and ranibizumab. The comparison is provided in Table 28, Appendix 2. The ERG agrees with the company that the study design and population inclusion/exclusion criteria were similar across the trials compared, and that baseline characteristics were broadly similar.

The ERG has checked the coding from the NMA, provided by the company in clarifications question A14, and did not identify any issues. The ERG were able to replicate the BCVA score mean change networks from baseline at 12m, injection frequency to 12 months, and injection frequency to 24 months. Furthermore, the ERG replicated the reduced network of aflibercept studies (provided in CQ A17), and also replicated the analysis for both injection frequency networks using this reduced network. The ERG regards the original NMA as unnecessarily complex and prefers the more focused (reduced) version.

The ERG identified an inconsistency for the injection frequency from baseline to 12m network in the data extraction from Mori 2017[1]. The two treatments in this paper were aflibercept 2mg IVT PRN loading and aflibercept 2 mg IVT Q8W. There were three monthly-loading doses, and the Q8W treatment group appears to be monthly instead of Q8W. Making these changes in the NMA increases the injection frequency for aflibercept 2 mg PRN loading, favouring faricimab further.

The ERG's focused NMA results are presented in Table 10, Table 11, and Table 12. In Table 10, we replicate the injection frequency analysis. In the key comparisons, with AFL 2 mg IVT Q8W, AFL 2 mg IVT TREX, and RAN 0.5 mg IVT TREX, differences in injection frequency were not clinically significant.

Table 11shows results from a more focused NMA using only trials involving either aflibercept or faricimab. The differences in injection frequency from baseline to 12 months remained inconsequential for the key comparisons against AFL 2 mg TREX and RAN 0.5 mg TREX, with differences in BCVA of 0.15 and 0.15 injections (rounded to two DPs).

Table 10. Results of the ERG's IF 12m NMA where Mori 2017 injection frequencies have increased

	ERG's results^		
	Estimate	**95% CrI**	
FAR 6 mg IVT Q8-16W	Ref		
AFL 2 mg IVT PRN loading	-2.155	-6.421	2.092
AFL 2 mg IVT Q4W	5.391*	1.409	9.370
AFL 2 mg IVT Q8W	1.049	-1.307	3.426
AFL 2 mg IVT TREX	1.247	-2.367	4.921
BEV 1.25 mg IVT PRN	1.286	-3.180	5.888
BEV 1.25 mg IVT PRN loading	2.276	-1.989	6.742
BEV 1.25 mg IVT Q4W	5.202*	0.419	10.080
BEV 1.25 mg IVT Q6W	6.981*	1.356	12.740
BEV 1.25 mg IVT TREX	3.287	-1.769	8.372
BRO 6 mg IVT Q12W/Q8W	0.552	-2.812	3.911
FAR 6 mg IVT Q12W	-1.470	-6.459	3.487
FAR 6 mg IVT Q16W	-1.965	-6.876	2.952

RAN 0.5 mg IVT Q4W	4.726*	1.125	8.314
RAN 0.5 mg IVT PRN	0.196	-4.637	5.043
RAN 0.5 mg IVT PRN loading	1.162	-2.831	5.269
RAN 0.5 mg IVT PRNX	0.274	-5.043	5.706
RAN 0.5 mg IVT Q8W	2.674	-1.710	7.241
RAN 0.5 mg IVT TREX	2.392	-1.313	6.157
RAN 100 mg/ml PDS Q24W	-4.985*	-9.937	-0.061
Sham/PBO	4.922*	0.575	9.272

^Changed Mori 2017: AFL 2 mg IVT PRN loading from 1.8 doses to 4.8 doses, and AFL 2 mg Q8W from 4 doses to 8 doses.
*95% credible interval does not contain 0, therefore a statistically meaningful difference exists.
Negative estimate favours the comparator over faricimab.
AFL = Aflibercept; BEV = Bevazicumab; BRO = Broluzicumab; CrI = Credible interval; FAR = Faricimab; IVT = Intravitreal injection; mg = Milligram; PBO = Placebo; PDS = Port delivery system; PRN = Pro re nata; PRNX = Pro re nata extend; Q12W = Every 12 weeks; Q16W = Every 16 weeks; Q4W = Every 4 weeks; Q6W = Every 6 weeks; Q8W = Every 8 weeks; RAN = Ranibizumab; TREX = Treat and extend.

Table 11. Results of the ERG's injection frequency 12m NMA using the reduced network of faricimab and aflibercept studies only

	Replicating company's			**Mori -> 4.8/8^**		
	Estimate	**95% CrI**		**Estimate**	**95% CrI**	
FAR 6 mg IVT Q8-16W	Ref			Ref		
AFL 2 mg IVT PRN loading	-1.145	-2.855	0.614	-2.139*	-3.835	-0.414
AFL 2 mg IVT Q4W	5.965*	4.457	7.560	5.964*	4.490	7.521
AFL 2 mg IVT Q8W	1.057*	0.205	1.975	1.056*	0.215	1.948
AFL 2 mg IVT TREX	0.153	-1.352	1.692	0.151	-1.321	1.643
BRO 6 mg IVT Q12W/Q8W	0.550	-0.645	1.824	0.548	-0.634	1.794
FAR 6 mg IVT Q12W	-0.338	-2.301	1.764	-0.337	-2.262	1.704
FAR 6 mg IVT Q16W	-0.832	-2.786	1.222	-0.831	-2.72	1.166
RAN 0.5 mg IVT Q4W	5.863*	4.339	7.470	5.863*	4.379	7.426
RAN 0.5 mg IVT TREX	0.153	-1.846	2.196	0.149	-1.818	2.144

^Changed Mori 2017: AFL 2 mg IVT PRN loading from 1.8 doses to 4.8 doses, and AFL 2 mg Q8W from 4 doses to 8 doses.
*95% credible interval does not contain 0, therefore a statistically meaningful difference exists.
Negative estimate favours the comparator over faricimab.
AFL = Aflibercept; BRO = Broluzicumab; CrI = Credible interval; FAR = Faricimab; IVT = Intravitreal injection; mg = Milligram; PRN = Pro re nata; Q12W = Every 12 weeks; Q16W = Every 16 weeks; Q4W = Every 4 weeks; Q8W = Every 8 weeks; RAN = Ranibizumab; TREX = Treat and extend.

Table 12 presents the results of the NMA for injection frequency from baseline to 24 months for the reduced network of trials involving either aflibercept or faricimab. It shows that, compared to aflibercept 2 mg Q8W, patients on either ranibizumab Q4W or aflibercept Q4W have more injections over 24 months. The difference in injections over two years for the other treatments compared to aflibercept Q8W are not statistically meaningful. This corresponds to the company's 24m injection frequency NMA results presented in figure 15 of the company submission which used the full network.

Table 12. Results of the ERG's injection frequency 24m NMA using the reduced network of faricimab and aflibercept studies only

	ERG's results – focussed

	network		
	Estimate	**95% CrI**	
AFL 2 mg IVT Q8W	Ref		
AFL 2 mg IVT Q4W	10.630*	6.485	14.72
AFL 2 mg IVT TREX	-1.142	-3.977	1.792
BRO 6 mg IVT Q12W/Q8W	-3.005	-7.204	1.153
RAN 0.5 mg IVT Q4W	10.440*	6.334	14.52
RAN 0.5 mg IVT TREX	-2.292	-8.210	3.611

*95% credible interval does not contain 0, therefore a statistically meaningful difference exists.
Negative estimate favours the comparator over faricimab.
AFL = Aflibercept; BRO = Broluzicumab; CrI = Credible interval; IVT = Intravitreal injection; mg = Milligram; Q12W = Every 12 weeks; Q4W = Every 4 weeks; Q8W = Every 8 weeks; RAN = Ranibizumab; TREX = Treat and extend.

5 Summary of the ERG's critique of cost evidence submitted

5.1 Summary of the company's submitted cost comparison

5.1.1 Model structure summary

The company submits a complicated bilateral eye model that tracks the BCVA of each eye of patients over time. It also has a probabilistic modelling facility. It appears to have been developed with a view to a full STA and the associated cost utility analysis. The ERG thinks that it is unnecessarily complicated for an FTA and comes at the cost of a lack of transparency and interrogability.

Given the assumptions of equivalent efficacy, identical adverse event rates and identical discontinuation rates for all treatments, the cost comparison the inputs required for to estimate the cohort flow are:

- The baseline age coupled with the associated general population mortality and resulting overall survival curve[*];
- Discontinuation rates, common to all treatments;
- Fellow eye AMD involvement at baseline; and,
- Fellow eye AMD annual incidence.

The resulting cohort flow can then be coupled with:

[*] There may be a small additional concern around the increased mortality risk associated with bilateral legal blindness but given the assumed clinical equivalence between treatments this is unlikely to have much if any material effect upon net results.

- The annual dosing frequencies for Year 1, Year 2 and Years 3+, differentiated by treatment;
- The cost per dose, differentiated by treatment; and,
- Administration and monitoring costs.

5.1.2 Population

The population reflects the faricimab trials, the inputs required for the cost comparison being a baseline age of 75 years with 41% male.

5.1.3 Interventions and comparators

The company NMA includes faricimab, aflibercept, ranibizumab, brolucizumab and bevacizumab as per the scope.

The company cost comparison only considers faricimab, aflibercept and ranibizumab. Brolucizumab is not considered due to its market share for Jan-Apr 2021 being only [redacted]. Bevacizumab is not considered due to cost comparison FTAs only considering comparators previously approved by NICE for the same indication.

The company base case assumes TREX dosing for aflibercept and ranibizumab. A scenario of PRN dosing for aflibercept and ranibizumab is presented.

5.1.4 Perspective, time horizon and discounting

The perspective and discounting is as per the NICE reference case. The time horizon is 25 years, which is sufficient to capture the extrapolated OS curves given the baseline age of 75 years.

5.1.5 Treatment effectiveness and extrapolation

Faricimab and its comparators are assumed to have equivalent efficacy, identical adverse events rates and identical discontinuation rates.

Only the discontinuation rates affect the cost comparison, since the faricimab cost per dose is not equal to the comparators' costs per dose. Annual discontinuation rates of [redacted] for Year1 and Year 2 are estimated from the faricimab trials' pooled arms, while the estimate of 8.90% for Year 3+ is taken from NG82.

Given the overall survival curve, the discontinuation rates result in the following proportions of patients remaining on treatment in their initially treated eye Figure 1. It should be borne in mind that the total number of eyes being treated will be higher due to the bilateral prevalence at baseline and the ongoing bilateral incidence.

Figure 1Modelled OS and proportion initial eyes remaining on treatment

5.1.6 Annual dosing: Year 1, Year 2 and Years 3+

The company uses the faricimab trials to estimates the mean annual Year 1 and Year 1+2 doses for faricimab of 6.79 and [redacted] and for aflibercept Q8W of 7.79 and [redacted].

For the comparators, the company uses the annual number of doses from its NMA for Year 1 and for Years 1+2 relative to ranibizumab 0.5mg Q4W, transforms these to be relative to aflibercept Q8W and then adds these to the mean doses for aflibercept Q8W from the faricimab trials. The Year 2 dosing is then simply the Years 1+2 dosing minus the Year 1 dosing. Due to there being no Year 1+2 estimate for aflibercept PRN (loading) its Year 2 dosing is assumed to be the same as that of ranibizumab PRN (loading).

Table 13: NMA annual dosing: Year 1 and Years 1+2

Year 1	FARI	AFLI	AFLI	RANI	AFLI	RANI	BROL
Regimen	..	Q8W	TREX	TREX	PRN (L)	PRN (L)	..
FARI trials	6.79	7.79					
vs RANI Q4W		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

vs AFLI Q8W	-1.00	0.00	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NMA Yr 1	6.79	7.79	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Years 1+2	FARI	AFLI	AFLI	RANI	AFLI	RANI	BROL
Regimen	..	Q8W	TREX	TREX	PRN (L)	PRN (L)	..
FARI trials	[redacted]	[redacted]					
vs RANI Q4W		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
vs AFLI Q8W	[redacted]	0.00	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NMA Yr 1+2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NMA Yr 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The mean numbers of aflibercept Q8W administrations in the faricimab trials provides the anchor against which all other administration frequencies are calculated. There is no particular requirement for this and the mean numbers from any of the other trials or pooled estimates could equally well have been applied. Similarly, given the company preference for the ranibizumab Q4W forming the pivot point of the NMA due to the number of trial arms' involving this, the mean numbers of ranibizumab Q4W administrations could have been chosen. This would only affect the total numbers of administrations and not the net numbers of administrations and is likely to have minimal effect upon net estimates.

For Years 3+ the company assumes that [redacted]. For the comparators the company assumes a common annual dosing of 4.00, taking this from TA294 and TA262.

This results in the number of annual administrations for the base case of faricimab compared to TREX dosing for aflibercept and ranibizumab, for the scenario of faricimab compared to PRN dosing for aflibercept and ranibizumab and also the annual number of administrations for brolucizumab for completeness.

Table 14: Company base case annual dosing

[redacted]							
[redacted]							
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

5.1.7 Fellow eye involvement

The baseline prevalence of 7.3% and annual incidence of 1.39% of bilateral involvement is taken from NG82.

5.2 Model validation

5.2.1 Cross check model rebuild

The ERG has rebuilt a simple bilateral eye cohort flow based on population mortality rates, discontinuation rates, fellow eye AMD prevalence at baseline and the ongoing incidence of fellow eye AMD. Applying the company base case assumptions and inputs within this ERG rebuild cohort flow results in faricimab being estimated to save [redacted] compared to ranibizumab and [redacted] compared to aflibercept. This compares with the company model estimates of savings of [redacted] and [redacted] respectively.

The discrepancies between the simple ERG rebuild and the company model seem to arise mainly due to differences in the method of estimating administration costs. Which is likely to be more accurate is debatable. The ERG thinks that these discrepancies are unlikely to affect decision making and that the company model structure can be relied upon.

5.2.2 Modelled number of doses vs NMA

The model applies a monthly discontinuation rate and monthly mortality rates derived from annual quantities. Since the annual doses inputted to the model are not adjusted for these, the model tends to underestimate the total number of doses for faricimab. This applies with similar force to the other comparators and the effect upon the net number of doses is more muted.

Table 15: Company base case: Model output vs NMA doses

	Model†		NMA	
	Year 1	Year 2‡	Year 1	Year 2
Faricimab	6.57	[redacted]	6.79	[redacted]
Ranibizumab net	[redacted]	[redacted]	[redacted]	[redacted]
Aflibercept	[redacted]	[redacted]	[redacted]	[redacted]

† Estimated from the direct drug costs, setting the discount rate to 0% and assuming no fellow eye involvement

‡ Adjusted for number remaining on treatment at start of Year 2.

net	[redacted]	[redacted]	[redacted]	[redacted]

The model may tend to underestimate the net reduction in administrations during Year 1 and Year 2 due to it applying monthly discontinuation and mortality rates

5.3 Correspondence between model inputs and cited sources

5.3.1 Aflibercept injections: Mori et al

Mori et al[1] provide Year 1 dosing estimates for aflibercept Q8W and aflibercept PRN within the company NMA. The Mori et al dosing was bimonthly rather than Q8W meaning that their "Q8W" dosing is one dose less then true Q8W dosing as shown below. The post-loading bi-monthly dosing corresponds with the 4 administrations reported in Table 2 of Mori et al.

Table 16: Aflibercept Q8W dosing vs bi-monthly dosing

Q8W		Bi-Monthly	
Week	Dose	Month	Dose
0	1	0	1
4	1	1	1
8	1	2	1
12		3	
16	1	4	1
20		5	
24	1	6	1
28		7	
32	1	8	1
36		9	
40	1	10	1
44		11	
48	1		
52			
Total	8		7

In the light of this, the ERG has re-run the NMA applying a Q8W dosing of 8 for Mori et al. In effect this is akin to assuming that Mori et al had a third arm that was truly Q8W dosing. The ERG uses these estimates for its revised base case, though this only affects the Year 1 PRN dose estimates.

5.3.2 Administration and monitoring costs: TA346

The administration cost is the sum of a consultant OP appointment at £102, an OCT at £126 and an additional £55 for the difference between the monitoring and the administration cost (assumed by the ERG during the STA of aflibercept for DMO [TA346]). This yields a total cost of £282 for an administration visit and £228 for a dedicated monitoring visit. The costs applied in TA346 were £194 and £139 respectively which if uprated from 2014 prices to 2021 prices using the PSSRU HSCS and NHSII pay and prices indices increase to £216 and £155 respectively.

There may be a degree of double counting within the company costing. Presumably the consultant OP cost covers the consultant doing something. Given this, the ERG revised base case will remove the separate consultant OP cost element from the administration cost, though it might be equally valid to remove the OCT cost element instead. The ERG will provide scenarios for an administration cost of £216 and of £282.

Note that monitoring costs do not feature in the base case, and that the ERG sensitivity analysis of PRN dosing equalises monitoring costs between treatments causing their net effect to be zero.

5.4 ERG critique: Main Issues

5.4.1 Year 3+ dosing estimates

For Years 3+ the company assumes [redacted] annual doses for faricimab and 4.00 for aflibercept and ranibizumab. At clarification the company justifies this by stating "T*he* [redacted] *applied for faricimab has been calculated based on the committee preferred assumptions from TA294 and TA672, where the committee and clinical expert assumed 4 injections would be administered from Year 3 onwards. No further rationale was provided for this figure, therefore an assumption was made that this has been derived assuming a Q12w dosing regimen for anti-VEGFs across a 52 week period. Using this as a basis, and taking into account that >40% of patients received faricimab on a Q16w interval during TENAYA and LUCERNE, it was deemed reasonable to assume patients would receive faricimab at a rate of* [redacted] *in the real world. The preliminary PTI data taken at the Week 60 snapshot also supports this assumption, with the data demonstrating that faricimab can be maintained longer term with lower injection frequencies. This Year 3+ assumption for faricimab was also validated with clinical experts, who also stated they would*

expect faricimab to be administered at least one injection less over the longer term versus currently available comparators".

The ERG disagrees that the preliminary PTI data supports an assumption that [redacted].

The company does not state how many experts it consulted, the format of the consultation(s), what questions were asked, what the individual expert responses were or why their responses imply that in the longer term there would be [redacted] fewer annual faricimab administration than aflibercept or ranibizumab administrations. The company also does not present any biological rational why it expects [redacted] annual doses for faricimab compared to [redacted] for aflibercept and ranibizumab for years 3+.

The ERG undertook the brolucizumab assessment and our recollection of the public TA672 brolucizumab FTA discussions is that the assumption of the same number of annual administrations in the longer term across treatments was due to a lack of evidence that these would differ between treatments, coupled with a lack of a biological rationale as to why a difference would be expected. Faricimab, aflibercept and ranibizumab are all anti-VEGFs. If it is reasonable to assume the same long term dosing frequencies for aflibercept and ranibizumab, the ERG thinks that in the absence of data it is reasonable to assume the same long term dosing frequencies for faricimab, aflibercept and ranibizumab. While faricimab has dual action through the VEGF and ANG pathways, the clinical significance of this is uncertain and the similar efficacy of faricimab and aflibercept in the trials does not support an assumption of extra benefit from dual action.

The ERG revised base case equalises the Years 3+ annual dosing across all treatments to 4.00. It provides scenario analyses of a common 2.00, 3.00 and 5.00 for all treatments during Years 3+, and scenarios of [redacted] for faricimab alone.

5.4.2 Faricimab trial doses: Year 2: company correction during clarification

The original company submission estimated mean dosing in Year 2 for faricimab and aflibercept Q8W of [redacted] and [redacted] respectively. This was based upon the denominator being the baseline number of patients. At clarification the company corrected these to [redacted] and [redacted] respectively, applying the number of patients on treatment at the start of Year 2 as the denominator.

The ERG thinks that the NMA estimates for the comparators are based upon the mean Year 1+2 dosing. This suggests using the faricimab trial Year 1+2 dosing; i.e. those of the original company submission. The resulting estimates for Year 2 can then be adjusted using the common Year 1 discontinuation plus mortality rate to take into account the modelled proportion of patients remaining at the start of Year 2.

5.4.3 TTD curves and discontinuation rates

The company has only supplied the real-world study KM time to treatment discontinuation (TTD) data on an annual basis. This yields annual discontinuation rates for ranibizumab and aflibercept, and annual anti-VEGF discontinuation rates for those starting on ranibizumab and those starting on aflibercept.

Table 17: Real world discontinuation data compared to model

			Anti-VEGF disc.		
Year	RANI	AFLI	RANI 1st	AFLI 1st	Model
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	8.9%
4	[redacted]	[redacted]	[redacted]	[redacted]	8.9%
5	[redacted]	[redacted]	[redacted]	[redacted]	8.9%

While the real-world study data will also include dying as an event the discontinuation rates are higher than those of the model base case, particularly in the early years. But the annual rate of discontinuation slows.

Bearing in mind that deaths and discontinuation rates are modelled separately, the 25 year time horizon and that discontinuation rates appear to slow the ERG thinks that for Years 3+ the company base case 8.9% coupled with the ERG scenario analysis of 13% are reasonable values to apply. But the above argues for scenario analyses which increase the Year 1 and Year 2 discontinuation rate to [redacted].

5.4.4 Aflibercept and ranibizumab PRN dosing

ERG expert opinion is that aflibercept and ranibizumab are mainly TREX dosed and that PRN dosing is clinically inferior. A UK consensus panel from nine ophthalmology centres supports this.[25] ERG expert opinion suggests that what PRN dosing remains reflects the fragmented service, a poor understanding of the current evidence base and work pressures. But it appears that some units may still dose aflibercept and ranibizumab as PRN. Since the current assessment is an FTA, given the different dose estimates for PRN compared to TREX the ERG will present scenarios comparing faricimab with aflibercept and ranibizumab PRN.

5.4.5 Comparator choice and brolucizumab

[redacted]Brolucizumab is listed in the scope as a comparator. The company NMA includes brolucizumab but does not take this through to a full cost comparison.

For the current FTA NICE appears to consider comparison with aflibercept and ranibizumab sufficient due to the brolucizumab FTA [TA672] FAD stating that "*Because it has similar costs and overall health benefits to aflibercept and ranibizumab, brolucizumab is recommended as an option for treating adults with wet age-related macular degeneration*". But the effective price of ranibizumab is now somewhat different from that which applied during TA672 and so the conclusions of TA672 with respect to ranibizumab no longer apply. The ERG also cannot confirm that the aflibercept PAS remains the same as during TA672 or that there has not been a CMU tender for brolucizumab which reduces its price to below that of TA672.

The company notes the very small brolucizumab market share of 0.4% during Jan-Apr 2021, but this was when brolucizumab was new to the market. Newly supplied market share data for Sep-Dec 2021 shows that this has only grown very slightly to 0.8% among AMD patients. The ERG notes that concerns about intraocular inflammation and retinal artery occlusion [25] may have limited brolucizumab adoption. Given the low market share the ERG agrees with the company that brolucizumab is not relevant as a comparator.

During Sep-Dec 2021 the majority of AMD patients, 75.8%, received aflibercept while a significant proportion of patients, 21.0%, received ranibizumab. The ERG thinks that aflibercept should be the main comparator.

5.5 [redacted] ERG critique: Other Issues

5.5.1 Faricimab trial dosing adjustments and draft SmPC

The faricimab trials did not permit dose interval extension or reduction during year 1 after the initial allocation to Q8W, Q12W or Q16W dosing. The data for the PTI extension period beyond week 60 as presented in Figure 7 of Document B (page 54 and 55) suggests that a number of patients reduced their dosing interval when the trial protocol permitted this at week 60, while others extended it. The ERG thinks that the draft SmPC would permit this to happen earlier than occurred during the trials.

Data supplied at clarification is difficult to completely reconcile with Figure 7 of Document B. From the data supplied at clarification coupled with visual inspection of Figure 7 it appears that:

[redacted]

Without the fixed dosing regimen to week 60, as specified by the trials' protocol, these patients could have had these week 60 dosing frequency adjustments made during the 1st year of treatment with faricimab. Unfortunately, it seems that disease activity was not assessed frequently enough during the 1st year of the trials to time when this might have occurred in practice.

Given the above, one possibility is an arbitrary assumption that those adjusting dosing frequency at week 60 would in practice have had their dosing frequency adjusted half way

through the 1st year, this suggesting a roughly [redacted] higher dosing frequency during this period. This assumes that those censored for follow-up had the same probabilities of increasing and reducing dosing frequencies.

The ERG revised base case assumes a [redacted] increase in faricimab dosing frequency during the 2nd half of the 1st year.

5.5.2 NMA dosing and discontinuation rate interactions

The mean number of doses from the various papers that are inputted to the company NMA will in part be determined by the discontinuation rates of the various treatments during the relevant trials. Other things being equal, the lower the discontinuation rate, the higher the mean number of doses per baseline patient is likely to be.

The company NMA for discontinuation rates results in the odds ratios and 95% confidence intervals for faricimab compared to the other treatments shown in Table 18. While none of the odds ratios are significantly different from 1 and the confidence intervals are wide, the central estimates for aflibercept TREX, ranibizumab TREX and ranibizumab PRN are noticeably higher than 1. This may suggest that discontinuation rates for aflibercept TREX, ranibizumab TREX and ranibizumab PRN were somewhat lower than that of faricimab. If their discontinuation rates had been higher and the same as that of faricimab, their mean doses per baseline patient in Year 1 and Year 1+2 would tend to have been lower.

Table 18: Company NMA: Discontinuation rates: Faricimab odds ratios

Comparator	OR	CI	Mid-point	End Yr2
Faricimab	[redacted]	[redacted]	[redacted]	[redacted]
Aflibercept TREX	[redacted]	[redacted]	[redacted]	[redacted]
Ranibizumab TREX	[redacted]	[redacted]	[redacted]	[redacted]
Aflibercept PRN (Loading)	[redacted]	[redacted]	[redacted]	[redacted]
Ranibizumab PRN (Loading)	[redacted]	[redacted]	[redacted]	[redacted]
Brolucizumab	[redacted]	[redacted]		[redacted]

Crude calculations by the ERG based upon the odds ratios and a Year 1+2 faricimab discontinuation rate of [redacted] suggest that the mid-point proportions of patients who have not discontinued are slightly higher for aflibercept TRX, ranibizumab TREX and ranibizumab

PRN (loading) than for faricimab: net effects of perhaps around 2-4% of the Year 1 + Year 2 drug costs. This may bias results in favour of faricimab.

It may not be possible to formally adjust the dosing NMA for discontinuation rates, but not doing so may bias the cost comparison against aflibercept TREX, ranibizumab TREX and ranibizumab PRN (loading).

5.5.3 Fellow eye involvement

A large US observational study by Khahani et al[27] with almost 99,000 eyes suggests fellow eye treatment of 6% at baseline and 27% by the end of year 1, with 30%, 32% and 33% by the ends of years 2, 3 and 4 respectively. Given the model structure the ERG will provide a scenario of 27% fellow eye treatment at baseline and an annual incidence thereafter of 2.8%.

5.5.4 Faricimab wastage

The company model assumes no faricimab wastage. The draft SmPC states that "[redacted]", which may suggest otherwise. The SmPCs of aflibercept, ranibizumab and brolucizumab have a similar qualification. The ERG did not make any clarification request about this or request data on faricimab wastage during the trials. ERG expert opinion notes that this is very minimal and arose due to concerns about the silicone lining of the syringes at times having some bubbling. Pre-filled syringes use a different plastic and do not have this issue.

5.5.5 PRN dosing and monitoring

The company compares the base case dosing for faricimab with PRN dosing and monitoring for aflibercept and ranibizumab. The company notes that there is an absence of evidence for the effectiveness of PRN dosing for faricimab, but this would also appear to apply to the faricimab dosing that is likely to occur in practice to some extent given that the faricimab trials did not permit dose interval extension or reduction during year 1 after the initial allocation to Q8W, Q12W or Q16W dosing but the SmPC does.

The consensus seems to be that TREX is superior to PRN. But if some units currently dose aflibercept and ranibizumab as PRN, they might similarly dose faricimab as PRN. This suggests that scenario analyses of PRN dosing could assume all treatments have the same number of monitoring visits.

5.5.6 Aflibercept PRN [loading] Year 2 dosing estimate

Due to there being no Year 1+2 dosing data for aflibercept PRN the company assumes that the annual number of doses in Year 2 for aflibercept PRN will be the same as that of ranibizumab PRN: [redacted]. This may not be reasonable. The company NMA estimates that Year 1 dosing is [redacted] for aflibercept PRN and [redacted] for ranibizumab: aflibercept PRN requiring only [redacted] that of ranibizumab PRN, while the ERG NMA estimates a ratio of only [redacted]. It may be more reasonable to apply these percentages for Year 2 which results in an estimate of [redacted] doses for aflibercept PRN. The ERG will apply this in its scenario analysis of PRN dosing, augmenting this with a scenario of the company base case PRN dosing.

6 COST EFFECTIVENESS RESULTS

6.1 Company's cost comparison results

The company base case cost comparison results inclusive of the faricimab PAS but not including the aflibercept CMU tender discount and the ranibizumab PAS are presented in Table 19 below.

Table 19: Company base case cost comparison

	Year 1	Year 2	Years 3+	Total
Faricimab	[redacted]	[redacted]	[redacted]	[redacted]
Ranibizumab	£8,534	£6,397	£25,232	£40,163
Net	[redacted]	[redacted]	[redacted]	[redacted]
Aflibercept	£9,870	£6,809	£32,538	£49,217
Net	[redacted]	[redacted]	[redacted]	[redacted]

Faricimab is estimated to [redacted] compared to ranibizumab and to [redacted] compared to aflibercept.

6.2 Company sensitivity analyses

The estimates of Table 20 and Table 21 are generated by the ERG using an ERG revised company model.

Table 20: ERG estimates of company sensitivity analyses: vs ranibizumab

	Low	Net cost	High	Net cost
Company base-case	[redacted]			
Time horizon: 25 years	20 years	[redacted]	30 years	[redacted]
Baseline age: 75 years	70 years	[redacted]	80 years	[redacted]

	Low	Net cost	High	Net cost
Admin. cost: £282	£226	[redacted]	£339	[redacted]
Admin. cost increase FE: 50%	0%	[redacted]	100%	[redacted]
Base prevalence AMD FE: 7.3%	5.8%	[redacted]	8.8%	[redacted]
Monthly incidence AMD FE: 1.4%	1.1%	[redacted]	1.7%	[redacted]
FE: Fellow eye				

Table 21: ERG estimates of company sensitivity analyses: vs aflibercept

	Low	Net cost	High	Net cost
Company base-case	[redacted]			
Time horizon: 25 years	20 years	[redacted]	30 years	[redacted]
Baseline age: 75 years	70 years	[redacted]	80 years	[redacted]
Admin. cost: £282	£226	[redacted]	£339	[redacted]
Admin. cost increase FE: 50%	0%	[redacted]	100%	[redacted]
Base prevalence AMD FE: 7.3%	5.8%	[redacted]	8.8%	[redacted]
Monthly incidence AMD FE: 1.4%	1.1%	[redacted]	1.7%	[redacted]
FE: Fellow eye				

Within the company univariate scenario analyses the inputs that results are most sensitive to are the baseline age, the administration cost and the fellow eye administration cost multiplier.

7 EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

7.1 ERG's preferred assumptions

The ERG revises the company base case as follows:

- ERG01: Equalise dosing frequency for years 3+ for all treatments.
- ERG02: Apply the ERG reduced network NMA results. Revise the Mori et al[1] dosing frequencies in the NMA, noting that this only really affects the comparison with aflibercept and ranibizumab PRN dosing.
- ERG03: Remove the additional consultant OP element from the administration cost due to probable double counting.

- ERG04: Retain original company faricimab trial dosing and adjust for all treatments in the cost comparison model.

- ERG05: Revise faricimab year 1 dose to account for week 60 dose frequency reductions and extensions that would probably have occurred in year 1 had it not been for the trials' protocol.

The ERG reduced network NMA changes the Year 1 and Year 2 dosing frequencies as follows, with the Years 3+ dosing also being changed.

Table 22: Base case annual dosing frequencies: Company vs ERG

	Year 1	Year 2	Years 3+
Company extended network NMA			
Faricimab	6.79	[redacted]	[redacted]
Ranibizumab	[redacted]	[redacted]	4.00
Aflibercept	[redacted]	[redacted]	4.00
ERG reduced network			
Faricimab	6.79	[redacted]	4.00
Ranibizumab	[redacted]	[redacted]	4.00
Aflibercept	[redacted]	[redacted]	4.00
ERG extended network NMA			
Faricimab	6.79	[redacted]	4.00
Ranibizumab	[redacted]	[redacted]	4.00
Aflibercept	[redacted]	[redacted]	4.00

These have the following individual effects, with the last row of Table 23 presenting their cumulative effect.

Table 23: ERG preferred cost comparison assumptions

		Faricimab net cost versus	
Preferred assumption	**Section**	**Ranibizumab**	**Aflibercept**
Company base-case	6.1	[redacted]	[redacted]
ERG01: Common year 3+ dosing	5.4.1	[redacted]	[redacted]
ERG02: ERG NMA	4.3	[redacted]	[redacted]
ERG03: Administration cost	5.3.2	[redacted]	[redacted]
ERG04: Retaining Yr2 dosing	5.4.2	[redacted]	[redacted]
ERG05: FARI Yr 1 dose adj.	5.5.1	[redacted]	[redacted]

Preferred assumption	Section	Faricimab net cost versus	
		Ranibizumab	Aflibercept
Cumulative: ERG01 – ERG05		[redacted]	[redacted]

The revised ERG base case is presented in Table 24: ERG revised base case cost comparison.

Table 24: ERG revised base case cost comparison

	Year 1	Year 2	Years 3+	Total
Faricimab	[redacted]	[redacted]	[redacted]	[redacted]
Ranibizumab	£5,784	£4,438	£21,428	£31,650
Net	[redacted]	[redacted]	[redacted]	[redacted]
Aflibercept	£7,845	£7,279	£29,983	£45,108
Net	[redacted]	[redacted]	[redacted]	[redacted]

7.2 ERG sensitivity analyses

The ERG presents the following sensitivity analyses:

- SA01: Years 3+ dosing for all comparators of (a) 2 doses, (b) 3 doses, (c) 5 doses.
- SA02: Years 3+ dosing for faricimab of [redacted]
- SA03: Annual Years 3+ discontinuation rates of (a) 5% and (b) 13%, and Year 1 and Year 2 discontinuation rate of [redacted] with Years 3+ (c) 8.9% and (d) 13%.
- SA04: Apply an administration cost of (a) £216 and (b) £282
- SA05: Baseline fellow eye involvement 27% and an annual incidence of 2.8%.
- SA06: Baseline ages of 70 years and 80 years.
- SA07: Applying the ERG NMA extended network results.
- SA08: Applying the company NMA results.

- SA09: PRN dosing[§] with equal monitoring visits for all treatments with aflibercept Year 2 dosing being (a) [redacted] and (b) [redacted] that of ranibizumab PRN Year 2 dosing, the ratios being based upon the Year 1 dosing ratios of the ERG NMA and the company NMA. An additional scenario (c) of aflibercept Year 2 dosing being the same as ranibizumab Year 2 dosing is also presented.

The results of these sensitivity analyses are presented in Table 25.

Table 25: ERG sensitivity analyses

	Faricimab net cost versus	
Sensitivity analysis	**Ranibizumab**	**Aflibercept**
ERG preferred base-case	[redacted]	[redacted]
SA01a: Years 3+ all treatments 2.00 doses	[redacted]	[redacted]
SA01b: Years 3+ all treatments 3.00 doses	[redacted]	[redacted]
SA01c: Years 3+ all treatments 5.00 doses	[redacted]	[redacted]
SA02a: Years 3+ faricimab [redacted] doses	[redacted]	[redacted]
SA02b: Years 3+ faricimab [redacted] doses	[redacted]	[redacted]
SA02c: Years 3+ faricimab [redacted] doses	[redacted]	[redacted]
SA03a: Discontinuation Years 3+ 5%	[redacted]	[redacted]
SA03b: Discontinuation Years 3+ 13%	[redacted]	[redacted]
SA03c: Discontinuation Year 1+2 [redacted] Years 3+ 8.9%	[redacted]	[redacted]
SA03d: Discontinuation Year 1+2 [redacted] Years 3+ 13%	[redacted]	[redacted]
SA04a: Administration cost £216	[redacted]	[redacted]
SA04b: Administration cost £282	[redacted]	[redacted]
SA05: Fellow eye 27% prevalence 2.8% incidence	[redacted]	[redacted]
SA06a: Baseline age 70	[redacted]	[redacted]
SA06b: Baseline age 80	[redacted]	[redacted]
SA07: ERG extended network NMA[**]	-£8,191	-£17,775
SA08: Company NMA	-£9,275	-£18,512

[§] PRN estimates being taken from the ERG full network due to the reduced network not including ranibizumab PRN dosing.

[**] This scenario may appear to change the cost savings for the comparison with ranibizumab by more than the change in Year 1 and Year 2 ranibizumab doses would suggest. It should be borne in mind that the dose changes also affect the costs of treating fellow eye involvement.

Sensitivity analysis	Faricimab net cost versus	
	Ranibizumab	Aflibercept
SA09a: PRN: ALFI vs RANI Year 2 dosing [redacted]	-£6,963	-£10,533
SA09b: PRN: ALFI vs RANI Year 2 dosing [redacted]	-£6,963	-£11,624
SA09c: PRN: AFLI vs RANI Year 2 dosing 100%	-£6,963	-£14,123

8 ERG commentary on the robustness of evidence submitted by the company

8.1 Strengths

8.2 Weaknesses and areas of uncertainty

- The company assumes a higher frequency of aflibercept doses than seen in a number of aflibercept trials and real-life studies
- The ERG does not think the trials TENAYA/LUCERNE used aflibercept as economically as it could have, because the interval between injections could not be extended.
- Given the high-quality trial evidence supporting similarity in clinical effectiveness between faricimab, brolucizumab, aflibercept, ranibizumab and bevacizumab (and no clear evidence indicating substantial difference in safety), the main considerations for selecting treatment options rests on costs, service delivery issues and patient preference. Injection frequencies stand out as the crucial issue.
- Injection frequency (IF) of the first year does not reflect IF of subsequent years, due to the dosing phase in year one. However, the evidence network is not well connected for RCT data beyond one year.
- The requirement for continuous treatment has been shown in observational studies from routine care, such as the 10-year study from Moorfields Hospital by Arpa et al. There is a paucity of evidence that compares faricimab to variable dosing regimens for aflibercept and ranibizumab.
- The ERG notes the FDA concern about unexpected serious risk of corneal endothelial cell loss. This was not an issue in the TENAYA/LUCERNE. The ERG is unaware why this was an FDA concern.

8.2.1 Research needs

The response to anti-VEGF treatment is poorer in occult lesions. In the TENAYA and LUCERNE trials, the BCVA gains in the occult groups were 4.7 and 4.8 letters, below the threshold of 5 letters

considered by some to be the threshold of clinically meaningful change. Others prefer a threshold of 10 letters for clinical meaningfulness. The gains in the classic group averaged 9 letters.

It should be noted that these gains under-estimate the benefit of treatment in wAMD since without it, it is likely that BCVA would decline.

The ERG recommends that an analysis be done to assess whether treatment of occult lesions is cost-effective. This should be done for all the anti-VEGF drugs and is outwith the scope of this ERG report.

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Appendix 1.

Subtypes of CNV

Neovascular AMD has subtypes according to appearances after fluorescein angiography. Classic CNV appears earlier after injection of dye and has clearly defined borders. Occult CNV appears more slowly and has poorly defined borders. There is an intermediate group called minimally classic. The NICE DP mentions classic and occult wet AMD.

This distinction was important was important in the NICE appraisal (TA68) of photodynamic therapy (PDT) for wet AMD. In PDT the drug, vertoporfin, is taken by mouth then activated by laser in the eye.

In classic wet AMD the neovascular changes are clearly demarcated and so more easily seen, and hence more easily targeted with the laser. NICE recommended PDT for classic only. That guidance from 2003 has been superseded by the clinical guideline on AMD.[28]

NICE no longer recommends PDT except in trials as an adjunct to anti-VEGF treatment.

In anti-VEGF treatment, the drug reaches the whole retina and so both forms of wet AMD are treated.

However, the occult type responds less well to anti-VEGF treatment so if trials of the different anti-VEGF drugs had different proportions of classic and occult, that might make their results less comparable.

Appendix E of the Roche submission reports that the NMA looked at classic vs occult subgroups. The change from baseline was greater in classic – 9.1 vs 4.8 letters gained with faricimab and 7.4 vs 5.1 with aflibercept.

The ERG has extracted data from a number of trials to show the proportions with classic and occult - Table 26Table 26. Proportions of CNV subtypes in some trials

Trial	Classic %	Minimally classic	Occult	Other
LUCERNE/TENAYA (Submission page 33)	31%	9%	50%	RAP 5%
VIEW[29]	29%	35%	36%	-
EXCITE[30]	21%	40%	39%	
CLEAR-IT Heier 2011[13]	38%	24%	38%	
ALTAIR[11]	31%	Mixed 13%	55%	
AVENUE[31]	16%	37%	47%	
Dugel 2017[32]	49%	23%	28%	

We have added “predominantly classic” to classic for the LUCERNE/TENAYA trial.

Figures rounded to whole numbers so may not add to 100%.

Data not reported in ARIES,[12] Mori,[1] Taipale 2020.[14]

The proportion reported as minimally classic in the TENAYA/LUCERNE trial is unusually small.

For the key comparison against aflibercept, we note that the proportions with classic are similar.

Table 27 was provided by the company at the clarification stage. As expected, it shows better results in classic than occult, with minimally classic intermediate. The BCVA gains in the occult groups were 4.7 and 4.8 letters, below the threshold of 5 letters considered by some to be the threshold of clinically meaningful change. There were no significant differences between faricimab and aflibercept. It should be noted that these gains may under-estimate the benefit of treatment in wAMD since without it, it is likely that BCVA would decline.

Table 27. Differences in response to treatment by CVN subtype

	TENAYA		LUCERNE	
	Faricimab	**Aflibercept**	**Faricimab**	**Aflibercept**
Occult (N)	[redacted]	[redacted]	[redacted]	[redacted]
n	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted mean (SE) change from baseline in BCVA	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
Classic (N)	[redacted]	[redacted]	[redacted]	[redacted]
n	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted mean (SE) change from baseline in BCVA	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
Minimally classic (N)	[redacted]	[redacted]	[redacted]	[redacted]
n	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted mean (SE) change from baseline in BCVA	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]

Treatment regimens

There are various ways in which anti-VEGF drugs can be given, including;

- Fixed dosing, often three loading doses at baseline then after 4 weeks and 8 weeks, followed by further doses at fixed intervals in the first year, usually reducing in later years. For example, in the q8w arm of the VIEW trials of aflibercept, patients had 3 loading doses at monthly intervals then further doses every 2 months for the rest of the first year.
- PRN dosing, where patients are assessed and treated according to the activity of the disease. It involves monthly monitoring so has implications for clinic capacity. This was done in year 2 of the VIEW trial, when patients were assessed monthly and treated if need be, but with a maximum interval of 12 weeks. This is known as "capped PRN". So, in year 2 of VIEW, patients received an average of 4 aflibercept injections, making an average of 11 injections over the 2 years.
- There is a variant of PRN where instead of patients being seen or assessment at fixed intervals, the intervals are extended if disease is inactive. PRNx

- Treat and extend (TREX), in which patients start with monthly loading doses, after which the treatment interval is gradually extended till the optimal interval for each patient is determined. If disease activity recurs, the interval can be reduced. In TA672 on brolucizumab, the appraisal committee concluded that TREX should be the recommended regimen.
- Fixed dosing but with several intervals based on disease activity at 20 or 24 weeks, as in the TENAYA/LUCERNE trial

Appendix 2.
Table 28. Study characteristics and key eligibility criteria for study participants of the reduced network

	Aflibercept					Faricimab	
	ARIES[33]	**HAWK/HARRIER**[34]	**MORI**[1]	**RIVAL**[35]	**VIEW 1 and 2**[17]	**STAIRWAY**[36]	**LUCERNE/TENAYA**
Characteristic							
Design	Open-label Multicentre international Phase IIIb/IV	Double-blinded Multicentre international Phase III	Randomised, single centre	Single-blind Multicentre Phase IV	Double-blinded Multicentre international Phase III	Double-blinded Multicentre international Phase II	Double-blinded Multicentre international Phase III
Target population	Adults aged 50+ years with CNV secondary to nAMD in study eye	Adults aged 50+ years with untreated, active CNV lesions secondary to AMD affecting the central subfield	70 patients with nAMD enrolled at Nihon University Hospital in Tokyo between Jan 2013 and Feb 2014	Patients aged 50+ years with nAMD	Adults aged 50+ years with nAMD	Adults aged 50+ years with nAMD and subfovieal CNV	Adults aged 50+ years with CNV secondary to nAMD in study eye
Intervention(s)	Aflibercept 2 mg IVT TREX	Broluzicumab 6 mg IVT Q12W/Q8W	Aflibercept 2 mg IVT Q8W	Ranibizumab 0.5 mg IVT TREX	Aflibercept 2 mg IVT Q8W Aflibercept 2 mg IVT Q4W	Faricimab 6 mg IVT Q16W Faricimab 6 mg IVT Q12W	Faricimab 6.0 mg IVTQ8-16W
Comparator(s)	Aflibercept 2 mg IVT Q8W	Aflibercept 2 mg IVT Q8W	Aflibercept 2 mg IVT PRN	Aflibercept 2 mg IVT TREX	Ranibizumab 0.5 mg IVT Q4W	Ranibizumab 0.5 mg IVT Q4W	Aflibercept 2.0 mg IVT Q8W
Eligibility criteria							
Inclusion	Patients aged ≥50 years with active choroidal neovascularization (CNV) lesions secondary to neovascular age-related macular degeneration (nAMD) with foveal involvement in the study eye were included. The	Active ANV secondary to AMD Total area of CNV > 50% of the total lesion area in study eye IRF/SRF affecting the central subfield of study eye BCVA between 78-23 letters	Presence of CNV below the fovea, serous retinal detachment, or haemorrhage covering the fovea or macular edema and no prior treatment for AMD	Baseline best-corrected visual acuity (BCVA) of 23 logarithm of minimum angle of resolution letters or more (approximate Snellen equivalent, 20/400 þ 3) diagnosed with	Patients 50 years of age and older with active, sub-foveal, CNV lesions (or juxta-foveal lesions with leakage affecting the fovea) secondary to neovascular AMD were eligible for enrolment if	Treatment-naive CNV secondary to AMD (nAMD) Subfoveal CNV or juxtafoveal CNV with a subfoveal component related to the CNV activity by FFA or SD-OCT CNV lesion of all types	Treatment-naïve CNV secondary to nAMD BCVA of 78-24 ;letters using ETDRS at initial testing distance of 4 meters on Day 1

	area of CNV had to occupy at least 50% of the total lesion. Patients were required to have best-corrected visual acuity (BCVA) Early Treatment Diabetic Retinopathy Study (ETDRS) of 73–25 letters (approximately 20/40–20/320 Snellen equivalent) in the study eye			CNV affecting the foveal centre without restriction of lesion size or type, secondary to nAMD in a treatment-naïve eye	CNV made up at least 50% of total lesion size and BCVA was between 25 and 73 Early Treatment Diabetic Retinopathy Study (ETDRS) letters (20/320-20/40 Snellen equivalent).	BCVA letter score of 73 to 24 letters	
Exclusion	Patients were excluded if they had prior or current use of anti-vascular endothelial growth factor therapy or had received prior ocular or systemic treatment or surgery for nAMD. Patients with active infection or intraocular inflammation in either eye, intraocular pressure ≥25 mmHg in the study eye, or any other ocular condition in the study eye that might impact vision were excluded	Any active intraocular or periocular infection or active intraocular inflammation at baseline Previous treatment for nAMD Evidence of concurrent intraocular condition in the study eye other than nAMD	Eyes with PCV or retinal angiomatous proliferation were excluded. Eyes with VA under 20/200, massive haemorrhage covering over 50% of the macula, and juxtafoveal CNV with leakage into the fovea were excluded	Patients with 1 or more patches of MA that were more than 250 mm in the greatest linear dimension in either eye (measured with multimodal imaging)	Patients with prior treatment for AMD (including an investigational agent or anti-VEGF therapy) in the study Prior treatment with anti-VEGF agents	CNV due to causes other than AMD, such as ocular histoplasmosis, trauma, pathological myopia, angioid streaks, choroidal rupture, or uveitis Any concurrent intraocular condition in the study eye	CNV due to causes other than AMD Any history of macular pathology unrelated to AMD
Follow-up	52 weeks	48 weeks	12 months	12 months	12 months	Week 40	Week 48

assessment of primary outcome	104 weeks	96 weeks		24 months		Week 52	