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Faricimab for treating macular oedema secondary to retinal vein occlusion [ID6197]

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Nigel Armstrong acted as project lead and health economist/reviews manager on this assessment, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Susan O'Meara acted as project lead and as a systematic reviewer, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Mubarak Patel and Jiongyu Chen acted as systematic reviewers, critiqued the clinical effectiveness methods and evidence, and contributed to the writing of the report. Maiwenn Al acted as health economic project lead, critiqued the company's economic evaluation, and contributed to the writing of the report. Venetia Qendri acted as health economist on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Caro Noake critiqued the search methods in the submission and contributed to the writing of the report. Robert Wolff critiqued the company's definition of the decision problem, contributed to the writing of the report and supervised the project.

Abbreviations

µm	Micrometre (or micron)
AE	Adverse event
AFL	Aflibercept
ANCOVA	Analysis of covariance
BCVA	Best-corrected visual acuity
BM	Bruch's membrane
BRVO	Branched retinal vein occlusion
BSC	Best supportive care
CDSR	Cochrane Database of Systematic Reviews
CENTRAL	Cochrane Central Register of Controlled Trials
CI	Confidence interval
CiC	Commercial in confidence
CMH	Cochran Mantel-Haenszel
CMU	Commercial Medicines Unit
CrI	Credible interval
CRVO	Central retinal vein occlusion
CS	Company submission
CSR	Clinical study report
CST	Central subfield thickness
DARE	Database of Abstracts of Reviews of Effects
DIC	Deviance Information Criterion
DMO	Diabetic macular oedema
DP	Decision problem
EAG	External Assessment Group
EMA	European Medicines Agency
EUR	Erasmus University Rotterdam
FAR	Faricimab
FDA	Food and Drug Administration
FFA	Fundus fluorescein angiography
HR	Hazard ratio
HRQoL	Health-related quality of life
HRVO	Hemi-retinal vein occlusion
HSUV	Health-state utility value
HTA	Health Technology Assessment
ILM	Internal limiting membrane
Incr.	Incremental
IRF	Intra-retinal fluid
ITT	Intention-to-treat
IVT	Intravitreal (injection)
KSR	Kleijnen Systematic Reviews Ltd
MA	Marketing authorisation
MMRM	Mixed-effect model of repeated measures
MO	Macular oedema
NA	Not available
N/A	Not applicable
NEI VFQ-25	National Eye Institute 25-Item Visual Function Questionnaire
NHS	National Health Service
NHS EED	National Health Service Economic Evaluation Database
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NL	Netherlands
NMA	Network meta-analysis
OCT	Optical coherence tomography

OR	Odds ratio
PAS	Patient Access Scheme
PRN	Pro re nata (meaning “when required”)
PTI	Personalised treatment interval
Q4W	Once every 4 weeks
Q8W	Once every 8 weeks
Q12W	Once every 12 weeks
Q16W	Once every 16 weeks
RAN	Ranibizumab
RCO	Royal College of Ophthalmologists
RCT	Randomised controlled trial
RE	Random effects
RoB	Risk of bias
RVO	Retinal vein occlusion
SD	Single dose
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
SmPC	Summary of product characteristics
SRF	Sub-retinal fluid
STA	Single Technology Appraisal
T&E	Treat and extend
TA	Technology Assessment
TSD	Technical Support Document
UK	United Kingdom
VA	Visual acuity
VEGF	Vascular endothelial growth factor

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1. Summary of the EAG's view of the company's cost-comparison case

The External Assessment Group (EAG) believes that the company has demonstrated that faricimab is equivalent to at least one of the other technologies in the treatment of macular oedema (MO) secondary to retinal vein occlusion (RVO), aflibercept, and therefore a cost-comparison case is appropriate. This is based on two randomised controlled trials (RCTs) of the same design (BALATON and COMINO[1, 2]) that compared faricimab 6 mg given once every four weeks (Q4W) with aflibercept 2 mg Q4W for a follow-up period of 24 weeks (Part 1), after which, in Part 2, there was no active control. The BALATON RCT[2] studied patients with MO secondary to branched retinal vein occlusion (BRVO) whilst COMINO[1] studied patients with MO due to central retinal vein occlusion (CRVO) or hemi-retinal vein occlusion (HRVO). Note that Part 1 employed a dose schedule that is consistent with the marketing authorisation (MA), at least until patients are switched to [redacted] (Table 2 of Document B of the company submission [CS]).[3] The dose of aflibercept was also consistent with that recommended in the latest Royal College of Ophthalmologists (RCO) guidelines although the dosing interval is specified as: "*...at least 4 weeks."* (page 19).[4] Therefore, the EAG would caveat the conclusion of equivalence with the assumption that the two treatments would be administered at a similar rate in clinical practice.

Generally, measures of effectiveness showed no statistically significant difference. There was overlap in the 95% confidence intervals (CIs) and differences in the point estimates were minimal, including for the primary outcome mean change from baseline in best-corrected visual acuity (BCVA) at week 24.[3] In BALATON,[2] the adjusted mean BCVA change from baseline was 16.9 and 17.5 letters in the faricimab Q4W and aflibercept Q4W arms, respectively; the difference was -0.6 letters (95% CI: -2.2, 1.1).[3] In COMINO[1], the adjusted mean change in BCVA from baseline was 16.9 and 17.3 letters in the faricimab Q4W and aflibercept Q4W arms, respectively; the difference was -0.4 letters (95% CI: -2.5, 1.6).[3] The difference in BCVA letters between faricimab and aflibercept in both BALATON[2] and COMINO[1] was within the +/- 4 letter non inferiority margin as defined in Document B of the CS (Section B.3.6.1).[3] Similar results were found for sensitivity analyses using a different method of imputation or analysis population (Table 10 of Document B of the CS).[3] At week 24, there was [redacted], in central subfield thickness (CST) (page 50 of Document B of the CS[3]) and the proportion of patients with absence of macular leakage at week 24 was actually statistically significantly higher for faricimab in both trials (33.6% versus 21.0% in BALATON[2] and 44.4% versus 30.0% in COMINO).[3] [redacted] Further details on outcomes for the BALATON[2] and COMINO[1] RCTs are provided in Section 3 of this report.

Note that the scope and MA preclude HRVO, which was the aetiology for some patients in COMINO[1], but the number of these patients was small [redacted] and [redacted] in the faricimab and aflibercept arms respectively).[1]

The company also claimed equivalence between faricimab and ranibizumab. For a cost-comparison to be appropriate, equivalence only has to be demonstrated with one treatment that is in use in United Kingdom (UK) clinical practice. However, the economic model does assume this for ranibizumab as

well as aflibercept and so its validity might be important to establish. The opinion of the EAG is that the network meta-analysis (NMA) used by the company to demonstrate equivalence does appear to show equivalence. However, the same caveat applies to the application of these results to clinical practice as with aflibercept i.e. it depends on the rate of dosing. In fact, the clinical expert consulted by the EAG indicated that aflibercept would be preferred to ranibizumab because of the greater potential to extend the dosing interval under the T&E regimen: *"First, Aflibercept is the anti-vascular endothelial growth factor (anti-VEGF) of choice nowadays. Both Aflibercept and Ranibizumab drugs have proven efficacy and safety. However, Aflibercept offers longer durability of effect (therefore longer treatment intervals) on patients requiring going on treat&extend regimens (the majority) due to recurrence of macular oedema after an initial loading phase of 3 monthly injections. This is mostly due to Aflibercept inhibiting various forms of VEGF as opposed to Ranibizumab. So, I would say with a high degree of confidence that Ranibizumab is becoming an obsolete drug due to being replaced by better and more durable alternatives."* (page 1).[5]

2. Critique of the decision problem in the company's submission

In terms of population, as opposed to the National Institute for Health and Care Excellence (NICE) Final Scope,[6] the company's decision problem (DP) focuses only on adults and those with visual impairment. This is consistent with the proposed MA.[3, 6] It is also consistent with the RCTs comparing faricimab with aflibercept, BALATON and COMINO,[1, 2] although with the extra criterion that patients should be naïve to anti-VEGF treatment.

EAG comment: The EAG would therefore suggest that a recommendation be made only for this subgroup, i.e., omitting children, those without a visual impairment or anyone with anti-VEGF treatment experience.

The intervention in the key trials and the cost-only comparison is consistent with that in the NICE Final Scope (which simply states "*Faricimab*").[3, 6] As outlined in Section 1, the BALATON and COMINO[1, 2] RCTs both compare faricimab 6 mg Q4W with aflibercept 2 mg Q4W for a follow-up period of 24 weeks (Part 1), followed by a phase with no active control (Part 2).[1, 2] Part 1 employed a dose schedule consistent with the MA, at least until patients are switched to [redacted]

Two of the comparators in the DP are consistent with the NICE Final Scope i.e. aflibercept and ranibizumab.[3, 6] As outlined in Section 1, the dose of aflibercept in the two RCTs comparing this with faricimab was also consistent with that recommended in the latest RCO guidelines although the dosing interval is specified as: "*…at least 4 weeks."* (page 19).[4] The dose of ranibizumab in the RCTs included in the NMA (see Appendix D of the CS[7]) is 0.5 mg, which is also consistent with the RCO guidelines. The dosing interval in the guidelines also seems to be identical to the faricimab MA i.e. *"The interval between 2 injections is at least 4 weeks."* (page 19).[4] In the NMA, the comparisons are only for the controlled period of the RCTs such that the dosing intervals for both faricimab and aflibercept are Q4W, but for ranibizumab two dosing intervals are compared, one of which is Q4W and the other is as required (i.e., pro re nata, or PRN). In fact, as stated in Section 1, the EAG clinical expert stated that he would not prescribe ranibizumab.[5]

An additional comparator, dexamethasone intravitreal implant (for BRVO only after laser photocoagulation has been tried, or is not suitable) is listed in the NICE Final Scope,[6] but does not feature in the company's DP.[3] The clinical experts enlisted by the company suggested that dexamethasone implants would not be used in clinical practice due to inferior efficacy compared to anti-VEGFs and a less favourable safety profile, and may only be used in patients who do not respond to anti-VEGF products (Section B.1.3.2 of Document B of the CS[3]). However, the clinical expert enlisted by the EAG confirmed that this product is used in clinical practice in the UK National Health Service (NHS) and this is also indicated by clinical guidelines.[4, 5] The EAG's clinical expert suggested that the proportion of aflibercept and dexamethasone implant prescription is 80/20% respectively at baseline, with 20% to 30% of anti-VEGF starters offered dexamethasone as an alternative treatment during the treatment course because of difficulty in committing to monthly anti-VEGF injections (dexamethasone implants have longer durability) and possible contraindication to anti-VEGF treatment because of a recent cardiovascular event. It is also important to note that the dosing of dexamethasone implant appears to be effectively PRN i.e. *"…re-treatment may be required at 4-6 monthly intervals until visual stability is obtained."* (page 35).[4] This 4–6-month durability was confirmed by the EAG clinical expert.[5] This would probably make the RCTs of PRN use in the NMA more relevant than single dose (SD) administration (see Section 3.3). This could be important given

that there seems to be equivalence with faricimab of effectiveness for PRN, but superiority for faricimab over SD.

All points considered, the EAG's view is that dexamethasone implant should have been considered as a comparator in the NMA and the cost-effectiveness analysis.

Two outcomes listed in the NICE Final Scope[6] and company's DP[3] are not represented in the NMA (overall visual function and health related quality of life [HRQoL][8, 9]).

The omission of potentially relevant outcomes constitutes a limitation to the presented evidence as comparability between treatments remains uncertain unless all relevant health outcomes are considered, particularly those that are patient-reported such as HRQoL.

3. Summary of the EAG's critique of clinical effectiveness evidence submitted

3.1 Systematic literature review methods

The study eligibility criteria for the systematic literature review (SLR)[7] are broadly aligned with the domains presented in the NICE Final Scope[6] and the company's DP[3] and with the therapeutic indication described in the proposed summary of product characteristics (SmPC) for faricimab.[10] However, the EAG noted that the SLR eligibility criteria included additional comparators (e.g., bevacizumab, laser therapy) and outcomes (e.g., SRF, IRF, treatment frequency, legal blindness) that were not listed in the NICE Final Scope or DP.[6, 7]

The searches covered a broad range of resources including MEDLINE (including In-Process & Other Non-Indexed Citations, Epub Ahead of Print and MEDLINE® Daily), EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews (CDSR) and Database of Abstracts of Reviews of Effects (DARE), all via OvidSP. Additional searches were carried out for nine conference proceedings held between 2019-2023, four Health Technology Assessment (HTA) agencies, Clinical Trials.gov and three Government websites: UK, United States Food and Drug Administration (FDA) and European Medicines Agency (EMA). Searches were conducted on 3 April 2023 and updated 6 December 2023. Full details can be found in Document B and Appendix D of the CS and the company's response to clarification questions.[3, 7, 11]

EAG comment: The CS, Appendix D and the company's response to clarification provided sufficient details for the EAG to appraise the literature searches. Searches were transparent and reproducible, and comprehensive strategies were used.[3, 7, 11] The SLR may have benefitted from separate adverse events (AEs) searches conducted to capture long-term, rare or unanticipated AEs that are less likely to be retrieved by searches containing an RCT filter[12] as reported in Appendix D of the CS.[7] Overall, the EAG has no major concerns about the literature searches conducted.

Identified studies were assessed for eligibility at both the title and abstract and full-text screening stages by two independent reviewers. Disagreements were resolved by consulting an advisor.[7] Data from included studies were extracted into a pre-specified data extraction table in Microsoft® Excel® by a single reviewer and checked by a second, independent reviewer. Disputes were referred to an advisor for reconciliation.[7, 11] Assessment of risk of bias (RoB) was undertaken by two reviewers and disagreements were resolved by discussion or consultation with additional referees. The reviewers used the seven-criteria checklist provided in Section 2.5 of the NICE Single Technology Appraisal (STA) user guide.[13] Tabulation of studies excluded at the full text screening stage together with reasons for exclusion was provided as part of the company's response to clarification questions.[11]

Considering the information provided in Appendix D of the CS[7] and the response to clarification questions,[11] the EAG is satisfied with the conduct of the clinical effectiveness SLR.

3.2 Identified randomised controlled trials

Information on the included RCTs was gleaned from Document B[3] and Appendices D to H (inclusive)[7] of the CS and the company's clarification response documents.[8, 9, 11]

Appendix D of the CS (Section D.1.7 and Figure 1) indicates that 39 studies (reported in 57 papers) were included in the clinical effectiveness SLR.[7] Of these, 20 RCTs were included in the NMA. The company's clinical feasibility assessment document provides details of eligibility for inclusion in the NMA (Table 2) as well as listing the 19 excluded studies, specifying reasons for exclusion (Table 4).[9] Of note, separate sets of eligibility criteria were presented for the SLR (Table 1 of Appendix D of the

CS[7]) and the NMA (Table 2 of the clinical feasibility assessment document[9]), with the latter being slightly narrower by comparison, particularly with regard to the list of outcomes.

The two aforementioned RCTs (BALATON and COMINO) were included in the NMA and had data available from CSRs.[1, 2, 14, 15] As outlined previously, these two RCTs shared similar protocols and both compared faricimab with aflibercept. The main distinction was in the population characteristics with BALATON[2] recruiting participants with MO secondary to BRVO whilst COMINO[1] enrolled those with CRVO or HRVO. The study design, methods, baseline data and outcomes from these two RCTs were reported in detail in the CS.[3, 7] Details of study design, population characteristics, endpoint definitions and RoB of the remaining 18 RCTs were made available as a result of the clarification process.[9]

As already outlined (see Section 2 of this report) the trial populations of BALATON and COMINO were narrower than that described in the company's DP in that eligible participants had to be naïve to anti-VEGF treatment.[1, 2] Otherwise, the two RCTs were aligned to the DP.[3]

Table 16 of Appendix D of the CS presented the company's RoB assessment of the BALATON and COMINO RCTs, assigning a low RoB judgement overall as well as for every individual domain.[7] The EAG conducted an independent assessment based on the CSRs[1, 2] and whilst agreeing with most parts of the company's assessment, noted the possibility of baseline imbalance in both RCTs.

BALATON recruited more males to the faricimab arm ([redacted] versus [redacted] in the aflibercept arm).[2] In addition, the number of participants from specific Asian races differed with respective proportions being [redacted] versus [redacted] Korean and [redacted] versus [redacted] Japanese participants. In terms of ocular baseline characteristics, fewer participants with a right-sided study eye were assigned to the faricimab arm ([redacted] versus [redacted] for aflibercept). In addition, the number of months since RVO diagnosis was more variable among participants assigned to aflibercept: minimum to maximum ranges were [redacted] for faricimab and [redacted] for aflibercept. However, these data could be explained by the presence of outliers.[2] In the COMINO RCT, the proportion of participants of unknown race was greater in the faricimab arm ([redacted] compared with [redacted] for aflibercept).[1] The impact of these potential baseline imbalances on estimation of treatment effect is unclear.

Table 1 provides an overview of outcomes during Part 1 of the BALATON[2] and COMINO[1] RCTs and includes outcomes listed in the NICE Final Scope[6] and DP and those assessed in the NMA. The results generally indicate equivalence between faricimab and aflibercept with the exception of the outcome of absence of macular leakage (also shown in Table 1) which suggests a more favourable outcome among participants assigned to faricimab. Only the main outcomes are shown in Table 1: these were generally consistent with other analyses, i.e., across population disease subgroups, different analysis populations and using different methods of estimation.[1-3]

Table 3.1: Overview of outcomes for Part 1 of BALATON and COMINO RCTs

	BALATON (BRVO)			COMINO (CRVO or HRVO)		
	FAR 6 mg Q4W (N=276[a]) Adjusted mean (95% CI) [a]	**AFL 2 mg Q4W (N=277[a]) Adjusted mean (95% CI) [a]**	**Difference in adjusted means (95% CI) [a]**	**FAR 6 mg Q4W (N=366[a]) Adjusted mean (95% CI) [a]**	**AFL 2 mg Q4W (N=363[a]) Adjusted mean (95% CI) [a]**	**Difference in adjusted means (95% CI) [a]**
Change from baseline in BCVA in the study eye at 24 weeks						
Mean (SE) baseline BCVA [b]	57.5 (0.78)	57.6 (0.73)	-	50.2 (0.85)	50.7 (0.86)	-
Main analysis (MMRM) in ITT population	16.9 (15.7 to 18.1)	17.5 (16.3 to 18.6)	-0.6 (-2.2 to 1.1) [c]	16.9 (15.4 to 18.3)	17.3 (15.9 to 18.8)	-0.4 (-2.5 to 1.6) [c]
Proportion of patients gaining ≥15 letters in BCVA from baseline at 24 weeks						
Main analysis in ITT population (CMH weighted estimates) [d]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of patients gaining ≥10 letters in BCVA from baseline at 24 weeks						
Main analysis in ITT population (CMH weighted estimates) [d]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of patients gaining ≥5 letters in BCVA from baseline at 24 weeks						
Main analysis in ITT population (CMH weighted estimates) [d]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of patients gaining >0 letters in BCVA from baseline at 24 weeks						
Main analysis in ITT population (CMH weighted estimates) [d]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	BALATON (BRVO)			COMINO (CRVO or HRVO)		
	FAR 6 mg Q4W (N=276[a]) Adjusted mean (95% CI) [a]	AFL 2 mg Q4W (N=277[a]) Adjusted mean (95% CI) [a]	Difference in adjusted means (95% CI) [a]	FAR 6 mg Q4W (N=366[a]) Adjusted mean (95% CI) [a]	AFL 2 mg Q4W (N=363[a]) Adjusted mean (95% CI) [a]	Difference in adjusted means (95% CI) [a]
Change from baseline in CST (ILM-BM) in the study eye at 24 weeks						
Mean (SE) baseline CST [d]	[redacted]	[redacted]	-	[redacted]	[redacted]	-
Analysis (MMRM) in ITT population [d]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change in NEI VFQ-25 composite score [e] at 24 weeks						
Mean baseline score [b, d]	[redacted]	[redacted]	-	[redacted]	[redacted]	-
Adjusted mean change from baseline (ANCOVA method) in ITT population [d]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocular AEs in the study eye prior to 24 weeks						
Number of patients with ≥1 ocular AE in safety-evaluable population [d]	[redacted]	[redacted]	-	[redacted]	[redacted]	-
Number of events in safety-evaluable population [d]	[redacted]	[redacted]	-	[redacted]	[redacted]	-
All cause discontinuation prior to 24 weeks						
Analysis in ITT population [d]	[redacted]	[redacted]	-	[redacted]	[redacted]	-

	BALATON (BRVO)			COMINO (CRVO or HRVO)		
	FAR 6 mg Q4W (N=276[a]) Adjusted mean (95% CI) [a]	**AFL 2 mg Q4W (N=277[a]) Adjusted mean (95% CI) [a]**	**Difference in adjusted means (95% CI) [a]**	**FAR 6 mg Q4W (N=366[a]) Adjusted mean (95% CI) [a]**	**AFL 2 mg Q4W (N=363[a]) Adjusted mean (95% CI) [a]**	**Difference in adjusted means (95% CI) [a]**
Patients with absence of macular leakage in the study eye [f] at 24 weeks						
Number of patient with absence of macular leakage at baseline [d, g]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of patients with absence of macular leakage at 24 weeks [d, g]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Based on Section B.3.6, Table 10 and Figure 21 of Document B of the CS;[3] Section 5.1.3.3.1, Tables 2, 9, 12 and 15 and pages 421 and 459 of the primary CSR for BALATON;[2] and Section 5.1.3.3.1, Tables 2, 9, 12 and 15 and pages 459 and 503 of the primary CSR for COMINO.[1]

The data cut-off dates are July 2022 for BALATON[2] and August 2022 for COMINO.[1]

[a] Unless otherwise stated; [b] Values are non-adjusted.[1-3]; [c] For the primary analysis, if the lower bound of the two-sided 95% CI for the difference in adjusted means of the two treatments is greater than − four letters (the non-inferiority margin), then faricimab is considered non-inferior to aflibercept.[3]; [d] From CSR.[1, 2]; [e] Maximum score 100; higher scores suggest better quality of life.[1, 2]; [f] Based on FFA.[1, 2]; [g] In population with FFA images of sufficient quality for macular leakage grading.[1, 2]

µm = micrometre (or micron); AE = adverse event; AFL = aflibercept; ANCOVA = analysis of covariance; BCVA = best-corrected visual acuity; BM = Bruch's membrane; BRVO = branch retinal vein occlusion; CI = confidence interval; CMH = Cochran Mantel-Haenszel; CRVO = central retinal vein occlusion; CS = company submission; CSR = clinical study report; CST = central subfield thickness; FAR = faricimab; FFA = fundus fluorescein angiography; HRVO = hemi-retinal vein occlusion; ILM = internal limiting membrane; ITT = intention-to-treat; MMRM = mixed-effect model of repeated measures; NEI VFQ-25 = National Eye Institute 25-Item Visual Function Questionnaire; Q4W = one injection every 4 weeks; RCTs = randomised controlled trials; SE = standard error

3.3 Observational studies

Appendix L of the CS describes a study performed to assess real-world treatment patterns and outcomes in patients with MO secondary to BRVO (n=4,484), CRVO (n=3,598) or HRVO (n=650). Patients were recruited from 16 participating NHS ophthalmology sites in the UK. Three patient cohorts were defined: Cohort 1 - "*real-world eyes*" (all eyes included in the study); Cohort 2 - "*trial-like eyes*" (eyes aligned to the participant eligibility criteria for BALATON and COMINO[1, 2]); and Cohort 3 – "*trial-matched eyes*" (subset of Cohort 2 comprising eyes matching on the BALATON[2] and COMINO[1] patient characteristics of sex, age, baseline visual acuity (VA) and RVO type (COMINO only).[7]

When asked for clarification about the contribution of the real-world study to the CS, the company stated that it was used "*as qualitative substantiation*" and suggested that the results were supportive of the notion that a greater proportion of patients receiving anti-VEGF therapy extended to once every 12 weeks (Q12W) and once every 16 weeks (Q16W) than was suggested in the BALATON and COMINO RCTs[1, 2] (response to clarification question A7[11]). At 68 weeks, the proportion of patients extending to Q12W and Q16W during Part 2 of the BALATON and COMINO RCTs was [redacted] and [redacted] and [redacted] respectively[1, 2]. The closest match to these figures from the real-world study are those for [redacted] and [redacted] in Cohort 3 (matched to COMINO[1] and BALATON[2] on sex, age, baseline VA, plus RVO type for COMINO).[7] The company have provided 'average' and 'latest' estimates, the latter being considerably higher (see Table 3.2).

Table 3.2: Treatment intervals from real-world study

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

Source: CS Appendices, Tables 62 and 63.[7]
BRVO = branch retinal vein occlusion; CRVO = central retinal vein occlusion; CS = company submission; HRVO = hemi-retinal vein occlusion

EAG comment: Although there is some variation, it does appear that the treatment intervals for ranibizumab and aflibercept are similar up to 5 years. Also, the match between the dosing intervals reported in the trials and the real-world study is imperfect, but it does appear to show that the treatment intervals for faricimab are at least as long as for the two comparators.

3.4 Summary and critique of network meta-analysis

Network meta-analyses were conducted at week 24 +/-4 weeks for six key outcomes: mean change from baseline in BCVA and CST, categorical vision changes from baseline, (serious) ocular AEs and all cause discontinuation.[8] BRVO and CRVO subgroups analyses for two outcomes, mean change from baseline in BCVA and CST, were also conducted. The NICE Final Scope outcome of HRQoL was not subjected to NMA, which might be considered a limitation.[6]

The NMAs conducted for BCVA, CST, categorical vision, ocular AEs, serious ocular AEs and all cause discontinuation demonstrated varying results (shown in Table 2).

- For mean change from baseline in BCVA, there was fairly clear evidence of faricimab 6 mg Q4W generally shows greater improvement in BCVA among all anti-VEGF treatments. The exception was when compared to aflibercept 2 mg Q4W, where the credible intervals (CrIs) include zero, suggesting non-significant differences. This was conducted with a random effects model, which was appropriate given the Deviance Information Criteria (DIC) showed the random effects model providing a better fit. For separate CRVO and BRVO studies, the overall findings support faricimab's efficacy. The BRVO analysis relies on only indirect comparisons with relatively weak comparators (laser and sham), which might be regarded as a significant limitation that could undermine the conclusions. The analysis of categorical BCVA change from baseline was consistent with the mean change analysis (results not shown here). The results indicate that faricimab 6 mg Q4W generally outperforms other anti-VEGF treatments, except for aflibercept 2 mg Q4W where the difference was not statistically significant.
- For mean change from baseline in CST, faricimab 6 mg Q4W was generally more effective compared to all anti-VEGF treatments except for dexamethasone 0.7 mg PRN where the difference was not statistically significant. However, faricimab led to a statistically significant reduction in CST compared to dexamethasone 0.7 mg SD. The use of the random effects model was considered reasonable, and, although the fixed effects model fitted the data slightly better than the random effects model according to DIC, the difference is not considered meaningful. Separate network analyses for CRVO and BRVO populations show consistency with the overall findings, but with larger uncertainties from fewer studies.
- For ocular AEs, faricimab 6 mg Q4W is associated with lower odds compared to other comparators, most notably dexamethasone 0.7 mg SD, with overall evidence suggesting a favourable safety profile for faricimab. The use of the random effects model was appropriate given the DIC shown the random effects model providing a better fit. Serious ocular AEs show the same advantage to faricimab.
- For all cause discontinuation, faricimab demonstrated a lower probability of discontinuation events compared to most comparators, except for aflibercept Q4W. However, the 95% CrIs crossed the line of no effect (odds ratios (ORs) = 1) for all comparators, which implies a lack of statistical significance in these differences. The choice of the random effects model as the best fit by DIC, and fixed effects model were consistent.

In analyses of BRVO and CRVO subgroups, a vague prior sensitivity analysis was used to address the high level of uncertainty due to the small number of studies and the poor robustness of the network and previous NMAs for faricimab in diabetic macular oedema (DMO) and neovascular age-related macular degeneration were used to inform mildly informative priors for between study standard deviation (SD). The current analysis is for a 6-month timeframe, but the choice was made to use the previous NMA to provide a priori information on the between-study SD of BCVA and CST scores at 12 months.

The EAG had two issues with the NMA. Firstly, although Appendix D contains a section referred to as *"Feasibility Assessment"*, the only mention of heterogeneity is that it has a *"high likelihood"* and, on this basis, a random effects model was chosen (see Technical Support Document [TSD] 3.[7, 16] There is no mention of consistency (see TSD 4).[17] Therefore, the EAG requested that the company perform a full feasibility assessment that systematically examines variation between trials in clinical and methodological characteristics, any potential treatment modifying effect and thus the implications for the network for any methods to mitigate heterogeneity or inconsistency[11] with reference to TSD 3[16] and TSD 4.[17] The EAG also requested a full list of all RCTs included in the NMA with full details including: trial design; participant flow; participant inclusion and exclusion criteria; participant demographic and baseline clinical data; treatment schedule for all arms; statistical hypotheses; methods of statistical analyses; analysis populations; list of all outcomes assessed together with methods of measurement; full details of all results (per arm and between-group differences) used to estimate clinical effectiveness and safety and to inform the cost comparison model; and results for relevant population subgroups. In response, the company have provided a full technical report and separate feasibility assessment.[8, 9] The EAG is satisfied that equivalence has largely been demonstrated with ranibizumab 0.5 mg with the same dosing interval as faricimab i.e. Q4W. There was overlap of the point of no difference of the 95% CrI for mean change in baseline in BCVA and CST, with the point estimate slightly in favour of faricimab when both CRVO and BRVO studies were included in the network. When the networks were limited by either CRVO or BRVO, there continued to be considerable overlap of the 95% CrI, although the point estimates were slightly in favour of ranibizumab for BCVA. For CST, this was also the case for the CRVO population, but the BRVO population did seem to show a point estimate advantage to ranibizumab that was more substantial.

Table 3.3: Overview of main outcomes from NMA for FAR versus AFL and FAR versus RAN

Outcome	Total number of studies in network	FAR 6 mg Q4W versus AFL 2 mg Q4W (95% CrI)	FAR 6 mg Q4W versus RAN 0.5 mg Q4W (95% CrI)
Difference (95% CrI) in mean change from baseline in BCVA at 24 weeks (RVO, RE model)	20	-0.54 (-4.79 to 3.87)	2.73 (-4.58 to 10.06)
Difference (95% CrI) in mean change from baseline in CST at 24 weeks (RVO, RE model)	17	-9.60 (-30.81 to 10.53)	-1.99 (-74.19 to 69.30)
OR (95% CrI) for patients with ≥1 ocular AE at 24 weeks (base-case, RE model)	10	0.77 (0.32 to 1.79)	NA
OR (95% CrI) for patients who discontinued due to any cause prior to 24 weeks (base-case, RE model)	16	1.28 (0.39 to 5.14)	0.65 (0.09 to 5.02)

Based on Section 4.4 of NMA report[8]

AE = adverse event; AFL = aflibercept; BCVA = best-corrected visual acuity; CrI = credible interval; CST = central subfield thickness; FAR = faricimab; NA = not available (estimate); NMA = network meta-analysis; OR = odds ratio; Q4W = one injection every 4 weeks; RAN = ranibizumab; RE = random effects; RVO = retinal vein occlusion

4. EAG critique of cost comparison evidence submitted

4.1 Decision problem for cost comparison

The NICE Final Scope defines as population patients with MO secondary to BRVO and CRVO. The patient population considered by the company in the cost comparison however is restricted to patients aged ≥18 years, thus excluding children.[6] The population considered in this cost comparison is similar to the anticipated MA for faricimab and in line with the populations evaluated in the BALATON and COMINO trials.[1, 2]

The company's analysis compares faricimab with aflibercept and ranibizumab. As mentioned in Section 2, the EAG's view is that dexamethasone implant should have been considered as a comparator.

4.2 Cost-effectiveness searches

Appendix I of the CS provided a report of the company's SLR of published cost-effectiveness and HRQoL studies that was conducted in order to identify: published evidence associated with trial-based and economic models for the treatment of patients with MO-related RVO; and health state utility values (HSUVs) associated with MO-RVO.[7]

The SLR searches covered a broad range of resources including MEDLINE (including In-Process & Other Non-Indexed Citations, Epub Ahead of Print and MEDLINE® Daily), EMBASE , EconLit and National Health Service Economic Evaluation Database (NHS EED) all via OvidSP. Additional searches were carried out for five conference proceedings held between 2019-2023, four HTA agencies and three Government websites: UK, United States (FDA and European Medicines Agency (EMA). Searches were conducted on 18 April 2023 (For full details please see the CS, Appendix I and response to clarification).[3, 7, 11]

EAG comment: The CS, Appendix I and the company's response to clarification provided sufficient details for the EAG to appraise the literature searches. Searches were transparent and reproducible, and comprehensive strategies were used.[3, 7, 11] Whilst the searches may have benefitted from an update, overall, the EAG has no major concerns regarding the searches.

4.3 Company cost comparison model

The Microsoft® Excel® model that was developed for the cost comparison has a time horizon of 25 years, and distinguishes between being on treatment, off treatment, and death (see CS Figure 22).[3] In each of these health states, patients are sub-divided over six VA states, with the best being >85 letters and the worst being ≤25 letters. The model allows for disease and treatment in both eyes.

It is important to note though, that patients that discontinue their treatment for any reason (this included patients successfully treated as well as patients who stop due to insufficient effects) are assumed to not receive further treatment. Further details regarding the model can be found in CS sections B 4.2.1 and B 4.2.2.[3]

EAG comment: The model structure for the current cost-comparison can be regarded as reasonable, and is in line with the models used for e.g. Technology Assessment (TA) 799[18] and TA800.[19] The assumption that patients who discontinue their treatment do not receive further treatment leads to an underestimation of the total costs per treatment arm but the impact on the incremental costs between faricimab and its comparators is unclear.

4.4 Model parameters

4.4.1 Treatment effect

The impact of treatment is modelled through a transition matrix describing the probability to move from one level of VA to another. The values in the matrix for the treatment phase (24 weeks) were derived from the BALATON[2] and COMINO[1] RCTs.[20] As the NMA indicated that faricimab, aflibercept, and ranibizumab are equally effective, the same transition matrix was applied to all three treatments.

For the maintenance phase (24 weeks to 5 years) and the rest-of-life phase it was assumed that patients would remain at the same VA level for their first eye. At any moment in the treatment and maintenance phase, disease may develop in the second eye as well (see CS Table 27[3]). When treated, the same transition matrices were applied to the second eye.

EAG comment: Based on the NMA, it is reasonable to assume that all three treatments are equivalent. However, as the NMA only considered outcomes at 24 weeks, there is currently no evidence regarding the long-term equivalence for faricimab, aflibercept, and ranibizumab.

4.4.2 Treatment discontinuation

During treatment, patients may discontinue treatment. The probabilities of discontinuation for faricimab for both the treatment phase and the maintenance phase were obtained from the BALATON[2] and COMINO[1] RCTs,[20] and it was assumed that these also apply to aflibercept and ranibizumab. For the treatment phase the trial data from the first 24 weeks was used to derive discontinuation probability, whilst for the maintenance phase the company applied the probability of discontinuation based on the observed discontinuation from week 24 to week 72 in the BALATON[2] and COMINO[1] RCTs (see Table 4.1).[20]

On top of this, the company assumed that after 60 months, 55% of patients still on treatment would discontinue, based on findings from the SCORE2 study.[21]

Table 4.1: Treatment discontinuation probabilities

	Patients discontinuing BALATON and COMINO	Deaths*	N	Factor to annualise	Annualised discontinuation probability	4-week probability
Treatment phase (until week 24)	26+12	3+1	729+553	52/24	5.7%	0.453%
Maintenance phase (weeks 24 - 72)	52+48	4+3	729+553	52/48	7.9%	0.625%

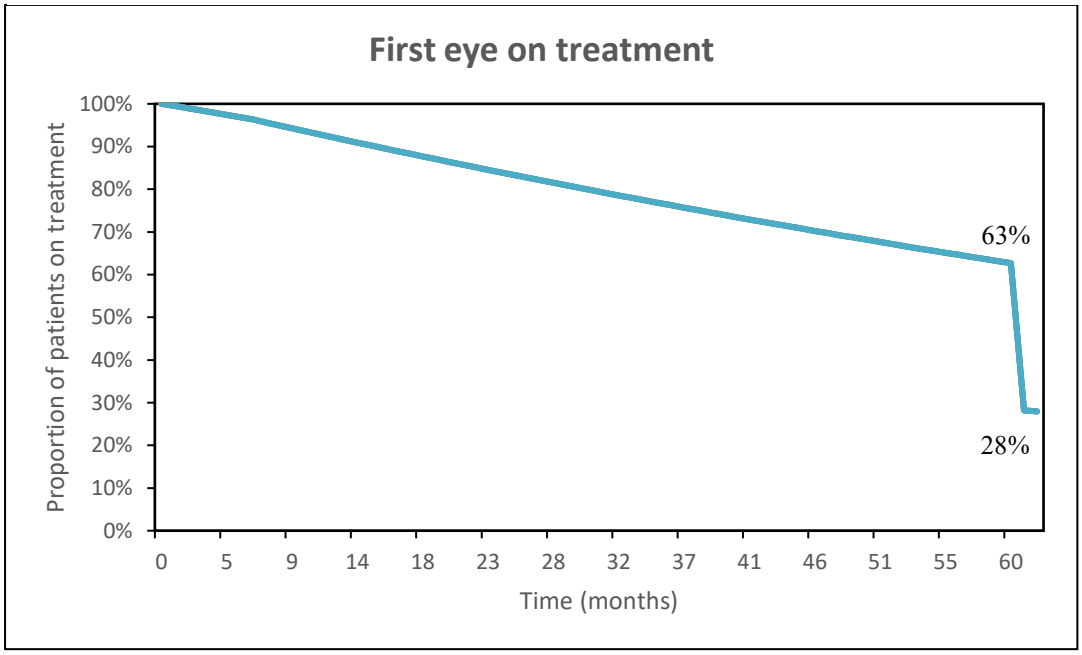
Based on Table 29 of the CS and the company's electronic model[3]
* Excluded as these are accounted for separately in the model

EAG comment: As mentioned above, the company assumes for the model that once patients discontinue, they will not move to another treatment option. This may be realistic for those patients discontinuing due to resolution of their disease but may not always be true for patients stopping treatment due to, for example, lack of effectiveness. During clarification, the EAG asked the company to what extent this is a realistic assumption, and how the results might change when switching to another

treatment would be allowed. The company cited studies that show indeed that a certain percentage of patients switch treatment either to an alternative anti-VEGF molecule, or to laser or steroid treatment.[22, 23] It would, however, be difficult to predict the impact of inclusion of switching on the cost comparison, given the confidential prices for many of the treatment options.

The EAG questions the approach the company used to estimate the percentage of patients still on treatment for the rest of life phase (starting after 60 months). In Figure 4.1 we see how the proportion of patients still on treatment (for their first eye) gradually declines to approximately 63% at 60 months, based on the 4-week discontinuation rates presented in Table 4.1.

Figure 4.1 Proportion of first eyes on treatment over time



Source: electronic model submitted by company;[3] percentages at 60 and 61 months added by EAG.

At that point (60 months) there is a sharp drop in the proportion of patients on treatment, as the company assumed that 55% of the 63% of patients still on treatment will discontinue treatment. As they state in their response to the clarification letter: "*UK clinical experts consulted by Roche suggested that in the majority of cases RVO could be well controlled with treatment, and patients would no longer receive anti-VEGF injections after 5 years of treatment. As a conservative assumption, and to reflect the findings in Scott 2022[21] meaning that a subset of patients may warrant long term treatment, out of those patients still on treatment after 5 years, about 55% are modelled to discontinue while 45% remain on treatment.*"

When applying the 55% discontinuation to the 63% that was still on treatment in month 60, it follows that from 61 months onwards only 28% (= 63*(100-55)%) of patients receive treatment for the first eye (see Figure 4.1). However, in the SCORE2 study, the value of 55% referred to the percentage of patients who did not attend the follow-up visit at 60 months out of those that started the long-term follow-up after having been treated for 1 year.[21] The interpretation of the company in applying the 55% clearly differs from the way the value was derived in the SCORE2 study.

In the current model, at 12 months 92% of the patients still receive treatment. Based on the SCORE2 study,[21] 45% of this 92% of patients should still be on treatment for the rest of life phase, which means that of patients who *started* treatment, 41% should be on treatment for the rest of life phase. In order to

find this percentage of 41% at 61 months, we need to assume that out of the 63% of patients still on treatment at 60 months, 35% will immediately discontinue.

If instead we follow the view of the scrutiny panel in TA799,[24] who preferred the scenario that 50% of patients with DMO have discontinued at 5 years, we need to assume that out of the 63% of patients still on treatment at 60 months, 20% will discontinue immediately.

In Section 4.6 the results are shown when using percentages discontinuation after 60 months of 35% and 20% for BRVO and CRVO.

4.4.3 Mortality

The company included mortality in the model by using general population all-cause mortality rates for 2020-2022, adjusted for the age and sex of the patient population in the BALATON[2] and COMINO[1] RCTs.[25] Furthermore, mortality was adjusted by applying hazard ratios (HRs) for patients being blind and visually impaired (HR 1.54 and 1.23).[26] The annual rate of mortality was assumed to be the same for faricimab, aflibercept, and ranibizumab.

4.4.4 Costs

- *Acquisition costs*

The acquisition costs for faricimab, aflibercept, and ranibizumab can be found in CS Table 28.[3]

- *Treatment frequency*

In the model base-case, it is assumed that the treatment phase consists of six injections each time with a 4-week interval. After that initial period of 24 weeks, the treatment frequency is based on the observed frequency for faricimab, which was guided by a protocol for personalised treatment intervals (PTI). The PTI protocol allowed for extension (or a reduction) of the period between injections in increments of 4 weeks up to 16 weeks, based on VA and CST (see Figure 4 of the CS[3]). Once the interval had had to be reduced, they could only extend the interval up to one level below the longest they had reached.

For aflibercept and ranibizumab, the same frequency of injections as for faricimab was assumed in each phase, based on the assumption that if the treatments are equivalent in terms of effectiveness, the frequency of receiving injections would also be equivalent.

The company also explored three other scenarios for the injection frequency for aflibercept and ranibizumab, based on frequencies from clinical trials with faricimab and ranibizumab.

1. The first scenario is the 'trial-based dosing' scenario, which is based on RCTs that used a T&E schedule for aflibercept and ranibizumab. Compared to the base-case, the yearly mean number of injections after week 24 is around 50% higher, which increases the total costs for aflibercept and ranibizumab (see Table 31 in the CS[3]).
2. The second scenario is based on clinical trials, where patients were regularly monitored, only receiving an injection when needed ('PRN dosing' scenario). See Table 31 in the CS for the number of injections and Table 32 for the sources for these values.[3]
3. The last scenario, 'proportional interval dosing' is based on the observed distribution of patients over the 'every 4 weeks', 'every 8 weeks', 'every 12 weeks', and 'every 16 weeks' schedule for each of the 3 treatment options (see Table 33 in the CS[3]).

EAG comment: During clarification, the EAG asked the company regarding the claim that the PTI protocol as used in the RCTs was conservative why this was so, and if a scenario could be defined that might be more reflective of clinical practice. The company explained that in the trial there was little possibility for patients whose treatment interval had been reduced to extend this interval again, whereas

in clinical practice this would not be a problem. This was illustrated with an exploratory post hoc analysis of patients who were downgraded from once every 8 weeks (Q8W) to Q4W in the faricimab arm. It showed that 90% of these patients could have extended the interval soon after the interval reduction, if the PTI protocol had not been in place.

As a scenario, the company assumed that after the 24-week treatment phase all patients would extend the treatment interval to 16 weeks, implying an annual number of injections of three. This scenario led to a decrease in the cost savings when treating patients with faricimab instead of aflibercept and ranibizumab (see Table 20 in the response to the clarification letter).[11]

- *Administration costs*

For the costs associated with an administration visit, it was assumed that intravitreal (IVT) injections would be administered in consultant led outpatient appointments, following an assessment of retinal fluid using optical coherence tomography (OCT) (see CS Tables 30 and 34 for unit prices).[3, 27, 28] The cost of performing an IVT injection was estimated as the difference in costs between an injection administration visit and a monitoring visit as calculated by the EAG in the appraisal of aflibercept for DMO (TA346).[27]

For visits where two eyes are treated, the company used a cost multiplier such that the total cost for treatment administration would be less than twice the costs of treating one eye (see TA346, page 285, based on physician survey).[27]

The scrutiny panel for the appraisal of faricimab in DMO and neovascular age-related macular degeneration preferred to assume that most IVT injections would be administered by others than consultants, the EAG performed a scenario analysis in which the cost price of a consultant led outpatient visit is replaced by that of a non-consultant led appointment.

- *Monitoring visits*

For the base-case and the non-PRN scenarios, a T&E regimen was followed, and the company assumed that in such a regimen patients will be monitored during their visit for an injection, i.e. no additional monitoring visits are necessary. This assumption was supported both by the clinical experts the company consulted, and the clinical expert consulted by the EAG.

For the PRN dosing scenario, it was assumed that aflibercept and ranibizumab patients would visit their doctor Q4W, and that at some of those, according to the values presented in Table 31 of the CS, an injection would be given. In the model, the difference between these two values represents the expected number of monitoring visits, as presented in Table 35 of the CS.[3]

The monitoring visit was assumed to comprise of a consultant led outpatient visit and an OCT to assess retinal fluid. Table 34 in the CS shows the unit costs for these resources.[3]

- *Adverse events*

The safety results from BALATON and COMINO[1, 2] found that the incidences of AEs was generally comparable across treatment arms and small (Section B.3.10.2, Table 16[3]). It should be noted though that patients in the COMINO[1] study were more likely to have a serious ocular AEs than patients in the BALATON[2] study.

The results of the NMA for ocular AEs, presented in Figure 9, Appendix D of the CS, show that there is little difference between faricimab, aflibercept and ranibizumab with regards to the likelihood of AEs occurring.[7] In the model, it is assumed that the safety of faricimab, aflibercept and ranibizumab is equivalent. Thus, the company decided not to include cost and resource use related to AEs, as they

expect that the omission of these costs from the analysis does not have a significant impact on the overall results.

4.5 EAG model check

The EAG conducted a range of checks on the company's cost-comparison model. This included a verification that the dosing scheme of the treatments in Microsoft® Excel® matched the described scheme in the CS and verification that the costs are in line with the costs described in the CS.[3] We also performed an inspection of the main formulae used in Microsoft® Excel®.

Main observations:

- The model included costs associated with vision loss in the model, however, the assumptions underlying these calculations and the data sources are not discussed in the CS.[3]
- For the base-case analysis, all elements of the model have been assumed to be the same between the three treatment arms, except for the cost of an injection. However, as can be seen in the base-case results, presented below in Table 4.1, there are (very) small differences in the administrations costs between the groups, where they should have been the same. The cause seems to be the distribution of patients over the four possible intervals between injections. This cannot easily be fixed, as the model was built in such a way that it does not allow for aflibercept and ranibizumab to be given in an interval of 16 weeks. However, the error is very small and is unlikely to be relevant for decision making.
- When patients discontinue treatment, they are assumed to follow a best supportive care (BSC) arm in the model. Various derivations of input for that arm are unclear and not described in Document B of the CS.[3] For example, during the maintenance phase patients are assumed to experience a reduction in VA, which was estimated based on the sham arm in the CRUISE trial,[29] which showed after 6 months a gain in letter score of 0.8, with SD of 16.2. In the model a normal distribution in letter score is assumed, which is used to estimate the percentage of patients who have lost one VA state, and the percentage who have lost two VA states. That normal distribution, however, uses a SD of 8, essentially halving the observed SD. It is unclear why this was done. In addition, it is also not clear why the model only permits patients to deteriorate in the BSC arm, when 16% of patients in the sham arm showed a gain of over 15 letters.
- On the Cost Inputs sheet, the distribution of patients over the Q4W to Q16W states is calculated for aflibercept and ranibizumab. However, no explanation is provided about how this was done. For example, the percentage in Q4W for ranibizumab is estimated with this formula: =NORM.DIST(6,6.6,ABS(5.2-8)/4,TRUE). It is clear that the first six reflects the midpoint between 4 weeks and 8 weeks, but no information has been provided about the other (hardcoded) values in this formula. Similarly, for aflibercept the formula =NORM.DIST(6,9.7,(3.8*2)/4,TRUE) was used without any explanation for the mean and SD used.

4.6 Company's model results

The company base-case cost comparison results compare the total costs for faricimab, aflibercept, and ranibizumab. For faricimab the PAS price was used whilst list prices were used for aflibercept and ranibizumab (see CS Table 69).[3] Results using discounted prices for aflibercept and ranibizumab as well can be found in the confidential appendix to this report.

Uncertainty over model assumptions was assessed with one-way sensitivity analyses and scenario analyses (response to clarification letter Tables 12 and 13).[11]

The results of the company's base-case analysis as well as from the sensitivity and scenario analyses are reported in the company's response to the clarification letter in Tables 21 to 24,[11]as the original results in the CS contained also the productivity gains, informal costs, and travel costs (thus not in agreement with the NHS perspective).[3] In the revised company's analysis, the EAG found that for the CVRO population, the total costs still included productivity gains. Thus, the base-case results that are presented in Table 4.2 below is a corrected version of Table 21 in the company's response to the clarification letter.[11]

From Table 4.2 below, it is clear that treatment with faricimab of patients with RVO is cost-saving compared to aflibercept and ranibizumab, both for those with BRVO or CRVO.

The conclusion that faricimab is a cost saving strategy compared to aflibercept and ranibizumab applies also to all the sensitivity analyses performed by the company. The outcome is extremely sensitive to changes in the dosing regimen assumed for aflibercept and ranibizumab; for ranibizumab PRN and ranibizumab T&E, [redacted] For most scenario analyses the cost-savings [redacted] but assuming that the average age of the population is 75 years [redacted] In addition, the scenario in which all patients move to a 'once every 16 weeks' schedule after the first 24 weeks [redacted]

Table 4.2: Company base-case (25 year time horizon, discounted)

Cost category	Costs faricimab (PAS price)		Costs aflibercept (list price)		Costs ranibizumab (list price)	
	BRVO	CRVO	BRVO	CRVO	BRVO	CRVO
Drug cost	[redacted]	[redacted]	£35,856	£34,551	£24,228	£23,350
Administration cost	[redacted]	[redacted]	£15,543	£15,096	£15,553	£15,108
Additional monitoring cost	£0	£0	£0	£0	£0	£0
AE management cost	£0	£0	£0	£0	£0	£0
Costs of visual impairment	£1,313	£760	£1,313	£760	£1,313	£760
Mean total cost	[redacted]	[redacted]	£52,712	£50,407	£41,094	£39,218
Incremental cost versus faricimab	N/A		[redacted]	[redacted]	[redacted]	[redacted]

Source: Table 21 response to clarification letter[11] with EAG correction to total cost and incremental cost for CRVO
AE = adverse events; BRVO = branch retinal vein occlusion; CRVO = central retinal vein occlusion; EAG = External Assessment Group; N/A = not applicable; PAS = Patient Access Scheme

4.7 EAG exploratory analysis

The EAG undertook two additional exploratory analyses using the company's Microsoft® Excel® model as submitted in response to the clarification letter. The analyses presented in this Section reflects the PAS discount price for faricimab whilst list prices were used for aflibercept and ranibizumab. Results using discounted prices for aflibercept and ranibizumab are shown in a confidential appendix to this report.

The first analysis is regarding the percentage of patients discontinuing treatment after 60 months, as discussed in Section 4.4.2, and the second analysis replaces the consultant led visit for an injection by a non-consultant led visit. Tables 4.3 and 4.4 present the results for BRVO and CRVO, respectively.

Table 4.3: EAG scenarios BRVO

Scenario	Base-case	Scenario	Incr. cost versus aflibercept	% change from base-case incr. cost	Incr. cost versus ranibizumab	% change from base-case incr. cost
Base-case	-	-	[redacted]	-	[redacted]	-
% discontinuing after 60 months	55%	35%	[redacted]	[redacted]	[redacted]	[redacted]
		20%	[redacted]	[redacted]	[redacted]	[redacted]
Care professional giving injection	Consultant led £143.93	Non-consultant led £105.46	[redacted]	[redacted]	[redacted]	[redacted]
BRVO = branch retinal vein occlusion; EAG = External Assessment Group; Incr. = incremental						

Table 4.4: EAG scenarios CRVO

Scenario	Base-case	Scenario	Incr. cost versus aflibercept	% change from base-case incr. cost	Incr. cost versus ranibizumab	% change from base-case incr. cost
Base-case	-	-	[redacted]	-	[redacted]	-
% discontinuing after 60 months	55%	35%	[redacted]	[redacted]	[redacted]	[redacted]
		20%	[redacted]	[redacted]	[redacted]	[redacted]
Care professional giving injection	Consultant led £143.93	Non-consultant led £105.46	[redacted]	[redacted]	[redacted]	[redacted]
CRVO = central retinal vein occlusion; EAG = External Assessment Group; Incr. = incremental						

5. EAG commentary on the robustness of evidence submitted by the company

The company's evidence appears to be robust enough to confirm comparability of efficacy and safety between faricimab and aflibercept given relatively high quality RCT data on most major outcomes (the NMA omitted HRQoL). It also is largely robust enough to confirm equivalence versus ranibizumab, although with more uncertainty given the use of an NMA, which showed some variation in results.

However, this equivalence is dependent on identical dosing in the trials, which is Q4W, and which is not the case according to the MA, guidelines or according to clinical expert opinion, where a T&E approach would be used. If T&E was implemented identically for all treatments, as is assumed in the company economic model, then equivalence might also be assumed. The real-world study reported by the company does seem to show equivalence of dosing interval in clinical practice between aflibercept and ranibizumab and that the dosing interval in the trials might be at least as long. However, the EAG clinical expert has cast doubt on this given his assertion that the dosing interval for aflibercept would probably be much greater than for ranibizumab to achieve the level of effect. This might still not be a problem for the comparison with ranibizumab if, as the clinical expert suggests, ranibizumab is not actually used in clinical practice. However, it might be an issue for the comparison with aflibercept. It is unclear what the dosing interval for faricimab might be in clinical practice.

The clinical expert also questioned the validity of omitting dexamethasone implant as a comparator, suggesting that he might use it on 20% of patients, the other 80% receiving aflibercept. In fact, although faricimab was superior to SD dosing of dexamethasone implant, the NMA seemed to show equivalence with dexamethasone 0.5 mg PRN, which might be closer to how the implant is given in clinical practice i.e. repeated every 4 to 6 months as required.

The EAG also would also suggest that the evidence, particularly from the BALATON and COMINO RCTs,[1, 2] is most applicable to the following subgroup of the population in the NICE Final Scope: omitting children, those without a visual impairment or anyone with anti-VEGF treatment experience.[6]

The model structure for the current cost-comparison can be regarded as reasonable, and is in line with the models used for e.g. TA799[18] and TA800.[19] The assumption that patients who discontinue their treatment do not receive further treatment leads to an underestimation of the total costs per treatment arm but the impact on the incremental costs between faricimab and its comparators is unclear.

The model assumes equal clinical efficacy for all three drugs. For the first 24 weeks this is supported by the NMA, but after that, no evidence is available for the equivalence of faricimab, aflibercept, and ranibizumab.

With the PAS price for faricimab and list prices for aflibercept and ranibizumab, faricimab is estimated to be [redacted] compared to the two comparators. This applies for the company's revised base-case analysis and for all the company and EAG scenario analyses. The outcome is very sensitive to changes in the dosing regimen assumed for aflibercept and ranibizumab; for ranibizumab PRN and ranibizumab T&E, [redacted] In contrast, the (relatively extreme) scenario in which all patients move to a Q16W schedule after the first 24 weeks, [redacted] Results with the PAS discounts for faricimab and ranibizumab and the Commercial Medicines Unit (CMU) discount for aflibercept are shown in a confidential appendix to this report.

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