NICE National Institute for Health and Care Excellence

Fast Track Appraisal

Faricimab for treating diabetic macular oedema [ID3899]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

FAST TRACK APPRAISAL

Faricimab for treating diabetic macular oedema [ID3899]

Contents:

The following documents are made available to consultees and commentators:

Final Scope and Final Stakeholder list

1. **Technical Briefing**

2. **Company cost comparison submission** from Roche Products

3. **Clarification questions and company responses**
   a. Clarification response
   b. Additional response post Scrutiny decision

4. **Patient group, professional group and NHS organisation submission** from:
   a. Diabetes UK
   b. Macular Society
   c. Royal National Institute of Blind People
   d. The College of Optometrists
   e. Royal College of Ophthalmologists

5. **Expert personal perspectives** from:
   a. Mr Jagdeep Singh – clinical expert, nominated by The College of Optometrists
   b. Professor Richard Gale – clinical expert, nominated by Novartis
   c. Mrs Bernadette Warren – patient expert, nominated by the Macular Society
   d. Mr Stephen Scowcroft – patient expert, nominated by the Macular Society

6. **Evidence Review Group report** prepared by SHTAC

7. **Evidence Review Group report – factual accuracy check**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NICE National Institute for Health and Care Excellence

Faricimab for treating diabetic macular oedema (DMO) and wet age-related macular degeneration (AMD)

Fast track appraisal

Lead team: Steve O'Brien, Matt Stevenson, Andrew Renehan, Ugochi Nwulu

ERGs: Southampton (DMO) and Warwick (AMD)

Technical team: Cara Gibbons, Alex Filby, Ross Dent

Company: Roche

Faricimab

Marketing authorisation	Faricimab will be indicated for the treatment of adults with: • visual impairment due to diabetic macular oedema (DMO) • neovascular (wet) age-related macular degeneration (nAMD) • Faricimab is being licensed in the UK through the MHRA
Mechanism of action	Faricimab is a humanised bispecific immunoglobulin G1 (IgG1) antibody that acts through inhibition of two distinct pathways by neutralisation of both angiopoietin-2 (Ang-2) and vascular endothelial growth factor A (VEGF-A).
Administration	IVT injection
SmPC	The recommended dose is 6 mg administered by intravitreal injection every 4 weeks for the first 4 doses. Thereafter, based on the qualified healthcare professional trained in intravitreal injection's judgement of the individual patient's visual and/or anatomic outcomes, the dosing interval may be extended up to every 16 weeks (4 months), in increments of 4 weeks
Price	List - £857 per injection PAS - [redacted] per injection

Treatment pathway

People with vision impairment due to diabetic macular oedema (DMO) and the eye has a central retinal thickness of 400 µm or more at the start of treatment

OR

People with wet age-related macular degeneration (AMD) if:

- there is no permanent structural damage to the central fovea,
- the best-corrected visual acuity is between 6/12 and 6/96,
- the lesion size is less than or equal to 12 disc areas in greatest linear dimension
- there is evidence of recent presumed disease progression (blood vessel growth, as indicated by fluorescein angiography, or recent visual acuity changes)

1st line treatment

Aflibercept	Ranibizumab	Proposed: Faricimab
(TA346 - DMO)	(TA274 - DMO)	(ID3899 - DMO)
(TA294 - AMD)	(TA155 – AMD)	(ID3898 – AMD)

Clinical trial evidence: aflibercept

Clinical trials: DMO - YOSEMITE and RHINE, AMD - TENAYA and LUCERNE

Primary outcome: mean change from baseline to 1 year in best-corrected visual acuity

Clinical effectiveness

- In the ITT population for the DMO and AMD trials, faricimab was non-inferior to aflibercept in the primary outcome.
  - **DMO**: 11.2 and 10.5 letters – difference 0.6 letters (95% CI: -0.4, 1.7)
  - **AMD**: 6.2 vs 5.9 letters - difference 0.4 letters (95% CI: -0.9 to 1.6)
- Non-inferior results were also seen in other secondary outcomes.
- Adverse events are likely to be similar between faricimab and aflibercept

CRT ≥400 µm subgroup analyses (DMO):

- In ID3899 for DMO, the company did not pre-specify a stratification of CRT </> 400µm so the company broke randomisation to provide subgroup analyses. ID3898 for AMD, the ITT population is correct for this FTA recommendation.
- In the ITT population [redacted] had a CRT ≥400 µm. This was similar across treatment arms.
- Findings showed [redacted](faricimab PTI and aflibercept [YOSEMITE [redacted]; RHINE [redacted]]).

Overall, the scrutiny panel considered faricimab is likely to have similar clinical effectiveness as aflibercept

NMA: ranibizumab

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Note: clinical experts advised that aflibercept is more effective and more commonly used of the two comparators

[redacted]

[redacted]

AMD - The ERG agreed that the company's claim of faricimab non-inferiority was supported through the company's NMA.

DMO - The ERG have several concerns which they believe may render these analyses potentially unreliable for decision-making. These included:

- The ranibizumab 0.3mg dose used is not recommended or used in clinical practice
- The statistical methods used for the meta-regressions were inappropriate.
- The applicability to the target population is uncertain.
- [redacted].

Company base-case

Includes treatment and comparator discounts

	Faricimab	Aflibercept	Ranibizumab
Acquisition cost	[redacted]	[redacted]	[redacted]
DMO			
Mean total cost	[redacted]	[redacted]	[redacted]
Incremental cost vs faricimab	N/A	[redacted]	[redacted]
AMD			
Mean total cost	[redacted]	[redacted]	[redacted]
Incremental cost vs faricimab	N/A	[redacted]	[redacted]

DMO	Year 1	Year 2	Year 3+
Faricimab	8.42	4.73	1.90
Aflibercept	9.20	5.00	2.37
Ranibizumab	9.40	5.40	2.17

AMD	Year 1	Year 2	Years 3+
Faricimab	6.79	4.69	3.25
Ranibizumab	9.13	7.14	4.00
Aflibercept	8.00	5.63	4.00

Scrutiny panel scenario: results

SPC dosing in yr 1 (completed doses only); T&E in subsequent years

Incremental cost	Faricimab vs aflibercept	Faricimab vs ranibizumab
AMD - Scrutiny panel scenario	[redacted]	[redacted]
DMO:		
Scrutiny panel scenario	[redacted]	[redacted]
Scenario 1 – 70% discontinuation	[redacted]	[redacted]
Scenario 2 – include OCT cost	[redacted]	[redacted]
Combined scenario 1 +2	[redacted]	[redacted]
Scenario 3 – company base case injection and monitoring visits	[redacted]	[redacted]

SPC dosing in yr 1 (including proportions of planned doses after month 12)

Incremental cost	Faricimab vs aflibercept	Faricimab vs ranibizumab
AMD – Scrutiny panel scenario	[redacted]	[redacted]
DMO:		
Scrutiny panel scenario	[redacted]	[redacted]
Scenario 1 – 70% discontinuation	[redacted]	[redacted]
Scenario 2 – include OCT cost	[redacted]	[redacted]
Combined scenario 1 +2	[redacted]	[redacted]

Additional scenarios 1, 2 and 3 are the company's preferred assumptions in response to the scrutiny panel scenario for DMO.

Scrutiny panel assumptions

- Year 1 injections based on the loading phases for each treatment as per SPC, followed by a T&E regimen for all treatments
- Number of injections should be the same for all treatments in subsequent years based on T&E
- Monitoring visits should be the same across arms.
- 50% discontinuation
- No OCT procedure for injection visits[7]

Potential recommendation?

The lead team concluded at the pre-meeting briefing that they were comfortable making a recommendation for ID3899 (DMO) and ID3898 (AMD) without a committee meeting based on the evidence provided.

Recommendations would be in line with the wording of previous aflibercept (TA346 – DMO, TA294 – AMD) and ranibizumab (TA274 – DMO, TA155 – AMD) guidance and would include:

- "If patients and their clinicians consider faricimab to be 1 of a range of suitable treatments, choose the least expensive (taking into account administration costs and commercial arrangements)"

Back up slides

The following slides contain more detail about the scrutiny panel decision making for DMO.

DMO: clinical & patient experts & professional groups

Professional organisations

- Faricimab has shown encouraging results that the treatment effect may last longer than current treatment options.
- Further investigation will be needed to provide recommendations on the appropriate intervals between treatment.

Patient experts

- Faricimab offers real hope for those who are yet to respond positively to treatment.
- The numbers of people with DMO is increasing and the treatment burden on patients and carers is significant and longer acting drugs can help to reduce this
- Patients should not have to wait for their vision to deteriorate before they can be treated - the ‘too good to treat’ situation.

Clinical experts

- Faricimab may dry the retina better than its comparator but the significance of this is unknown and requires further investigation.
- No clinically meaningful new safety signals have been identified
- Clarity on treatment posology recommendations that are easily implemented, are required. Patient and clinician education will be required.
- There is an unmet need of treatments to provide, better efficacy with reduced burden on patients and services

DMO: dosing assumptions

Company dosing assumptions:

	Faricimab "PTI"	Aflibercept	Ranibizumab
Dose	6 mg	2 mg	0.5 mg
Dosing regimen	Loading phase → T&E →PRN	Loading phase →PRN	Loading phase →PRN

Professional organisation: aflibercept and ranibizumab are both recommended to be more effective on a T&E regime rather than PRN.

NICE clinical experts:

- The faricimab PTI arm dosing used in the trial is too complex for clinical practice.
- Many clinicians may use either a simpler T&E approach after the loading phase or less commonly, a form of PRN posology.
- Most centres use predominantly one drug or another. Many clinicians will use the same dosage for either treatment, especially if both treatments are used in one centre to reduce posology error.
- There is inconsistency as different treatments exist and a number of different posologies have been studied.
  - This has led to treatment switching and different patients receiving different doses of the same drug.

The scrutiny panel preferred to use T&E for all treatments

Note: T&E = a regimen that allows extension of treatment intervals in the absence of disease activity. PRN = "as required" regimens involve frequent, often monthly visits where an injection is given only after the reoccurrence of disease activity.

DMO: Injection visits assumptions

Company assumptions:

	Year 1	Year 2	Year 3+
Faricimab	Trial data	Trial and Protocol T	Trial and Protocol T
Aflibercept	PRN dosing from the NMA	Protocol T	Trial and Protocol T
Ranibizumab	PRN dosing from the NMA	Protocol T	Protocol T

- Year 1 injection visits for comparators is higher than what was assumed and accepted in TA346. They were similar for year 2.

ERG:

- The number of injection administration visits does not reflect clinical practice.
  - Clinical experts suggest there are less than 9 injection visits in year 1 and fewer thereafter, reflecting NHS capacity limitations.
- Did scenario analyses; a) varied the number of visits between 6 and 8 in year 1 and between 2 and 4 in year 2, b) assumed visits were similar across the DMO treatments

Scrutiny panel preferred a conservative scenario using the same number of injections in each arm after loading dose

Protocol T = a phase III clinical trial that compares ranibizumab, aflibercept and intravitreal bevacizumab in people with diabetic macular oedema. It assumed a PRN regimen for each arm.

DMO: injection visit resource use

Company:

- One injection visit = cost of administering the injection + consultant led outpatient appointment + and assessment of retinal fluid using OCT (£282.22 - 2021).
  - Assumed the same across faricimab, aflibercept and ranibizumab.
  - Similar to the assumptions made in TA346 (£193.76 - 2012).

ERG:

- In UK clinical practice, most IVT injections are administered by specialist nurses and optometrists.
- OCT procedure is unlikely to be performed during an injection administration visit in the initial doses.
- Often vision testing and OCT are performed prior to an injection.
- Ran scenario removing the OCT cost during injection visits from the company base case.

The scrutiny panel preferred to remove OCT from the injection visit and use a non-consultant led appointment

NICE

Note: if all visits are assumed equal after year 1 (as preferred by scrutiny panel), OCT impact on cost comparison results should be negligible

DMO: monitoring visits assumptions

Company:

- Faricimab: no monitoring visits for the first 2 years based on a T&E approach.
- Comparators: assumed a PRN regimen, so additional monitoring visits applied to all years of the model based on the average number of visits in Protocol T.
- All treatments in years 3-5 were based on a PRN regimes. This dosing schedule assumes more monitoring visits than TA346.

ERG:

- Clinical experts said faricimab is likely to have the same monitoring visits as the comparators
- The comparator monitoring visits appear to be lower than what is observed in NHS clinical practice.

NICE's clinical experts

- Changes to the SmPC for ranibizumab may mean more clinicians will use a T&E approach and reduce the number of monitoring visits.
- Aflibercept SmPC recommends a loading phase, then no monitoring required between injections for the first year - base case needs revising down for the first 2 years to reflect this i.e., zero if not close to zero.
- Reasonable to assume that at year 3, more monitoring visits will be required (ERG scenario)

The scrutiny panel preferred to set monitoring visits equal across treatment arms

DMO treatment discontinuation

Company

- Model assumed a treatment duration of 5 years from baseline, applied to the study eye.
- 85% of those alive and on treatment were assumed to discontinue treatment and 15% remained on treatment to reflect that some people with DMO require long-term treatment.
- If bilateral DMO had developed, the second eye is also treated for a maximum of 5 years after bilateral DMO diagnosis.

ERG

- Expert clinical advice is that the treatment duration assumption aligns more with neovascular oedema than DMO.
- In DMO, the on/off treatment cycle could go back and forth
- In clinical practice, 50% of people who are alive would discontinue treatment after 5 years.

The scrutiny panel preferred a 50% discontinuation scenario

Scrutiny panel conclusions

- Cost-comparison appropriate methodology because faricimab is likely to be similarly clinically effective compared with comparators.
- Faricimab has [redacted] than the main comparator, aflibercept. (**A new PAS has been submitted since the scrutiny panel decision, acquisition costs [redacted]).**
- Given the complexity of the proposed faricimab dosing regimen and NHS pressures, the scrutiny panel requested a new scenario.

Scrutiny panel assumptions:

1. 50% treatment discontinuation at 5 years
2. Non-consultant led appointments for treatment and monitoring
3. No OCT procedure for injection administration
4. Monitoring visits should be the same across arms.
5. Year 1 injections based on the loading phases for each treatment as per SPC, followed by a T&E regimen for all treatments
6. Number of injections should be the same for all treatments in subsequent years based on T&E

Company response:

- Acknowledge the amount of people on treatment beyond 5 years is uncertain.
- The request fails to recognise that treatment intervals could be extended further and with more confidence on faricimab than aflibercept or ranibizumab after year 1.
- Year 2 injection assumptions are from 2014. UK clinical experts in 2021, validated the company base case assumptions so are more representative of current clinical practice.

DMO: summary of company, scrutiny panel assumptions & company response

	Company base case	Scrutiny panel view	Company response
Discontinuation rate	85% at 5 years	50% at 5 years	A midpoint of 70% would be a more appropriate.
Injection visit frequency	Faricimab T&E, comparators PRN	T&E most plausible for all treatments after the initial loading phase.	Faricimab T&E, comparators PRN
Injection visit resource cost	Each visit is consultant led and includes the cost of an OCT	Replace consultant cost with non-consultant led visit and remove OCT at injection visits.	Include the cost of OCT procedures during injection visits (used to determine whether treatment intervals should be changed or maintained).
Monitoring visit frequency	Faricimab T&E, comparators PRN	T&E most plausible for all treatment and visits should be equal for faricimab and comparators	Additional monitoring is required for PRN, but not T&E.

ERG response : Agree treatment intervals could be extended on faricimab.

- However, the company does not present a relative comparison of the extension of treatment intervals for faricimab vs aflibercept and ranibizumab, and so this is based on expert opinion. Uncertainty around Q16W dosing could be reduced if 2-year trials results become available.

Scrutiny panel scenario: results

Dosing regimen	Injections			Monitoring visits		
	Year 1	Year 2	Year 3+	Year 1	Year 2	Year 3+
Scenario 1 - SPC dosing in year 1 (completed doses only); T&E in subsequent years						
Faricimab (LP → T&E)	6	4	2	0	0	2
Aflibercept (LP → T&E)	8	4	2	0	0	2
Ranibizumab (LP → T&E)	8	4	2	0	0	2
Scenario 2 - SPC dosing in year 1 (including proportions of planned doses beyond month 12); T&E in subsequent years						
Faricimab (LP → T&E)	6.75	4	2	0	0	2
Aflibercept (LP → T&E)	8.5	4	2	0	0	2
Ranibizumab (LP → T&E)	8.5	4	2	0	0	2

Cost	Faricimab	Aflibercept	Ranibizumab
Scenario 1 (Incremental cost vs faricimab)			
DMO	N/A	[redacted]	[redacted]
AMD	N/A	[redacted]	[redacted]
Scenario 2 (Incremental cost vs faricimab)			
DMO	N/A	[redacted]	[redacted]
AMD	N/A	[redacted]	[redacted]

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Faricimab is [redacted] compared to [redacted]

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Fast track appraisal: cost-comparison case

Faricimab for treating diabetic macular oedema [ID3899]

Document B

Company evidence submission

October 2021

File name	Version	Contains confidential information	Date
ID3899_Faricimab for DMO_Doc B_REDACTED_RPL 151121	3.0	No	15 November 2021

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Tables and figures

Tables

Figures

Abbreviations

AE	Adverse events
AESI	Adverse events of special interest
ALT	Alanine aminotransferase
AMD	Age-related macular degeneration
APTC	Antiplatelet Trialists' Collaboration
ARVO	The Association for Research in Vision and Ophthalmology
AST	Aspartate transferase
AWE	Average weekly earnings
BCVA	Best corrected visual acuity
CCOD	Clinical cut-off date
CFT	Central foveal thickness
CMH	Cochran Mantel-Haenszel
CMT	Central macular thickness
CRC	Central reading centre
CRT	Central retinal thickness
CSR	Clinical study report
CST	Central subfield thickness
DIC	Deviance information criterion
DMO	Diabetic macular oedema
DR	Diabetic retinopathy
DRCR	Diabetic Retinopathy Clinical Research Network
DRSS	Diabetic Retinopathy Severity Scale
DSA	Deterministic sensitivity analysis
ETDRS	Early Treatment Diabetic Retinopathy Study
FTA	Fast track appraisal
ILM	Internal lifting membrane
IOI	Intraocular Inflammation
IRF	Intraretinal fluid
ITC	Indirect treatment comparison
ITT	Intention to treat
IVT	Intravitreal injection
LOCF	Last observation carried forward
LP	Loading phase
LPLV	Last patient last visit
MAA	Marketing authorisation application
MAR	Missing at random
MMRM	Mixed model for repeated measures
MNAR	Missing not at random

NEI-VFQ 25	National Eye Institute-Visual Function Questionnaire 25
NMA	Network meta-analysis
NPDR	Non-proliferative diabetic retinopathy
ONS	Office for National Statistics
PAS	Patient access scheme
PDR	Proliferative diabetic retinopathy
PRN	Treatment as needed
PSS	Personal social services
PTI	Personalised treatment interval
QXW	One injection every x weeks
RCT	Randomised clinical trial
SAE	Serious adverse event
SAP	Statistical analysis plan
SD-OCT	Spectral-domain optical coherence tomography
SLR	Systematic literature review
T&E	Treat and extend
VA	Visual acuity
VEGF	Vascular endothelial growth factor

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 Decision problem

Population

The submission covers the technology's full marketing authorisation for this indication.

The submission covers the full population for the comparator, as recommended by NICE.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with visual impairment because of diabetic macular oedema	People with visual impairment because of diabetic macular oedema	N/A in line with NICE final scope
Intervention	Faricimab	Faricimab	N/A in line with NICE final scope
Comparator(s)	• Laser photocoagulation alone The following technologies alone or in combination with laser photocoagulation: • Aflibercept • Bevacizumab (does not currently have a marketing authorisation in the UK for this indication) • Dexamethasone intravitreal implant • Fluocinolone acetonide intravitreal implant • Ranibizumab	• Aflibercept • Ranibizumab	Bevacizumab is not a relevant comparator as it is neither standard of care nor has a marketing authorisation in the UK for DMO. Moreover, bevacizumab has an estimated market share in DMO of [redacted] in the UK – this is derived from national market share data from January to April 2021 therefore, bevacizumab cannot be considered established clinical practice in the NHS for DMO. Laser photocoagulation is no longer the standard of care for DMO since the availability of intravitreal (IVT)-based treatments, therefore this is not considered a relevant comparator (1). Dexamethasone (TA349) and fluocinolone acetonide (TA301) are recommended by NICE for patients who are unresponsive to non-steroidal treatments (and not specifically for patients with central retinal thickness [CRT] ≥400 µm), and are thus positioned as second-line treatments. Faricimab is positioned as a first-line treatment option for patients with CRT ≥400 µm, therefore dexamethasone and

			fluocinolone acetonide are not considered to be relevant comparators
Outcomes	The outcome measures to be considered include: • Best corrected visual acuity (BCVA) (affected eye) • Best corrected visual acuity (both eyes) • Central foveal subfield thickness • Central retinal thickness • Contrast sensitivity • Disease severity • Intraretinal and subretinal fluid • Mortality • Need for cataract surgery • Adverse effects of treatment • Health-related quality of life.	• Best corrected visual acuity (affected eye) • Best corrected visual acuity (both eyes) • Central subfield thickness • Intraretinal and subretinal fluid • Mortality • Adverse effects of treatment, including cataracts and glaucoma • Health-related quality of life, including the effects of changes in visual acuity	In line with TA274 (2), best corrected visual acuity outcomes are presented. Information on contrast sensitivity was not measured in the pivotal trials YOSEMITE and RHINE.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost-comparison may be carried out. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.	A cost-comparison model has been developed to undertake a cost-comparison of faricimab versus aflibercept and ranibizumab. A lifetime time horizon (25 years) has been adopted. This time horizon is considered to be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared All costs are considered from an NHS and PSS perspective	Faricimab should be appraised through the NICE FTA cost-comparison process, with aflibercept and ranibizumab as the existing licensed and NICE recommended comparator (2, 3). The results of the YOSEMITE and RHINE trials demonstrate faricimab to be associated with comparable efficacy in terms of BCVA versus aflibercept that is achieved with a lower injection frequency, as well as a comparable safety profile (4). The results of the anatomical outcomes, namely a greater reduction in CST, higher proportion of patients with absence of DMO, and absence of IRF, suggest a trend of improved vascular stability with both faricimab

	Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability of any managed access arrangement for the intervention will be taken into account. Cost effectiveness analysis should include consideration of the benefit in the best and worst seeing eye.		treatment regimens compared with aflibercept Q8W and provide robust evidence for the improved duration of treatment effect (4). The results of the NMA detailed in Section B.3.8 also demonstrate faricimab to be associated with comparable efficacy in terms of BCVA and safety compared with both aflibercept and ranibizumab.
Subgroups to be considered	• type of DMO (focal or diffuse, central involvement, ischaemic or non-ischaemic maculopathy) • duration of DMO • baseline visual acuity • baseline central retinal thickness • previous treatment history (including people who have received no prior treatment, and those who have received and/or whose disease is refractory to laser photocoagulation, ranibizumab or bevacizumab) • prior cataract surgery	• Change from baseline in BCVA at Week 48/52/56 across baseline demographic subgroups	Data was not available to present subgroup analyses for all of the specific groups in the scope. No economic subgroup analyses are deemed relevant for this appraisal. Analysing the primary endpoint (change from baseline in BCVA) at Week 48/52/56 was across various baseline demographic subgroups (e.g. by age, gender, race, baseline HbA1c, baseline visual acuity, prior intravitreal anti VEGF therapy) found subgroup results were consistent with the overall population.
Special considerations including issues related to equity or equality			If a person is registered as blind or partially sighted they are considered disabled, as stated in the Equality Act 2010. Therefore, the patient population addressed in this submission is a protected group under this act.

B.1.2 Description of the technology being appraised

Table 2: Technology being appraised

UK approved name and brand name	Faricimab [redacted]
Mechanism of action	Faricimab is a humanised bispecific immunoglobulin G1 (IgG1) antibody that acts through inhibition of two distinct pathways by neutralisation of both angiopoietin-2 (Ang-2) and vascular endothelial growth factor A (VEGF-A). Ang-2 causes vascular instability by promoting endothelial destabilisation, pericyte loss, and pathological angiogenesis, thus potentiating vascular leakage and inflammation. It also sensitises blood vessels to the activity of VEGF-A resulting in further vascular destabilisation. Ang-2 and VEGF-A synergistically increase vascular permeability and stimulate neovascularisation. By dual inhibition of Ang-2 and VEGF-A, faricimab reduces vascular permeability and inflammation, inhibits pathological angiogenesis and restores vascular stability. See B.1.3.3 for further details
Marketing authorisation/CE mark status	A Marketing Authorisation Application (MAA) was submitted to the European Medicines Agency (EMA) in [redacted]; regulatory approval is anticipated in [redacted] in the EU. A submission for marketing authorisation of faricimab was made to the MHRA in [redacted], via the MHRA ACCESS route; approval is anticipated [redacted].
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Faricimab will be indicated for the treatment of adults with: • [redacted] • [redacted]
Method of administration and dosage	The recommended dose for faricimab is 6.0 mg (0.05 mL solution) administered by IVT injection [redacted]
Additional tests or investigations	None required
List price and average cost of a course of treatment	£857
Patient access scheme/commercial arrangement (if applicable)	[redacted]

B.1.3 Health condition and position of the technology in the treatment pathway

B.1.3.1 Disease overview

Diabetic retinopathy (DR) is a common microvascular complication of diabetes that can lead to vision loss and blindness (6). The disease is one of the leading causes of vision impairment in the working age population (7-11), accounting for 2.5% of all blindness and 1.4% of all moderate and severe vision impairment (12).

Diabetic macular oedema (DMO) is a serious manifestation of DR and is the primary cause of central vision loss among patients with DR (13, 14). DMO can develop at any stage of DR severity (15), with the average age of patients with DMO being dependent on the diabetes type; a mean age of 60–70 years is reported in patients with Type 2 diabetes (16, 17), and a mean age of 37–50 years reported in patients with Type 1 diabetes (17, 18). If left untreated, DMO can lead to a loss of 10 or more letters in visual acuity (VA) within 2 years in approximately 50% of patients (19).

In 2019, there were an estimated 29 million prevalent cases of DMO worldwide, and this is expected to increase by 45% to 42 million by 2030 (20). It is estimated that 7.5% of patients with diabetes aged 20–79 years have DMO (21). In the UK, the diabetic screening programme showed the 5-year cumulative incidence in type 2 diabetes mellitus of any DR was 36%, proliferative DR (PDR) 0.7% and DMO 0.6%, which approximately doubled at the 10-year time point to 66%, 1.5%, and 1.2% respectively (22). The worldwide population of people living with diabetes is estimated to grow from approximately 463 million in 2019 to 548 million by 2045 (23); therefore, the global burden of DMO is expected to increase significantly, with considerable public health, socioeconomic, and quality of life (QoL) consequences due to the combined impact on patients, caregivers, family members, and healthcare professionals (24, 25).

Pathogenesis

DMO is a complication of diabetes in which persistent hyperglycaemic conditions in the retina lead to several biochemical changes, resulting in microvascular dysfunction and increased vascular permeability (26-28). Pathological processes in the retinal vasculature that can contribute to the development of DMO are breakdown of the inner blood-retina barrier due to alteration of the intercellular junction proteins, increased transendothelial transport, loss of cells constituting the barrier (endothelial cells, pericytes, and microglial cells), monocyte and leukocyte attachment to the vascular wall (leukostasis), and development of pathological neovascularisation (28, 29).

As a result of the breakdown of the inner blood-retina barrier in patients with DR, fluid and macromolecules leak from the intraretinal vasculature into the interstitial spaces of the surrounding retina. This accumulation of intraretinal fluid within the macular area causes DMO, with or without cystoid changes, photoreceptor degeneration, and irreversible loss of central vision. One of the factors found to be elevated in intraocular fluids of subjects with DMO is VEGF, which not only drives new vascular growth, but also induces vascular leakage (30, 31).

An additional factor shown to play a key role in regulating vascular stability and inflammation under healthy and pathological conditions is the angiopoietin/tyrosine kinase with immunoglobulin-like and endothelial growth factor-like domains (Tie) pathway (32). Angiopoietins Ang-1 and Ang-2 are growth factors that compete for binding to the Tie2 receptor (33). Under normal conditions, Ang-1 binds to and activates Tie2 on vascular endothelial cells, leading to Tie2 autophosphorylation (34). Activated Tie2 promotes survival of endothelial cells and stability of cell junctions, thereby stabilising vasculature (35).

Under disease conditions, an "angiogenic switch" may occur, involving a shift in the balance of pro- and anti-angiogenic factors which leads to an overexpression of growth factors (including VEGF), pro-inflammatory cytokines, and Ang-2. This shift is induced by conditions of stress, such as non-homeostatic glucose concentrations, ischaemia, hypoxia, and the presence of growth factors, and inflammatory cytokines (26, 32, 33, 36).

In DMO, vitreous levels of Ang-2 are elevated. Ang-2 binds to Tie2 and integrin receptors: Ang-2 binding to Tie2 prevents its downstream signalling, promoting the destabilisation of blood vessels (26), while Ang-2 binding to integrin receptors promotes endothelial cell destabilisation and pericyte apoptosis (37). Ang-2 also promotes inflammation via upregulation of pro-inflammatory cytokines and by enhancing cytokine-induced leukocyte adhesion and transmigration (38). Moreover, monocytes and neutrophils adhere to the vascular endothelium (leukostasis) in an integrin-dependent manner, resulting in endothelial dysfunction and capillary non-perfusion induced via several mediators (39-42).

Moreover, VEGF binds to VEGF receptor 2 (VEGFR2), working synergistically with Ang-2 to further drive blood vessel destabilisation, with increasing vascular leakage and retinal thickening in DMO. In cases where DMO is associated with PDR, there is also development of pathological neovascularisation. These new vessels are immature and exhibit structural deficits that make them leaky, thereby contributing to further vascular leakage and DMO (26, 33, 36).

Burden of disease

Approximately 50% of all patients who have DR may go on to develop DMO (10). Retinal diseases impact on patient independence and the ability to participate in social and day-to-day activities. Visual impairment as a result of DR/DMO can diminish a patient's ability to drive, reduce participation in daily and social activities and lead to a sense of social isolation (43-45). Given that the onset of DMO typically occurs during working age, vision loss due to DMO can lead to inability to work or work at full capacity, reduced workplace productivity (46), and may result in early retirement (47).

DMO negatively impacts quality of life (QoL) more than other common chronic conditions (e.g. diabetes, asthma, hypertension) and other common retinal diseases (e.g. glaucoma, retinal vein occlusion) given the treatment burden and impact on vision (48). DMO has been demonstrated to affect patient QoL at all stages of the disease, from preliminary symptoms to vision loss (49). A study comparing vision function and self-reported QoL in patients with DMO using the National Eye Institute-Visual Function Questionnaire 25 (NEI-VFQ 25) found lower mean baseline scores for the near vision activities and distance vision activities domains, compared with scores observed in other eye diseases. Additionally, lower mean baseline scores reported for the "Mental Health", "Role Difficulties" (i.e. work-related

limitations), and “Dependency” domains relative to those of patients with other ocular conditions indicate that patients with DMO may feel particularly isolated (49).

Patients with visual impairment also commonly experience worsening health conditions. The impact of a reduction in VA on patient self-sufficiency as a result of DMO has implications for an individual’s ability to monitor and manage their diabetes, given that diabetes care is largely self-managed (50, 51). In this way, visual impairment, the impact on the ability to self-manage, and the impact in turn on glycaemic control, risks creating a vicious circle with consequences for additional downstream complications (52). Patients with visual impairment due to DMO are also more likely to also have chronic comorbid conditions such as cardiovascular disease, leading to deteriorating health and accumulating medical costs (53, 54).

Visual impairment across a wide range of causes and severities is associated with direct medical costs approximately twice those of non-impaired individuals, primarily because of hospitalisation and the use of healthcare services around the time of diagnosis and treatment (55). DMO is associated with significant healthcare costs (compared with patients with diabetes but with no history of retinal disease) that increase as vision worsens (56, 57). Additionally, a study of all-cause visual impairment and blindness in high-income countries found that long-term care, home-based nursing, assistive devices, and home modifications contribute to levels of non-medical services more than 10-fold higher than for those with normal vision (58).

B.1.3.2 Clinical management

Current treatment options for patients with DMO in UK clinical practice include IVT anti-VEGF therapy, corticosteroids, and laser photocoagulation. Treatment with IVT anti-VEGF therapy is the current recommended treatment by clinical guidelines (1, 59). Laser photocoagulation therapy was the standard of care prior to the advent of IVT-based treatments and is no longer recommended for the treatment of DMO by EURETINA (1).

IVT anti-VEGF therapy is the current recommended first-line treatment for patients with DMO due to its safety and effectiveness in reducing macular oedema and improving visual gains in most patients (59, 60). Two anti-VEGF agents are currently recommended by NICE for the treatment of visual impairment caused by DMO if the eye has a central retinal thickness (CRT) of 400 µm or more at the start of treatment: ranibizumab (TA274) (2) and aflibercept (TA346) (3). Market share data collected from January to April 2021 suggest that [redacted]

Table 3: Aflibercept and ranibizumab dosing regimens

	Aflibercept	Ranibizumab
Loading dose	Monthly injection for 5 consecutive doses (5 x Q4W)	Minimum three month loading phase of monthly IVT injections (3 x Q4W)
Maintenance dose	Treatment extended to every 2 months	Monthly injection until maximum VA is achieved and/or no signs of disease activity
Flexible dosing regimen	T&E regimen: After the first 12 months, and based on visual and/or anatomic outcomes, the treatment interval may be	PRN regimen: Monitoring and treatment intervals should be determined by the physician and should be based on disease

	extended such as with a treat-and-extend regimen, where the treatment intervals are gradually increased to maintain stable visual and/or anatomic outcomes. If outcomes deteriorate, treatment interval should be shortened accordingly	activity, assessed by VA and/or anatomical parameters T&E regimen: Once maximum VA is achieved and/or no signs of disease activity, the treatment intervals can be extended stepwise until signs of disease activity or vision impairment recur. Treatment interval may be extended by up to 1 month at a time for DMO

DMO, diabetic macular oedema; PRN, pro re nata; Q4W, every 4 weeks; T&E, treat and extend; VA, visual acuity

Despite bevacizumab being acknowledged in guidelines for off-label use to treat DMO (1, 61), it is not licensed or formulated for ocular use and would require compounding of vials. As it is not routinely used in UK clinical practice, bevacizumab is therefore not considered a relevant comparator for this submission.

Corticosteroids are an option for treating patients with DMO, predominantly in patients who have previously received IVT anti-VEGF therapy (1). Long-acting steroid implants are administered for use in patients who are unable to come back for frequent visits and have a strong inflammatory component of the disease. NICE recommends dexamethasone intravitreal implant as an option for treating DMO in patients unresponsive or unsuitable for non-steroidal treatment but only if the implant is to be used in an eye with an intraocular (pseudophakic) lens (TA349) (62). Fluocinolone acetonide intravitreal implant is recommended as an option for treating chronic DMO that is insufficiently responsive to available therapies only if the implant is to be used in an eye with an intraocular (pseudophakic) lens (TA301) (63). Given that both treatments are recommended in the second-line setting and not specifically for patients with CRT ≥400 µm, these regimens are not considered to be relevant comparators for the current appraisal.

Limitations of current treatment and unmet need

Although anti-VEGF therapy is efficacious for many patients with DMO, these treatments alone do not completely address the inflammatory component of the condition (64-66). Moreover, while corticosteroids have anti-inflammatory effects, these agents are associated with raised intraocular pressure and increased risk of cataract development (67). Therefore, there is a need for novel treatment options with favourable safety and tolerability profiles that can address the inflammatory component of this multifactorial disease and improve disease control, thereby reducing the need for frequent injections to maintain vision.

Current treatment options for patients with DMO are onerous for patients, physicians, caregivers, and healthcare systems, impacting adherence to treatment and limiting patients' ability to maintain their vision over time. Currently available anti-VEGF therapies require frequent injections to maintain efficacy. Ocular injections can be a source of fear, stress and anxiety for patients with retinal diseases (48), and the frequent clinic visits, injections, and patient monitoring required to achieve optimal long-term outcomes for patients with DMO results in a high burden of treatment for patients and their caregivers (59, 68).

Clinical expert advice obtained by Roche confirmed that better results in managing DMO are obtained with early, intense treatment (4–6 injections in the loading phase), with patients receiving 3 doses or fewer in the loading phase are expected to respond poorly and require

more injections in later years (69). This is corroborated by real-world data in patients with DMO that suggests that the high treatment burden creates a barrier to optimal anti-VEGF treatment, leading to poorer and unsustained vision outcomes that decline over time, as patients undergo fewer injections and exhibit worse vision outcomes at 1 year compared with patients in clinical trials (68). Moreover, data from the United Kingdom Diabetic Retinopathy Electronic Medical Record Users Group demonstrate that patients are not receiving optimal treatment; ranibizumab-treated patients followed-up for at least 6 months only received a mean of 3.3 injections, with a mean of 6.9 outpatient visits in the first year of follow up (70).

Innovations that reduce injection frequency are highly valued by patients with retinal diseases. In a survey conducted in European patients to determine the most desired improvements to injection treatment regimen, having fewer appointments to achieve the same visual results (42%) and having fewer appointments to attend (22%) rated as the most desired, and second most desired improvements, respectively (48).

DMO presents a significant burden on healthcare systems, an issue that is expected to become increasingly relevant due to the rising prevalence of diabetes and DMO. Many ophthalmology clinics, particularly those within publicly funded health systems, lack the capacity and personnel to manage the volume of visits from patients with retinal diseases. As the demand for recommended follow-up appointments and the frequency of treatment increases, many clinics in the UK, for example, are running at capacity and failing to meet the needs of their retinal disease patients (48). The frequency of anti-VEGF injections may result in clinics reaching their capacity levels and resources (including funds and/or personnel) being redirected from other eye care services to support anti-VEGF clinic appointments (48, 71, 72).

Prior to the COVID-19 pandemic, ophthalmology was the busiest specialty in England with the highest number of attendances for outpatient appointments (73), with delays in hospital eye care services resulting in permanently reduced vision in some patients (74). The COVID-19 pandemic brought additional pressures on the system and a desire among patients with diabetes (who are at greater risk of COVID-19 complications) to attend hospital less frequently. In fact, the Royal College of Ophthalmologists introduced guidance to defer treatment in patients with DMO in order to ensure that care in patients with age-related macular degeneration (AMD) can be maintained (75). Therefore, the need for longer-acting treatments for patients with DMO has perhaps never been more evident, as these can minimise the number of future treatment visits, help patients retain continuity of treatment in the event of further lockdowns or insufficient clinic capacity, minimise the backlog of untreated or undertreated patients, and ultimately maintain vision in people with DMO (76).

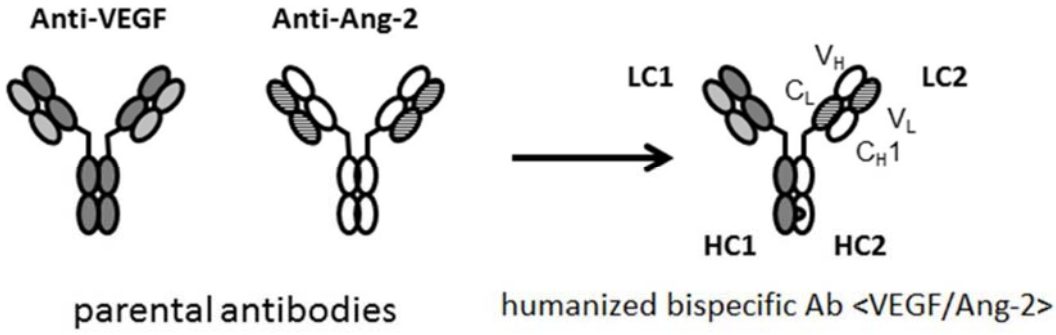
As a result of the high treatment burden and unsustained vision outcomes associated with current anti-VEGF IVT therapy in the real-world setting, as well as the multifactorial nature of the DMO disease, there is a need for novel treatment options beyond anti-VEGF monotherapy that can extend treatment intervals for longer, without compromising efficacy and safety.

B.1.3.3 Faricimab for the treatment of visual impairment caused by DMO

Faricimab is a humanised bispecific immunoglobulin G1 (IgG1) antibody that acts through inhibition of two distinct pathways by neutralisation of both angiopoietin-2 (Ang-2) and vascular endothelial growth factor A (VEGF-A).

Faricimab is the first bispecific antibody designed for ocular use, and was generated utilising the Roche CrossMAb technology (Figure 1). It independently binds and neutralises both Ang-2 and VEGF-A with high specificity and potency and without steric hindrance (33, 77, 78). The inhibition of two distinct pathways that drive retinal diseases enhances vascular stability by reducing vascular leakage, neovascularisation, and inflammation. The better vascular stability afforded by the unique dual mechanism of action of faricimab provides comprehensive disease control allowing physicians to extend treatment intervals up to every 16 weeks, while maintaining vision gains and safety comparable to aflibercept Q8W.

Figure 1: Design of the CrossMAb faricimab



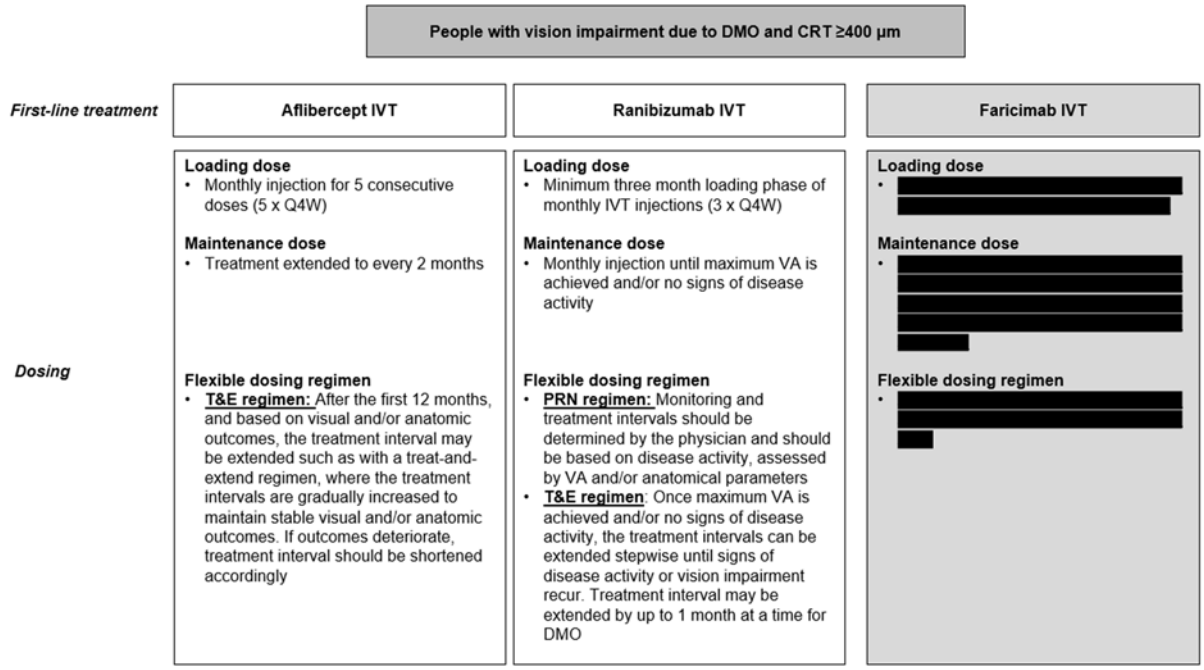
Ab, antibody; Ang-2, angiopoietin-2; HC, heavy chain; LC, light chain; VEGF, vascular endothelial growth factor.
Source: Investigator's Brochure RO686746

In the Phase II BOULEVARD study, 6.0 mg faricimab dose demonstrated a statistically significant gain in visual acuity and a longer time to re-treatment during the observation period compared with ranibizumab (79). Moreover, results from Phase III clinical trials (Section B.3) demonstrate that patients receiving faricimab can maintain vision gains comparable to every 8 weeks (bimonthly) aflibercept with the longest possible treatment intervals (up to every 16 weeks). At Week 52, more than 70% of patients were on a faricimab Q12W or Q16W dosing regimen after the loading phase, and more than 50% of patients were on a Q16W regimen after the loading phase, highlighting the increased durability of effect.

By helping patients regain and maintain vision with fewer injections compared with current IVT anti-VEGF therapy, faricimab supports patient, caregiver, and HCP priorities of reduced treatment burden. This is achieved whilst maintaining sustained efficacy, and comparable safety, to current IVT anti-VEGF therapy, thereby enabling more patients to keep their independence and overall quality of life.

Based on the anticipated marketing authorisation indication, which covers the equivalent populations as the comparators aflibercept and ranibizumab, faricimab is positioned as an alternative option to these regimens for the treatment of adults with visual impairment due to DMO, as presented below.

Figure 2: Proposed positioning of faricimab in treatment pathway for DMO



CRT, central retinal thickness; DMO, diabetic macular oedema; IVT, intravitreal; PRN, pro re nata; T&E, treat and extend; VA, visual acuity

B.1.4 Equality considerations

If a person is registered as blind or partially sighted they are considered disabled, as stated in the Equality Act 2010. Therefore, the patient population addressed in this submission is a protected group under this act.

B.2 Key drivers of the cost effectiveness of the comparator(s)

A summary of the clinical outcomes and measures included within the cost-effectiveness analyses conducted for the NICE appraisals for aflibercept (TA346) (3) and ranibizumab (TA274) (2), followed by the key drivers of the cost-effectiveness analyses are presented in this section.

B.2.1 Clinical outcomes and measures

The comparators to faricimab in this appraisal are the licensed anti-VEGF therapies aflibercept and ranibizumab. Both therapies have been evaluated by NICE and recommended for patients with DMO in NICE TA346 (aflibercept; published 2015) (3) and TA274 (ranibizumab; published in 2013) (2), respectively.

Aflibercept (TA346)

The pivotal clinical trials for aflibercept considered in TA346 were VIVID and VISTA (80).

- VISTA (n=466) is a double-blind, randomised (1:1:1) active controlled superiority study carried out at 54 sites in the USA
- VIVID (n=406) is was a prospective, randomised, double-blind, active-controlled superiority study carried out at 73 sites across Japan, Europe and Australia.

Both trials administered once monthly intravitreal doses of 2 mg aflibercept for 5 months followed by either aflibercept 2 mg every 4 weeks or aflibercept 2 mg every 8 weeks with laser photocoagulation. The primary outcome in the trials was the mean change from baseline to 52 weeks in best corrected visual acuity (BCVA), based on the Early Treatment of Diabetic Retinopathy Study (ETDRS) letter score, in eyes with diabetic macular oedema (DMO) involving the centre of the macula, for aflibercept compared with laser photocoagulation.

Ranibizumab (TA274)

In the appraisal of ranibizumab for DMO, two main clinical trials were considered: RESTORE and Protocol I.

- RESTORE was a multicentre (73 centres in 13 countries), sham-controlled randomised trial that compared ranibizumab plus sham laser photocoagulation (n=116) with ranibizumab plus laser photocoagulation (n=118) and laser photocoagulation plus sham injections (n=111) (81). Ranibizumab or sham injections were administered monthly in months 1 to 3; after this, they continued on a monthly basis until vision was stabilised for 2 visits or visual acuity reached 85 letters or more. Laser photocoagulation or sham laser photocoagulation was administered on day 1 and repeated at intervals of at least 13 weeks, if deemed necessary by the treating clinician.
- Protocol I, was a multicentre (52 clinical sites in the United States), randomised trial, which compared ranibizumab with immediate focal/grid laser, ranibizumab with macular laser given only for persistent DMO after 6 months, intraocular triamcinolone plus immediate macular laser, and macular laser with sham injections (82). The

group of people who received triamcinolone was not considered because it was not used in UK clinical practice at the time of the TA274 (2) and was not included the appraisal scope. Investigators administered ranibizumab or sham injections every 4 weeks until the fourth study visit (that is, after 12 weeks of treatment). At subsequent 4-weekly visits, the decision to give another injection depended on visual acuity and retinal thickness of the treated eye. Investigators repeated laser photocoagulation or sham laser photocoagulation, if needed, at intervals of at least 13 weeks (3-monthly).

The primary outcome measure of both RESTORE and Protocol I was mean change in visual acuity in the treated eye after 12 monthly follow-up visits (81, 82). The RESTORE analysis was based on the average of changes in visual acuity from baseline, measured monthly over the period from month 1 to month 12 ('mean average change'), whereas Protocol I compared the visual acuity measured at baseline with that measured at 12 months ('mean change') (81, 82).

Table 4 presents the key clinical outcomes and measures considered in TA346 and TA274 (2, 3).

Table 4: Clinical outcomes and measures appraised in the published NICE guidance for the comparators

TA	Outcome category	Outcome	Used cost-effectiveness model?	Source
Aflibercept for DMO [TA346] (3)	Visual acuity (study eye)	Mean change from baseline to 52 weeks BCVA based on ETDRS	Yes	VIVID, VISTA (80)
		Proportion of patients gaining 10 or more ETDRS letters and 15 or more ETDRS letters from baseline to week 52	No	VIVID, VISTA (80)
	Visual function	Mean change in CRT from baseline to week 52, assessed by OCT	No	VIVID, VISTA (80)
	Adverse events	Ocular AEs, non-ocular AEs	Yes	VIVID, VISTA (80)
	HRQoL	Change in vision-related quality of life (assessed by NEI VFQ-25) from baseline to week 52	No	VIVID, VISTA (80)
		Change in quality of life (assessed by EQ-5D) from baseline to week 52	Yes	VIVID, VISTA (80)
Ranibizumab for DMO [TA274] (2)	Visual acuity (study eye)	Mean average change from baseline to 52 weeks BCVA based on ETDRS	Yes	RESTORE (81)
		Mean change from baseline to 52 weeks BCVA based on Electronic-ETDRS	Yes	Protocol I (82)
		Proportion of patients gaining 10 or more ETDRS letters from baseline to week 52	No	RESTORE, Protocol I (81, 82)
	Visual function	Mean change in CRT from baseline to week 52, assessed by OCT	No	RESTORE (81)
	Adverse events	Ocular AEs, non-ocular AEs	Yes (treatment-specific adverse events costs)	RESTORE, Protocol I (81, 82)
	HRQoL	Change in vision-related quality of life (assessed by NEI VFQ-25) from baseline to week 52	No	RESTORE (81)
		Change in quality of life (assessed by EQ-5D) from baseline to week 52	Yes	RESTORE (81)

AE: adverse event; BCVA: best corrected visual acuity; CRT: central retinal thickness; ETDRS: Early Treatment Diabetic Retinopathy Study; EQ-5D: 5-dimension European Quality of Life questionnaire; HRQoL: health-related quality of life; NEI: National Eye Institute; OCT: Optical coherence tomography; VA: visual acuity; VFQ-25: Visual Functioning Questionnaire.

B.2.2 Summary of the key drivers of the cost-effectiveness of the comparators

The key drivers of the ranibizumab cost-effectiveness analysis, as described in TA274 (2), included: the need to treat both eyes of people with diabetic macular oedema, the utility associated with changes in vision of the treated eye, likely frequency of ranibizumab injections, the expected duration of benefit from ranibizumab treatment, the number of treatment visits and monitoring visits needed, and the generalisability of the economic evidence, especially about glycaemic control in the treated population. The key drivers of the aflibercept cost-effectiveness analysis, as described in TA346 (3), included: the model time horizon, the relative efficacy for both aflibercept and ranibizumab, the cohort starting age and the number of ranibizumab injection at year 1.

The key drivers of cost-effectiveness from TA274 and TA346 (2, 3), relevant to the cost comparison analysis, have been explored in scenario analyses and are presented in section B.4.4.

B.3 Clinical effectiveness

B.3.1 Identification and selection of relevant studies

See appendix D for full details of the process and methods used to identify and select the clinical evidence relevant to the technology being appraised.

B.3.2 List of relevant clinical effectiveness evidence

A summary of the clinical effectiveness evidence pertinent to the current appraisal is provided below. Evidence from the BOULEVARD study is not included since this was a Phase II study in US patients only.

Table 5: Clinical effectiveness evidence

Study	YOSEMITE/GR40349, NCT03622580 (83)			RHINE/GR40398, NCT03622593 (84)						
Study publications	Primary clinical study report (85) 1-year efficacy, safety, durability results (ARVO 2021) (4)			Primary clinical study report (86) 1-year efficacy, safety, durability results (ARVO 2021) (4)						
Study design	Phase III, double-masked, multicentre, randomised, active comparator-controlled, parallel-group study, evaluating the efficacy, safety, pharmacokinetics, and optimal treatment frequency of faricimab administered by intravitreal injection at 8-week intervals or PTI of approximately 100 weeks' duration (excluding the screening period) in patients with DMO. YOSEMITE and RHINE have identical study designs.									
Population	Adults aged 18 years and older with DMO who were naive to anti-VEGF therapy in the study eye and patients who had previously been treated with anti-VEGF therapy in the study eye, provided that the last treatment was at least 3 months prior to the Day 1 visit (the first study treatment).									
Intervention(s)	Faricimab solution for intravitreal injection at a dose of 6.0 mg									
Comparator(s)	Aflibercept solution for intravitreal injection at a dose of 2 mg									
Indicate if trial supports application for marketing authorisation	**Yes**	✓	Indicate if trial used in the economic model	**Yes**	✓	**Yes**	✓	Indicate if trial used in the economic model	**Yes**	✓
	No			**No**		**No**			**No**	
Rationale for use/non-use in the model	YOSEMITE and RHINE are Phase III trials providing efficacy, safety and durability evidence for faricimab in patients with DMO. Data from YOSEMITE and RHINE were used to inform the efficacy and safety of faricimab in the economic model.									
Reported outcomes specified in the decision problem	• Best corrected visual acuity (BCVA) (affected eye) • Best corrected visual acuity (both eyes) • Central retinal thickness (specifically central subfield thickness) • Mortality • Adverse effects of treatment, including cataracts and glaucoma • Health-related quality of life, including the effects of changes in visual acuity									

B.3.3 Summary of methodology of the relevant clinical effectiveness evidence

Unless otherwise stated, information on the YOSEMITE and RHINE studies were sourced from the primary clinical study reports (85, 86).

B.3.3.1 Study design

The YOSEMITE and RHINE trials were identically designed, double masked, multicentre, randomised, parallel-group, active-comparator controlled Phase III studies evaluating the efficacy, safety, pharmacokinetics, and optimal treatment frequency of IVT faricimab 6.0 mg for the treatment of DMO, when dosed either every eight weeks (Q8W) or according to a personalised treatment interval (PTI) regimen in adjustable intervals (up to every 16 weeks [Q16W]), compared with IVT aflibercept 2.0 mg dosed Q8W.

The studies recruited both patients naive to anti-VEGF therapy in the study eye and patients previously treated with anti-VEGF therapy in the study eye, provided that the last treatment was at least 3 months prior to the Day 1 visit (the first study treatment). Study participation of previously anti-VEGF-treated patients was capped at a maximum 25% of enrolment. The rationale for capping the number of previously anti-VEGF-treated patients was based on the heterogeneous nature of this population with potentially a history of long-standing DMO and irreversible retinal damage that may limit the possibility of detecting additional visual acuity improvements.

A total of 940 and 951 patients were enrolled globally in YOSEMITE and RHINE respectively and were randomised in a 1:1:1 ratio to one of three treatment arms:

- Arm A (faricimab administered Q8W) (n=315 [YOSEMITE] and n=317 [RHINE]): Patients randomised to Arm A received 6.0 mg intravitreal faricimab injections Q4W to Week 20, followed by 6.0 mg intravitreal faricimab injections Q8W to Week 96, followed by the final study visit at Week 100.
- Arm B (faricimab PTI) (n=313 and n=319): Patients randomised to Arm B received 6.0 mg intravitreal faricimab injections Q4W to at least Week 12, followed by PTI dosing of 6.0 mg intravitreal faricimab injections to Week 96, followed by the final study visit at Week 100.
- Arm C (aflibercept administered Q8W) (n=312 and n=315): Patients randomised to Arm C received 2.0 mg intravitreal aflibercept injections Q4W to Week 16, followed by 2.0 mg intravitreal aflibercept injections Q8W to Week 96, followed by the final study visit at Week 100.

Patients in all three treatment arms were to complete scheduled study visits Q4W for the entire study duration (100 weeks). A sham procedure was administered to patients in all three treatment arms at applicable visits to maintain masking among treatment arms.

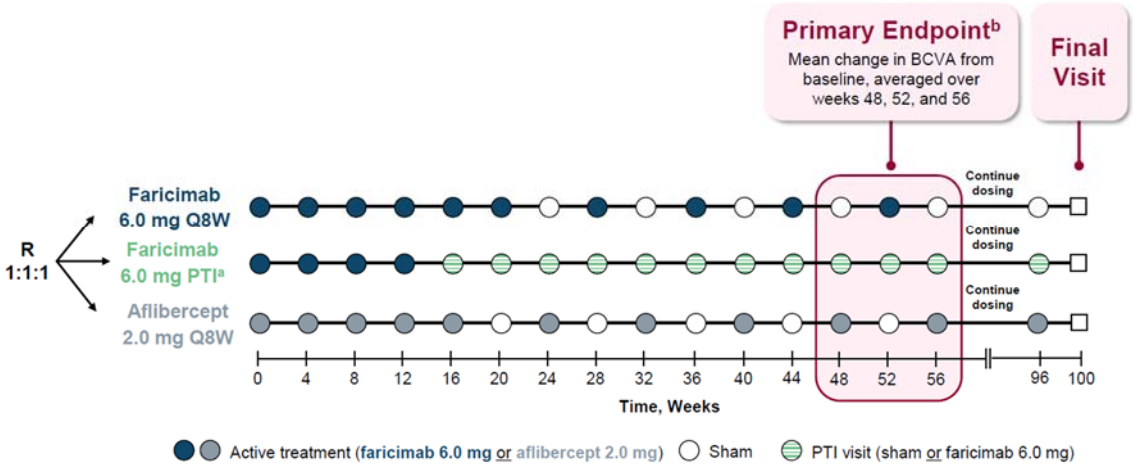
Randomisation was stratified by the following baseline factors:

- Baseline best correct visual acuity (BCVA) Early Treatment DR Study (ETDRS) letter score (≥64 letters vs <64 letters);

- Prior intravitreal anti-VEGF treatment (yes vs no);
- Region (United States and Canada, Asia, and the rest of the world).

The primary endpoint was change from baseline in BCVA (as measured on the ETDRS chart at a starting distance of 4 metres) at 1 year, with 1 year being the average of the Week 48, 52, and 56 visits. An averaged endpoint for the Phase III trials was agreed by the FDA and EMA and was designed to best control for differences in the time from last treatment between arms, as well as to allow for a fairer comparison across treatment arms.

Figure 3: Study schema for YOSEMITE and RHINE



BCVA, best-corrected visual acuity; IVT, intravitreal; PTI, personalised treatment interval; Q8W, every 8 weeks;

[a]The personalised treatment interval algorithm is a protocol driven regimen based on the treat and extend concept. [b] BCVA was measured using the Early Treatment Diabetic Retinopathy Study visual acuity chart at a starting distance of 4 m.

Treatment schedule for patients in the PTI Arm (Arm B)

Study drug dosing interval decisions in the PTI arm were automatically calculated by the Interactive Voice/Web Response System (IxRS) based on the algorithm described below. Study drug dosing visits were visits when a patient was assigned to receive faricimab.

Patients randomised to the PTI arm (Arm B) were treated with faricimab on a Q4W dosing interval until at least the patient's Week 12 visit, or a later visit when central subfield thickness (CST[1]) met the predefined reference CST threshold (CST <325 µm for Spectralis SD-OCT, or <315 µm for Cirrus SD-OCT or Topcon SD-OCT), as determined by the central reading centre (CRC). The reference CST was used at study drug dosing visits by the IxRS for the drug dosing interval decision-making.

After a patient's initial reference CST was established, their study drug dosing interval was increased by 4 weeks to an initial Q8W dosing interval by the IxRS. From this point forward, the study drug dosing interval was extended, reduced, or maintained based on assessments made at study drug dosing visits, with a maximum interval of every 16 weeks (Q16W). The algorithm used by the IxRS for interval decision-making, which is based on the relative

[1] The central subfield is defined as the circular area 1 mm in diameter centered around the center point of the fovea, with its thickness provided as a quantifiable value via OCT imaging

change of the CST and BCVA compared with reference CST and reference BCVA, is outlined below.

Interval extended by 4 weeks:

- If the CST value increased or decreased by ≤10% without an associated ≥10 letter BCVA decrease

Interval maintained:

- If the CST decreased by >10% **or**
- CST value increased or decreased by ≤10% **with** an associated ≥10-letter BCVA decrease **or**
- CST value increased between >10% and ≤20% **without** an associated ≥5 letter BCVA decrease

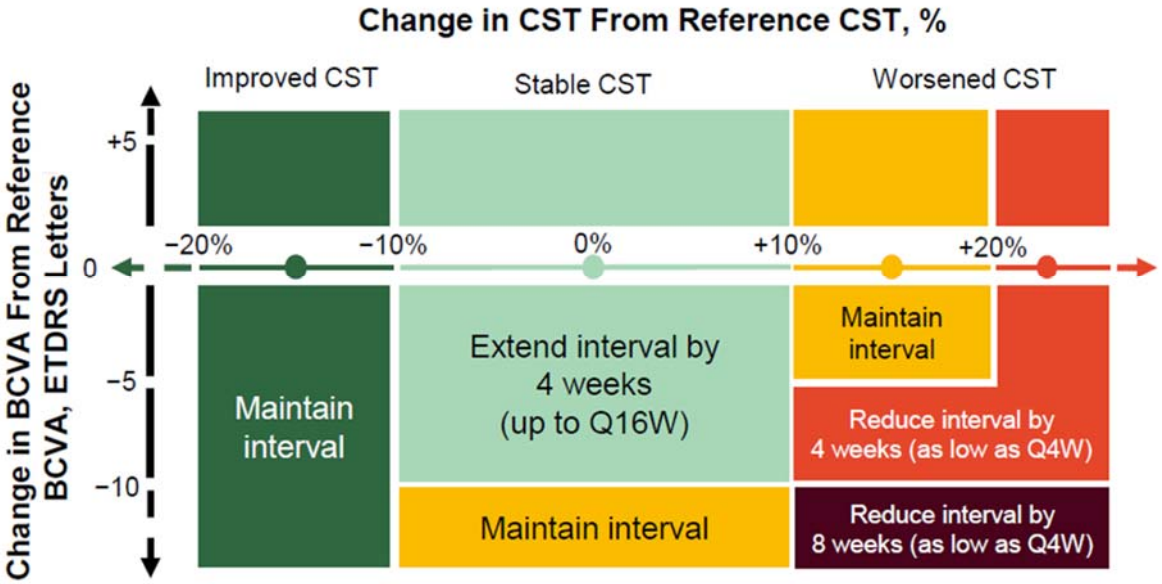
Interval reduced by 4 weeks:

- If the CST value increased between >10% and ≤20% **with** an associated ≥ 5- to < 10-letter BCVA decrease **or**
- CST value increased by >20% **without** an associated ≥10-letter BCVA decrease

Interval reduced by 8 weeks:

- If the CST value increased by >10% **with** an associated ≥10-letter BCVA decrease.

Figure 4: Algorithm for IxRS-Determined Study Drug Dosing Intervals



CST was measured as the distance from the internal limiting membrane to Bruch's membrane. Reference BCVA was defined as the mean of the 3 best BCVA values achieved at any prior active dosing visit. Reference CST was defined as the CST value when the original reference value (CST < 325 µm) was achieved. Reference CST was adjusted if CST decreased b y > 10% from the previous reference CST for 2 consecutive active dosing visits and the values obtained were within 30 µm. The CST value obtained at the latter visit served as the new reference CST. BCVA, best corrected visual acuity; CST, central subfield thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; PTI, personalised treatment interval; Q4W, every 4 weeks; Q16W, every 16 weeks.

B.3.3.2 Summary of study methodology

	YOSEMITE, NCT03622580 (83)	RHINE, NCT03622593 (84)
Settings and locations of data collection	YOSEMITE was conducted in 16 countries (179 sites): Austria, Bulgaria, France, Germany, Hungary, Israel, Italy, Japan, Mexico, Peru, Poland, Russian Federation, Slovakia, Spain, Turkey, United States.	RHINE was conducted in 24 countries (174 sites): Argentina, Australia, Brazil, Canada, China, Czech Republic, Denmark, France, Germany, Hong Kong, Hungary, Italy, Poland, Portugal, Russian Federation, Singapore, South Korea, Spain, Switzerland, Taiwan, Thailand, Turkey, United States. United Kingdom ([redacted])
Trial design	Phase 3,double masked, multicentre, randomised, parallel-group study in patients with DMO	
Eligibility criteria	**Key inclusion criteria** • Adult (≥18 years) with diabetes mellitus (Type 1 or Type 2) • Treatment-naive or previously anti-VEGF treated (capped at a maximum of 25% of enrolment) • HbA1c ≤10% • BCVA of 73 to 25 letters inclusive (Snellen equivalent of 20/40 to 20/320) • CST ≥325 µm (on Spectralis SD-OCT) or CST ≥315 µm (on Cirrus SD-OCT or Topcon SD-OCT) **Key exclusion criteria (see protocol for further details)** • Anti-VEGF injection within 3 months prior to Day 1 • Untreated diabetes mellitus or serious systemic condition (e.g., cancer, infection) • Uncontrolled blood pressure (>180/100 mmHg) • Cardiovascular accident or myocardial infarction within 6 months prior to Day 1 • Pregnancy or breastfeeding or intention to become pregnant • High-risk proliferative diabetic retinopathy • Panretinal photocoagulation or macular laser within 3 months prior to Day 1 • Any use of medicated intraocular implants, including Ozurdex®, within 6 months prior to Day 1 • Any use of Iluvien® implants at any time before Day 1 • Any ocular condition that may confound the assessment of the study drugs (i.e., epiretinal membrane disrupting the macular architecture)	
Trial drugs and concomitant medications	**Trial drugs** • Arm A: 6.0 mg intravitreal faricimab injections Q4W to Week 20, followed by 6.0 mg intravitreal faricimab injections Q8W to Week 96, followed by the final study visit at Week 100 (n=315 [YOSEMITE] and n=317 [RHINE]) • Arm B: 6.0 mg intravitreal faricimab injections Q4W to at least Week 12, followed by PTI dosing of 6.0 mg intravitreal faricimab injections to Week 96, followed by the final study visit at Week 100 (n=313 and n=319)	

	• 2 mg intravitreal aflibercept injections Q4W to Week 16, followed by 2 mg intravitreal aflibercept injections Q8W to Week 96, followed by the final study visit at Week 1(n=312 and n=315) **Sham procedure** • All three treatment arms (faricimab Q8W, faricimab PTI, and aflibercept Q8W) maintained Q4W study visits for the 100-week study duration. The sham procedure mimicked an intravitreal injection and involved the blunt end of an empty syringe (without a needle) being pressed against the anaesthetised eye. To preserve the randomised treatment arm masking, patients had the sham procedure performed at study treatment visits when they were not treated with either faricimab or aflibercept as applicable per their treatment arm schedule **Concomitant medications** **Prohibited concomitant medications:** • Systemic anti-VEGF therapy • Systemic drugs known to cause macular oedema (fingolimod, tamoxifen) • Intravitreal anti-VEGF agents (other than study-assigned aflibercept or faricimab) in study eye • Intravitreal, periocular (subtenon), steroid implants (i.e., Ozurdex®, Iluvien®), or chronic topical ocular corticosteroids in study eye • Treatment with Visudyne® in study eye • Administration of micropulse and focal or grid laser in study eye • Other experimental therapies (except those comprising vitamins and minerals **Permitted concomitant medications:** Patients who use maintenance therapies could continue their use. The following therapies were permitted: • Onset of ocular hypertension or glaucoma in the study eye during a patient's study participation was treated as clinically indicated • Onset of cataract or posterior capsular opacification in either eye during a patient's study participation could be treated as clinically indicated. Dose interruption criteria may have applied with cataract surgery • Short-term use of topical ocular corticosteroids after cataract surgery, yttrium-aluminum garnet capsulotomy, peripheral iridotomy, argon/selective laser trabeculoplasty, or ocular allergic conditions • PRP may have been allowed for the treatment of DR after discussion with the Medical Monitor.
Primary outcome	**Primary endpoint:** • Change from baseline in BCVA (as measured on the ETDRS chart at a starting distance of 4 metres) at 1 year. The definition of 1 year is the average of the Week 48, 52, and 56 visits
Other outcomes used in the economic model/specified in the scope	**Secondary endpoints:** • Proportion of patients with a ≥2-step DRSS improvement from baseline on the ETDRS DRSS at Week 52

	• Change from baseline in BCVA (as measured on the ETDRS chart at a starting distance of 4 metres) over time • Proportion of patients gaining ≥15 or ≥10 letters in BCVA from baseline over time and at 1 year[a] • Proportion of patients avoiding a loss of ≥15 or ≥10 letters in BCVA from baseline over time and at 1 year[a] • Proportion of patients gaining ≥15 letters from baseline or achieving BCVA of ≥84 letters over time and at 1 year[a] • Proportion of patients in the PTI arm on a Q4W, Q8W, Q12W, or Q16W treatment interval at Week 52, and over time • Proportion of patients in the PTI arm at Week 52 who achieved a Q12W or Q16W treatment interval without an injection interval decrease below Q12W • Change from baseline in CST at 1 year[a] • Change from baseline in CST over time • Proportion of patients with absence of DMO (CST <325 µm for Spectralis SD-OCT) over time and at 1 year[a] • Proportion of patients with absence of intraretinal fluid and subretinal fluid over time and at Week 52 • Change from baseline in NEI VFQ-25 composite score over time and at Week 52 **Exploratory objectives:** • Change from baseline in the NEI VFQ-25 Near Activities, Distance Activities, and Driving subscales over time • Proportion of patients with a ≥4-point improvement from baseline in NEI VFQ-25 composite score over time **Safety endpoints** • Incidence and severity of ocular adverse events • Incidence and severity of non-ocular adverse events
Pre-planned subgroups	In the ITT population, the primary endpoint of the adjusted mean change from baseline in BCVA at Week 48/52/56 was analysed across subgroups including: • Baseline BCVA (≥64 letters and ≤63 letters) • Region (US and Canada, Asia, and the rest of the world) • Prior IVT anti-VEGF therapy (yes and no) • Baseline DRS (<47, 47–53 and >53 ETDRS DRSS) • Baseline HbA_{1c} (≤8% and >8%) • Age (<65 years and ≥65 years) • Gender • Race (White, Asian, and other)

BCVA, best corrected visual acuity; CST, central subfield thickness; DMO, diabetic macular oedema; DR, diabetic retinopathy; DRS, diabetic retinopathy severity; DRSS, diabetic retinopathy severity scale; ETDRS Early Treatment Diabetic Retinopathy Study; HbA_{1c}, glycated haemoglobin; nAMD, neovascular age-related macular degeneration; NEI VFQ-25, National Eye Institute 25-Item Visual Function Questionnaire; OCT, optical coherence tomography; PDR, proliferative diabetic retinopathy; PTI, personalised treatment interval; SD-OCT, spectral-domain optical coherence tomography; VEGF, vascular endothelial growth factor.

[a] The definition of 1 year is the average of the Week 48, 52, and 56 visits

B.3.3.3 Patient demographics and baseline characteristics

Patient demographic and baseline ocular characteristics of the study eye were well balanced and generally comparable across the treatment arms within each study, and between studies. Demographics and baseline ocular characteristics in the treatment-naive patients were similar to the ITT population.

Patient demographics were comparable across the two studies, except a greater proportion of patients were predominantly from North America in YOSEMITE (~53%), and Rest of the World (i.e., not North America or Asia) in RHINE (~56%). The majority of patients were male (~60%) and White (>75%). Approximately 12% of patients in YOSEMITE and approximately 21% of patients in RHINE were of Hispanic/Latino ethnicity. In the pooled ITT population, patient ages ranged from 28 to 86 years, with a mean of 62.3 years.

As per study design, the majority of patients (approximately 78%) in both studies were naive to anti-VEGF treatment in the study eye, with a comparable proportion of treatment-naive patients across treatment arms and across studies.

Overall, at baseline, BCVA values, the proportion of patients with macular ischaemic non-perfusion, and time since last treatment in previously treated patients were comparable across treatment arms in YOSEMITE and RHINE, comparable across studies, and comparable in the pooled ITT population. In the pooled ITT population, in the faricimab Q8W, faricimab PTI, and aflibercept arms, respectively: mean BCVA values were [redacted] letters.

Mean baseline CST was comparable across the treatment arms within each study, although slightly greater in YOSEMITE (487.5 µm) compared with RHINE (471.6 µm). In the pooled ITT population, mean baseline CST in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arms was [redacted] respectively.

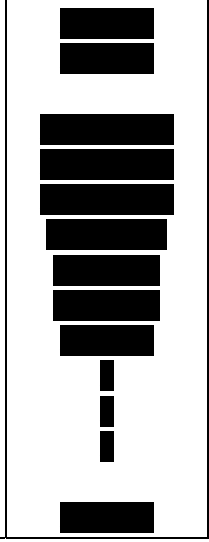
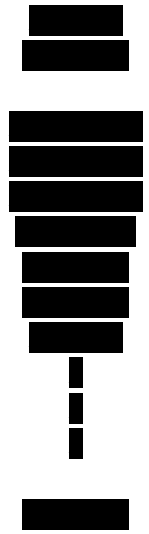
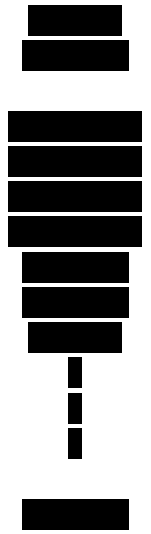
DR status at baseline was generally comparable across treatment arms in YOSEMITE and RHINE, comparable across studies, and comparable in the pooled ITT population.

In the pooled ITT population, mean (SD) time since DMO diagnosis in the faricimab Q8W, faricimab PTI, and aflibercept arms was [redacted], respectively.

Overall, similar baseline ocular characteristics to the pooled ITT population were observed for the pooled TN population. Since approximately [redacted] of the pooled ITT population were treatment-naive patients, there were expected differences between populations with respect to time since DMO diagnosis. In the pooled TN population, the mean (SD) time since DMO diagnosis in the faricimab Q8W, faricimab PTI, and aflibercept arms was [redacted], respectively.

Table 6: Baseline demographics and patient characteristics: YOSEMITE and RHINE

	YOSEMITE			RHINE			Pooled YOSEMITE and RHINE		
	Fari 6.0 mg Q8W (n=315)	Fari 6.0 mg PTI (n=313)	Afli 2.0 mg Q8W (n=312)	Fari 6.0 mg Q8W (n=317)	Fari 6.0 mg PTI (n=319)	Afli 2.0 mg Q8W (n=315)	Fari 6.0 mg Q8W (n=632)	Fari 6.0 mg PTI (n=632)	Afli 2.0 mg Q8W (n=627)
Region, n (%) US and Canada Rest of the World Asia	 167 (53.0) 127 (40.3) 21 (6.7)	 168 (53.7) 126 (40.3) 19 (6.1)	 168 (53.8) 124 (39.7) 20 (6.4)	 110 (34.7) 178 (56.2) 29 (9.1)	 111 (34.8) 179 (56.1) 29 (9.1)	 109 (34.6) 180 (57.1) 26 (8.3)	[redacted]	[redacted]	[redacted]
Age, years Median Min–Max ≥65, n (%)	 62.0 26 – 85 127 (40.3)	 64.0 24–85 144 (46.0)	 63.0 28–84 132 (42.3)	 63.0 27–91 141 (44.5)	 63.0 26–87 136 (42.6)	 63.0 28–86 132 (41.9)	[redacted]	[redacted]	[redacted]
Sex, male, n (%)	187 (59.4)	197 (62.9)	178 (57.1)	194 (61.2)	199 (62.4)	186 (59.0)	[redacted]	[redacted]	[redacted]
Ethnicity, n (%) Not hispanic or latino Hispanic or latino Not reported Unknown	 273 (86.7) 37 (11.7) 2 (0.6) 3 (1.0)	 268 (85.6) 40 (12.8) 4 (1.3) 1 (0.3)	 272 (87.2) 37 (11.9) 2 (0.6) 1 (0.3)	 252 (79.5) 56 (17.7) 6 (1.9) 3 (0.9)	 232 (72.7) 78 (24.5) 4 (1.3) 5 (1.6)	 240 (76.2) 67 (21.3) 5 (1.6) 3 (1.0)	[redacted]	[redacted]	[redacted]
Months since DMO diagnosis, mean (SD)	14.0 (21.7)	17.6 (36.2)	17.5 (27.6)	18.9 (32.2)	20.7 (33.0)	20.3 (37.1)	[redacted]	[redacted]	[redacted]
BCVA, letters, mean (SD) Categories, n (%) ≤38	62.0 (9.9) 15 (4.8)	61.9 (10.2) 12 (3.8)	62.2 (9.5) 12 (3.8)	61.9 (10.1)	62.5 (9.3) 11 (3.4)	62.1 (9.4) 9 (2.9)	[redacted]	[redacted]	[redacted]

39–63 ≥64 Missing/invalid	132 (41.9) 168 (53.3) 0	126 (40.3) 175 (55.9) 0	132 (42.3) 168 (53.8) 0	14 (4.4) 128 (40.4) 174 (54.9) 1 (0.3)	132 (41.4) 174 (54.5) 2 (0.6)	132 (41.9) 174 (55.2) 0			
CST (ILM-BM) (microns), mean (SD)	492.3 (135.8)	485.8 (130.8)	484.5 (131.1)	466.2 (119.4)	471.3 (127.0)	477.3 (129.4)			
Macular Ischaemic Non-Perfusion, n (%)	127 (40.3)	117 (37.4)	122 (39.1)	126 (39.7)	138 (43.3)	132 (41.9)			
Macular leakage, n (%)	305 (96.8)	301 (96.2)	293 (93.9)	300 (94.6)	309 (96.9)	299 (94.9)			
Previous anti-VEGF treated, n (%)	77 (24.4)	68 (21.7)	70 (22.4)	63 (19.9)	64 (20.1)	67 (21.3)			
Time since last anti-VEGF treatment, months, mean (SD)	20.5 (20.5)	17.6 (17.2)	16.6 (12.6)	20.7 (20.8)	15.5 (19.5)	19.9 (17.4)			
DRSS, n (%) 1 – DR absent 2 – DR questionable/ microaneurysms only 3 – Mild NPDR 4 – Moderate NPDR 5 – Moderately severe NPDR 6 – Severe NPDR 7 – Mild PDR 8 – Moderate PDR 9 – High risk PDR 10 – High risk PDR (level 75) 11 – Advanced PDR	 2 (0.6) 4 (1.3) 84 (26.7) 84 (26.7) 67 (21.3) 46 (14.6) 16 (5.1) 6 (1.9) 0 0 0 0 4 (1.3)	 3 (1.0) 6 (1.9) 92 (29.4) 86 (27.5) 59 (18.8) 40 (12.8) 11 (3.5) 9 (2.9) 1 (0.3) 0 0 0 5 (1.6)	 4 (1.3) 10 (3.2) 83 (26.6) 85 (27.2) 54 (17.3) 49 (15.7) 9 (2.9) 7 (2.2) 2 (0.6) 0 0 0 7 (2.2)	 2 (0.6) 3 (0.9) 90 (28.4) 88 (27.8) 59 (18.6) 50 (15.8) 12 (3.8) 6 (1.9) 2 (0.6) 0 0 0 2 (0.6)	 4 (1.3) 10 (3.1) 92 (28.8) 72 (22.6) 63 (19.7) 36 (11.3) 26 (8.2) 10 (3.1) 1 (0.3) 0 0 0 5 (1.6)	 1 (0.3) 6 (1.9) 94 (29.8) 75 (25.1) 54 (17.1) 51 (16.2) 11 (3.5) 6 (1.9) 3 (1.0) 0 0 0 5 (1.6)			

12 – Advanced PDR (level 85A, 85B) 90 – Cannot grade Missing	2 (0.6)	1 (0.3)	2 (0.6)	3 (0.9)	0	5 (1.6)	[redacted]	[redacted]	[redacted]

BCVA, Best Corrected Visual Acuity; CST, Central Subfield Thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; ILM, Internal Limiting Membrane; NPDR, non-proliferative diabetic retinopathy; PTI = Personalised Treatment Interval (from Q4W up to Q16W); PDR, proliferative diabetic retinopathy; VEGF, Vascular Endothelial Growth Factor.

Baseline is the last available value taken on or prior to randomisation. Age is at randomisation

Invalid BCVA values are excluded from analysis. CST is defined as the distance between ILM and Bruch's membrane (BM) as assessed by the CRC

B.3.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

B.3.4.1 Analysis timing

The primary analysis was performed when all patients from the global enrolment phase had either completed the study through Week 56 or had discontinued from the study prior to Week 56, whichever came later (i.e., timing was defined as the primary analysis last patient, last visit [LPLV]), and all data collected prior to the primary LPLV in the global enrolment phase were in the database and had been cleaned and verified. At the time of the primary analysis, the study was ongoing.

The final analysis will be performed when all patients from the global enrolment phase have either completed the study through Week 100 or have discontinued early from the study, all data from the global enrolment phase are in the database and have been cleaned and verified.

B.3.4.2 Statistical hypothesis

For each of the two faricimab arms (Q8W and PTI), the following three hypotheses were tested separately against the active comparator (aflibercept Q8W) at an overall significance level of α=0.0496 using a graph-based testing procedure (87, 88) to control for the overall type I error rate:

- Non-inferiority of faricimab compared with aflibercept Q8W in the intent-to-treat (ITT) population with a non-inferiority margin of 4 letters
- Superiority of faricimab compared with aflibercept Q8W in the TN population
- Superiority of faricimab compared with aflibercept Q8W in the ITT population

For each faricimab group (Q8W or PTI) the null hypothesis for the non-inferiority comparison: H_0: $\mu^{faricimab} - \mu^{aflibercept} \leq -4$ letters, and the alternative hypothesis: H_a: $\mu^{faricimab} - \mu^{aflibercept} > -4$ letters, will be tested, for which $\mu^{faricimab}$ and $\mu^{aflibercept}$ are the expected change from baseline in BCVA averaged over Weeks 48, 52, and 56 for the treatment group in question (faricimab Q8W or PTI) and the active comparator (aflibercept Q8W), respectively.

B.3.4.3 Planned sample size

Approximately 900 patients each were planned to be randomised in the global enrollment phase of YOSEMITE and RHINE. Patients were randomised in a 1:1:1 ratio to receive treatment with faricimab Q8W (Arm A), faricimab PTI (Arm B), or aflibercept Q8W (Arm C). The primary comparisons were the pairwise comparisons between the active comparator (aflibercept Q8W) and each of the faricimab arms (Q8W and PTI).

A sample size of approximately 300 patients in each arm provided greater than 90% power to show non-inferiority of faricimab to aflibercept (pairwise comparisons between the active comparator and each of the faricimab arms) in the ITT population, using a non-inferiority margin of 4 letters and under the following assumptions:

- True mean difference between faricimab and aflibercept of 0 letters
- Standard deviation (SD) of 11 letters for the change from baseline in BCVA averaged over Week 48, Week 52, and Week 56
- Two-sample t-test
- 1.25% one-sided type I error rate
- 10% dropout rate

Assuming 75–90% of patients recruited would be treatment naive, approximately 225–270 TN patients would be enrolled per arm. A sample size of 225–270 patients per arm provided greater than 80% power to show a 3.5-letter superiority of faricimab over aflibercept (pairwise comparisons between the active comparator and each of the faricimab arms) in the TN population, using the same SD, test, and dropout assumptions above, and a two-sided type I error rate of 2.5%.

Furthermore, a sample size of approximately 300 patients per arm provided greater than 80% power to show a 3-letter superiority of faricimab over aflibercept (pairwise comparisons between the active comparator and each of the faricimab arms) in the ITT population, under the same SD, test, and dropout assumptions above, and a two-sided type I error rate of 2.5%.

As per health authority feedback, for each unmasked independent data monitoring committee (iDMC) safety review performed prior to the primary analysis (four in total), a nominal type I error penalty of 0.0001 was taken such that efficacy analyses were performed with a family wise significance level of 0.0496. This type I error adjustment was not expected to impact the sample size or power.

B.3.4.4 Analysis populations

Table 7: YOSEMITE and RHINE analysis populations

Population	Description
Intent-to-treat population (ITT)	All patients who were randomised in the study, grouped according to the treatment assigned at randomisation
Treatment-naïve population (TN)	All patients randomised in the study who had not received any intravitreal anti-VEGF agents in the study eye prior to randomisation, grouped according to the treatment assigned at randomisation
Per-protocol population (PP)	All patients randomised in the study who received at least one dose of study treatment and who did not have a major protocol violation that impacted the efficacy evaluation or the treatment interval determination. Patients were grouped according to the actual treatment received, as follows: • If the only active treatment received by a patient in the study eye was aflibercept, the patient's treatment group was aflibercept Q8W. • If the only active treatment received by a patient in the study eye was faricimab, the patient's treatment group was as randomised if the patient was randomised to one of the faricimab arms; otherwise, the patient's treatment group was faricimab Q8W.

	• If a patient received a combination of different active treatments (faricimab and aflibercept) in the study eye, the patient's treatment group was as randomised Efficacy analysis based on this patient population were supplementary.
Safety evaluable population (SE)	All patients who received at least one injection of active study drug (faricimab or aflibercept) in the study eye, grouped according to the actual treatment received as described for the per-protocol population

B.3.4.5 Efficacy analysis and statistical methods

Efficacy analyses were based on the ITT population and the TN population, unless otherwise specified. Baseline was defined as the last available measurement obtained on or prior to randomisation. Patients with missing baseline assessments were not imputed.

Unless otherwise noted, analyses of efficacy outcome measures were stratified by baseline BCVA ETDRS letter score, as assessed on Day 1 (64 letters or better vs 63 letters or worse), prior intravitreal anti-VEGF therapy (yes vs no), and region (U.S. and Canada, Asia, and the rest of the world). The stratification factors as recorded in IxRS were used.

The primary comparisons were the pairwise comparisons between the active comparator (aflibercept Q8W) and each of the faricimab arms (Q8W and PTI).

Continuous outcomes were analysed using a mixed model for repeated measures (MMRM). Binary endpoints were analysed using stratified estimation for binomial proportions. The estimates and confidence intervals (CIs) were provided for the mean (for continuous variables) or proportion (for binary variables) for each of the three treatment arms and for the difference in means or proportions between pairwise comparisons of active comparator (aflibercept Q8W) and each of the faricimab arms (Q8W and PTI).

Primary efficacy endpoint and hypothesis testing

The primary efficacy endpoint was the change from baseline in BCVA averaged over Weeks 48, 52, and 56. The BCVA outcome measure was based on the ETDRS VA chart assessed at a starting distance of four meters. The primary estimand applied a treatment policy strategy for non-COVID-19 related intercurrent events and a hypothetical strategy for COVID-19 related intercurrent events.

Selected supplementary primary endpoint analyses were:

- Per-protocol analysis: Same analysis as primary but on the per-protocol population
- MMRM method using treatment policy strategy for all intercurrent events
- MMRM method using hypothetical strategy for all intercurrent events
- Trimmed mean analysis using a truncated distribution, truncating patients with the worst outcome, with the assumption that patients had the worst outcome after non-COVID-19 related intercurrent events

The order in which hypothesis tests for the primary endpoint were performed is illustrated in Figure 5, with arrows denoting the direction of α-propagation. If the tests for one treatment sequence were all positive, at the α/2 (=0.0248) level then α/2 was propagated to the beginning of the other treatment sequence, which was tested at a significance level of α=0.0496. Of note, non-inferiority was tested one-sided at half of the designated significance

level shown in Figure 5. If the lower bound of the two-sided confidence limit for the difference in adjusted mean for the treatment group in question (faricimab Q8W or PTI) and the active comparator (aflibercept Q8W) was greater than –4 letters, then that faricimab treatment group in question (Q8W or PTI) was considered non-inferior to aflibercept.

Figure 5: Graph-based testing procedure for the primary endpoint

PTI, personalised treatment interval; Q8W, every 8 weeks.
Note: α=0.0496

The primary analysis was performed using a MMRM. The model included the change from baseline at Weeks 4–56 as the response variable and included the categorical covariates of treatment group, visit, visit-by-treatment group interaction, baseline BCVA (continuous), as well as randomisation stratification factors as fixed effects.

Comparisons between each faricimab arm and the aflibercept Q8W arm were made using a composite contrast over Weeks 48, 52, and 56. The MMRM model assumed an unstructured covariance structure. If there were convergence problems with the model, then a heterogeneous compound symmetry or an AR (1) covariance structure could have been fitted, as pre-specified in the SAP. Of note, all MMRM analyses for the primary and continuous secondary endpoints and for the subgroup analyses used an unstructured covariance structure, with the exception of the following subgroup analyses in which there were convergence issues due to small sample size and were run with an AR(1) covariance structure:

- Change from Baseline in BCVA in the Study Eye averaged over Weeks 48, 52 and 56: MMRM Method, Asia (Region) Subgroup, Treatment-Naive Population
- Change from Baseline in BCVA in the Study Eye averaged over Weeks 48, 52 and 56: MMRM Method, Baseline DRS >53 ETDRS Diabetic Retinopathy Severity Scale (DRSS) Subgroup, Treatment-Naive Population

Missing data was implicitly imputed by the MMRM model, assuming a missing at random missing data mechanism. Non-standard BCVA data and invalid BCVA data were excluded from the analyses.

Sensitivity/supplemental analyses

Sensitivity/supplemental analyses were performed to assess the robustness of the results using the same MMRM method as the main analysis, but applying different handling strategies for the intercurrent events and missing data:

- Last observation carried forward (LOCF): missing BCVA assessments due to any reason were imputed using the last available post-baseline observation prior to the occurrence of missing data
- Treatment policy strategy for all intercurrent events
- Hypothetical strategy for all intercurrent events

In addition, the following analyses were also performed using the analysis of covariance (ANCOVA) method and different handling strategies for the intercurrent events and missing data:

- Trimmed means analysis performed using a truncated distribution, truncating patients with the worst outcome, with the assumption that patients have the worst outcome after non-COVID-19 related intercurrent events. Missing data and measurements after COVID-19 related intercurrent events, as well as missing data due to other reasons, were considered missing at random (MAR) and were censored
- Multiple imputation, assuming a missing not at random (MNAR) mechanism for non-COVID-19 related missingness. Missing data and measurements after COVID-19 related intercurrent events, as well as missing data due to other reasons, were imputed using multiple imputation method assuming MAR
- ANCOVA analysis with the average of non-missing values of Weeks 48, 52, and 56 assessments as the dependent variable. Measurements after COVID-19 related intercurrent events were censored and missing observations were not imputed

Key secondary endpoint and hypothesis testing

The key secondary endpoint was the proportion of patients with a ≥2-step improvement in DRSS from baseline on the ETDRS DRSS at Week 52.

Testing for the key secondary endpoint was performed for each faricimab comparison in which non inferiority of the primary endpoint in the corresponding treatment arm was achieved compared with the aflibercept Q8W. A fixed sequence testing procedure (89) was performed at the 0.0248 two-sided significance level in the following order:

- Non-inferiority of faricimab compared with aflibercept in the ITT population, with a non-inferiority margin of 10%
- Superiority of faricimab compared with aflibercept in the TN population
- Superiority of faricimab compared with aflibercept in the ITT population

Of note, non-inferiority was tested one-sided at half of the designated significance level. If the lower 97.52% confidence limit for the difference in adjusted proportions for the treatment group in question (faricimab Q8W or PTI) and the active comparator (aflibercept Q8W) was greater than -10%, then that faricimab treatment group in question (Q8W or PTI) was considered non-inferior to aflibercept.

The proportion of patients in each treatment group and the overall difference in proportions between treatment groups was estimated using the weighted average of the observed proportions and the differences in observed proportions over the strata defined by the randomisation stratification factors of baseline BCVA score (64 letters or better vs. 63 letters or worse), prior intravitreal anti-VEGF therapy (yes vs. no), and region (U.S. and Canada, Asia, and the rest of the world) using the Cochran Mantel-Haenszel (CMH) weights. Confidence intervals of the proportion of patients in each treatment group and the overall difference in proportions between treatment groups were calculated using the normal approximation to the weighted proportions (90). Superiority was assessed, as appropriate, using a CMH test stratified by the randomisation stratification factors. Due to a small number of patients enrolled from Asia, the Asia and rest of the world regions were combined to calculate the CMH weighted estimates and for the CMH analyses.

Analysis was based on observed data, missing ETDRS DRSS assessments were not imputed.

B.3.4.5 Safety reporting and analysis

Safety assessments included AEs, standard laboratory and ocular assessments, and vital signs.

Safety analyses were based on the safety-evaluable population. Safety was assessed through descriptive summary of ocular and non-ocular AEs, deaths, and ocular assessments. Clinically significant laboratory abnormalities and clinically significant vital sign abnormalities were reported as AEs and evaluated as part of the AE assessments.

At the time of the primary analysis, safety data were summarised based on the complete Week 56 data in the safety-evaluable population.

Baseline for safety analyses was defined as the last available measurement prior to first exposure to study drug.

B.3.5 Quality assessment of the relevant clinical effectiveness evidence

An overview of the quality assessment for YOSEMITE and RHINE is presented in Table 8. Both studies were deemed moderate-to-high quality with a majority reporting clear details. Please refer to Appendix D for the full quality assessment.

Table 8: Clinical effectiveness evidence quality assessment

Study question	YOSEMITE (NCT03622580)	RHINE (NCT03622593)
Was randomisation carried out appropriately?	Yes	Yes
Was the concealment of treatment allocation adequate?	Unclear	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Unclear
Were there any unexpected imbalances in drop-outs between groups?	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes

B.3.6 Clinical effectiveness results of the relevant trials

Data from the Phase III studies YOSEMITE and RHINE were pooled, as these studies were identically designed and were conducted in parallel. This section provides data from the pooled analysis, based on data up to Week 56 (91).

B.3.6.1 Primary endpoint: change from baseline in BCVA at 1 Year

ITT population

Both YOSEMITE and RHINE met the primary endpoint of non-inferiority; patients treated with faricimab Q8W or PTI had a non-inferior mean change from baseline in BCVA averaged over Weeks 48, 52, and 56 (henceforth referred to as 'Week 48/52/56') compared with patients treated with aflibercept Q8W, as the lower bound of the 97.5% confidence intervals for the adjusted mean difference between both the faricimab arms and aflibercept arm was greater than the non-inferiority margin of 4 letters. The primary efficacy results were consistent across the two studies.

In the pooled ITT population, the adjusted mean change from baseline in BCVA at Week 48/52/56 was 11.2, 11.2 and 10.5 letters in the faricimab Q8W, PTI, and aflibercept Q8W arms, respectively; the difference between the faricimab Q8W and PTI dosing arms when compared with the aflibercept Q8W arm was 0.7 letters (95% CI: -0.4, 1.7) and 0.6 letters (95% CI: -0.4, 1.7), respectively.

TN population

In both YOSEMITE and RHINE, patients treated with faricimab Q8W or PTI did not have a superior mean change from baseline in BCVA at Week 48/52/56 compared with patients treated with aflibercept Q8W. The results were consistent across the two studies.

In the pooled TN population, the difference in adjusted mean change from baseline in BCVA between the faricimab Q8W and PTI dosing arms when compared with the aflibercept Q8W arm was [redacted] at Week 48/52/56.
[redacted]

Supplementary analysis

The primary efficacy results were consistent between the ITT and PP populations and were supported by multiple supplementary analyses (Table 10).

Table 9: Change from Baseline in BCVA in the study eye from the individual and pooled Phase III DMO studies at Week 48/52/56: MMRM Method (primary estimand) (ITT population)

	YOSEMITE			RHINE			Pooled YOSEMITE and RHINE		
	Fari 6.0 mg Q8W (n=315)	Fari 6.0 mg PTI (n=313)	Afli 2.0 mg Q8W (n=312)	Fari 6.0 mg Q8W (n=317)	Fari 6.0 mg PTI (n=319)	Afli 2.0 mg Q8W (n=315)	Fari 6.0 mg Q8W (n=632)	Fari 6.0 mg PTI (n=632)	Afli 2.0 mg Q8W (n=627)
Average of week 48, 52 and 56									
n	271	276	276	268	293	279	539	569	555
Adjusted mean (SE)	10.7 (0.56)	11.6 (0.56)	10.9 (0.56)	11.8 (0.52)	10.8 (0.51)	10.3 (0.52)	11.2 (0.38)	11.2 (0.38)	10.5 (0.38)
97.5% CI for adj mean	(9.4, 12.0)	(10.3, 12.9)	(9.6, 12.2)	(10.6, 13.0)	(9.6, 11.9)	(9.1, 11.4)	(10.5, 12.0)	(10.4, 11.9)	(9.8, 11.3)
Diff in adj means vs afli (SE)	-0.2 (0.79)	0.7 (0.79)		1.5 (0.73)	0.5 (0.73)		0.7 (0.54)	0.6 (0.54)	
97.5% CI for adj mean diff[a]	(-2.0, 1.6)	(-1.1, 2.5)		(-0.1, 3.2)	(-1.1, 2.1)		(-0.4, 1.7)[b]	(-0.4, 1.7)[b]	

Units: letters. BCVA, Best Corrected Visual Acuity; IVT, Intravitreal; MMRM, Mixed-Model Repeated-Measures; PTI, personalised treatment interval (from Q4W up to Q16W). VEGF, Vascular Endothelial Growth Factor. For the MMRM analysis, the model adjusted for treatment group, visit, visit-by-treatment group interaction, baseline BCVA (continuous), baseline BCVA (< 64 letters vs. >= 64 letters), prior IVT anti-VEGF therapy (yes vs. no), and region (U.S. and Canada, Asia, and the rest of the world) and study (GR40349 vs GR40398). An unstructured covariance structure is used. The estimate of the difference between the two groups uses a composite contrast over Weeks 48, 52 and 56. Treatment policy strategy and hypothetical strategy were applied to non-COVID-19 related and COVID-19 related intercurrent events, respectively. Missing data were implicitly imputed by MMRM. Invalid BCVA values are excluded from analysis.

a 97.5% CI is a rounding of 97.52%.

b 95% CI is reported for both arms in the pooled analysis

Table 10: Summary of change from baseline in BCVA in the study eye at Week 48/52/56: primary and supplementary analyses (Pooled YOSEMITE and RHINE)

	Faricimab 6.0 mg Q8W Adjusted Mean (SE) (95% CI)	Faricimab 6.0 mg PTI Adjusted Mean (SE) (95% CI)	Aflibercept 2 mg Q4W Adjusted Mean (SE) (95% CI)	Difference in Adjusted Means (SE) (95% CI) Faricimab Q8W vs. Aflibercept	Difference in Adjusted Means (SE) (95% CI) Faricimab PTI vs. Aflibercept
Primary Analysis – MMRM Method					
ITT Population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TN Population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Supplementary Analyses					
Per Protocol Analysis – MMRM Method					
PP Population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Analysis using Treatment Policy Strategy for All Intercurrent Events – MMRM Method					
ITT Population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Analysis using Hypothetical Strategy for All Intercurrent Events – MMRM Method					
ITT Population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Trimmed Mean Analysis – ANCOVA Method					
ITT Population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ANCOVA, analysis of covariance; CI, confidence interval; ITT, Intent-to-Treat; MMRM, mixed model for repeated measures; PP, per protocol; PTI, personalised treatment interval; Q4W, every 4 weeks; Q8W, every 8 weeks; SE, standard error; TN, treatment-naive

Note: ITT population: faricimab Q8W (n=632), faricimab PTI (n=632), aflibercept Q8W (n=627); TN population: faricimab Q8W (n=492), faricimab PTI (n=500), aflibercept Q8W (n=490); PP population: faricimab Q8W (n=509), faricimab PTI (n=546), aflibercept Q8W (n=547)

Intercurrent events

Intercurrent events for the primary efficacy endpoint are defined identically in YOSEMITE and RHINE.

Through Week 56, the proportion of patients in each treatment arm who experienced at least one intercurrent event was comparable across studies YOSEMITE and RHINE. In the pooled ITT population, 76 patients (12.0%) in the faricimab Q8W arm, 50 patients (7.9%) in the faricimab PTI arm, and 49 patients (7.8%) in the aflibercept Q8W arm experienced at least one intercurrent event.

The type and frequency of intercurrent events were also similar across studies. The most common intercurrent event in both YOSEMITE and RHINE was missed dose (i.e., faricimab or aflibercept) with a potentially major impact on efficacy (Weeks 44, 48, 52) due to COVID-19. In the pooled ITT population, as expected based on doses scheduled at Weeks 44 and 52 for patients in the faricimab Q8W arm, [redacted]. Despite the missing data due to COVID-19, the benefit-risk profile of faricimab was still able to be conclusively established as both efficacy and safety data were interpretable.

Table 11: Summary of intercurrent events through Week 56 from pooled phase III DMO Studies (ITT Population)

n (%)	Fari 6.0 mg Q8W (n=632)	Fari 6.0 mg PTI (n=632)	Afli 2 mg Q8W (n=637)
Pts with at least one intercurrent event*	[redacted]	[redacted]	[redacted]
Pts who discontinued study treatment due to AEs or lack of efficacy (not COVID-19)**	[redacted]	[redacted]	[redacted]
Pts who received any prohibited systemic treatment or prohibited treatment in the study eye (not due to COVID-19)***	[redacted]	[redacted]	[redacted]
Pts who discontinued study treatment due to COVID-19	[redacted]	[redacted]	[redacted]
Pts who received any prohibited systemic treatment or prohibited treatment in the study eye (not due to COVID-19)***	[redacted]	[redacted]	[redacted]
Pts with missed dose(s) with potentially major impact on efficacy due to COVID-19	[redacted]	[redacted]	[redacted]
COVID-19 death	[redacted]	[redacted]	[redacted]

PTI, personalised treatment interval (from Q4W up to Q16W); VEGF, vascular endothelial growth factor.
Percentages are based on N in the column headings.
* Includes events occurred on or prior to Day 405 (last day of Week 56 analysis visit window).
** Lack of efficacy is by investigator judgment for efficacy analyses lack of efficacy, progressive disease, disease relapse, symptomatic deterioration are combined as lack of efficacy.
*** Prohibited therapy is concurrent use of any systemic anti-VEGF agents or any protocol defined prohibited study eye therapy.

B.3.6.2 Secondary endpoints

≥2-Step DRSS Improvement at Week 52

In both YOSEMITE and RHINE studies, clinically meaningful proportions of patients achieved ≥2-step improvement in DR severity from baseline as measured on the ETDRS DRSS at Week 52 across both faricimab arms and the aflibercept arm.

The adjusted proportions of patients with ≥2-step DRS improvement from baseline were 42.5–46.0% across all four faricimab arms across both studies, and 35.8% and 46.8% in aflibercept arms in YOSEMITE and RHINE, respectively. In YOSEMITE, the pre specified DRSS non-inferiority margin of 10% was met as the lower bound of the 97.5% CI for the difference in the adjusted proportions between the faricimab and aflibercept arms was greater than -10% for both the faricimab Q8W and PTI arms at Week 52: 10.2% (97.5% CI: 0.3%, 20.0%) and 6.1% (97.5% CI: -3.6%, 15.8%), respectively. In RHINE, non-inferiority was not met as the lower bound of the 97.5% CI for the difference in the adjusted proportions between the faricimab and aflibercept arms was less than -10% for both the faricimab Q8W and PTI arms at Week 52: -2.6% (97.5% CI: -12.6%, 7.4%) and -3.5% (97.5% CI: -13.4%, 6.3%), respectively.

Because the individual studies, YOSEMITE and RHINE, each had an insufficient sample size to power for the ≥2-step DRSS improvement endpoint, analyses of the pooled studies were also performed. Since the two Phase III studies were identically designed and conducted in parallel, and since no imbalances in baseline characteristics (except for time since DMO diagnosis) were observed between the two studies, the pooled analyses approach is valid and provides more robust evaluation of the key secondary endpoint outcome.

In the pooled ITT population, the adjusted proportion of patients who had a ≥2-step DRSS improvement from baseline at Week 52 was [redacted] The difference in adjusted proportions between the faricimab Q8W and PTI arms when compared with the aflibercept Q8W arm [redacted] at Week 52.

Results from the analysis in the pooled TN population were [redacted].

Table 12: Proportion of patients with ≥2-step DRSS Improvement in the study eye from baseline on the ETDRS DRSS in the individual and pooled phase III DMO studies at Week 52: CMH method (primary estimand) (ITT population)

	YOSEMITE			RHINE			Pooled YOSEMITE and RHINE		
	Fari 6.0 mg Q8W (n=315)	Fari 6.0 mg PTI (n=313)	Afli 2 mg Q8W (n=312)	Fari 6.0 mg Q8W (n=317)	Fari 6.0 mg PTI (n=319)	Afli 2 mg Q8W (n=315)	Fari 6.0 mg Q8W (n=632)	Fari 6.0 mg PTI (n=632)	Afli 2 mg Q8W (n=627)
Week 52									
N	237	242	229	231	251	238			
CMH weighted estimate									
%	46.0	42.5	35.8	44.2	43.7	46.8			
97.5% CI	(38.8, 53.1)	(35.5, 49.5)	(29.1, 42.5)	(37.1, 51.4)	(36.8, 50.7)	(39.8, 53.8)			
Difference									
Diff in CMH weighted % vs afli	10.2	6.1		-2.6	-3.5				
97.5% CI for CMH weighted % diff	(0.3, 20.0)	(-3.6, 15.8)		(-12.6, 7.4)	(-13.4, 6.3)				

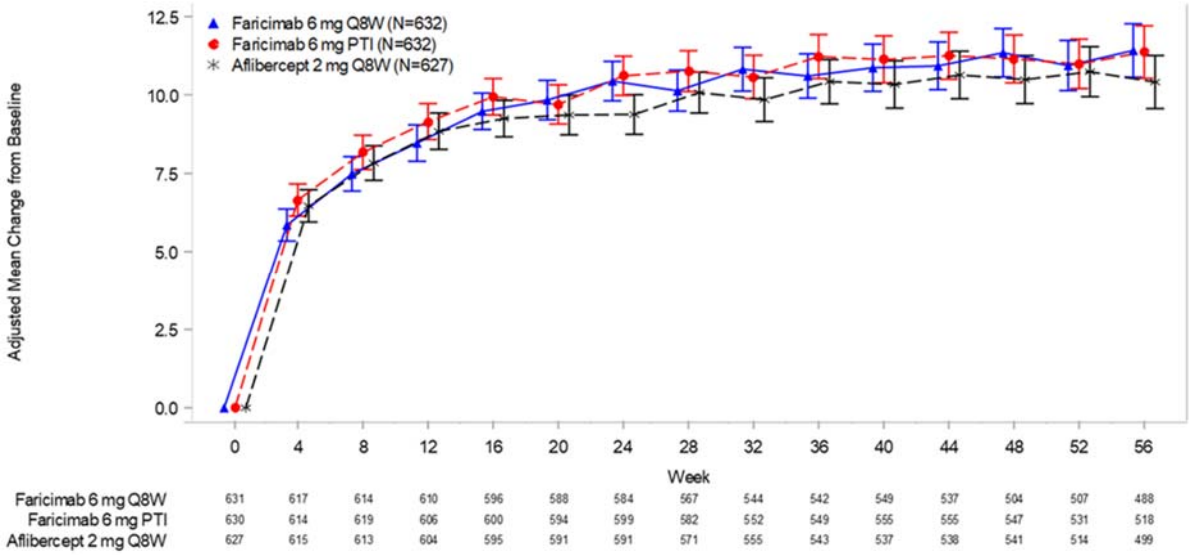
BCVA, best-corrected visual acuity; CMH, Cochran-Mantel-Haenszel; DRS, diabetic retinopathy severity; ETDRS, early treatment diabetic retinopathy study; PTI, personalised treatment interval (from Q4W up to Q16W).

The weighted estimate is based on CMH test stratified by baseline BCVA score (< 64 letters vs. ≥64 letters), prior IVT anti-VEGF therapy (yes vs. no), and region (U.S. and Canada, and the rest of the world) and study (GR40349 vs GR40398). Asia and rest of the world regions are combined due to a small number of enrolled patients. Treatment policy strategy and hypothetical strategy were applied to non-COVID-19 related and COVID-19 related intercurrent events, respectively. Missing assessments were not imputed. 97.52% CI is reported for pooled. 97.52% CI is reported for the individual studies. Estimates below 0% or above 100% are imputed as 0% or 100%, respectively. Baseline is defined as the last available measurement obtained on or prior to randomization.

Change from baseline in BCVA over time

The adjusted mean change from baseline in BCVA over time was comparable between the faricimab and aflibercept arms in both YOSEMITE and RHINE. Results were consistent across studies. In the pooled ITT population, the adjusted mean change from baseline in BCVA over time was comparable across treatment arms.

Figure 6: Pooled phase III DMO studies: plot of change from baseline in BCVA in the study eye through Week 56: MMRM Method (primary estimand) (ITT population)



Proportion of patients gaining ≥15 or ≥10 Letters in BCVA from baseline at Week 48/52/56

In both YOSEMITE and RHINE, comparable adjusted proportions of patients treated with faricimab Q8W or PTI compared with patients treated with aflibercept Q8W gained ≥15 letters from baseline at Week 48/52/56. Results were consistent across studies for all four faricimab arms and for aflibercept Q8W arms.

In the pooled ITT population, [redacted] of patients in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arms, respectively, gained ≥15 letters in BCVA score from baseline at Week 48/52/56. The difference in the adjusted proportion of patients who gained ≥15 letters from baseline between the faricimab Q8W and PTI arms when compared with the aflibercept Q8W arm was [redacted] and [redacted] at Week 48/52/56.

Similarly, the adjusted proportion of patients who gained ≥10 letters in BCVA score from baseline at Week 48/52/56 was comparable across treatment arms in YOSEMITE and RHINE, and consistent across studies.

Table 13: Proportion of patients gaining ≥15 letters in the study eye BCVA in the individual and pooled phase III DMO studies at Week 48/52/56: CMH method (primary estimand) (ITT population)

	YOSEMITE			RHINE			Pooled YOSEMITE and RHINE		
	Fari 6.0 mg Q8W (n=315)	Fari 6.0 mg PTI (n=313)	Afli 2 mg Q8W (n=312)	Fari 6.0 mg Q8W (n=317)	Fari 6.0 mg PTI (n=319)	Afli 2 mg Q8W (n=315)	Fari 6.0 mg Q8W (n=632)	Fari 6.0 mg PTI (n=632)	Afli 2 mg Q8W (n=627)
Average over week 48, 52, 56									
N	271	276	276	268	293	279			
CMH weighted estimate									
%	29.2	35.5	31.8	33.8	28.5	30.3			
95% CI	(23.9, 34.5)	(30.1, 40.9)	(26.6, 37.0)	(28.4, 39.2)	(23.6, 33.3)	(25.0, 35.5)			
Difference									
Diff in CMH weighted % vs afli	-2.6	3.5		3.5	-2.0				
95% CI for CMH weighted % diff	(-10.0, 4.9)	(-4.0, 11.1)		(-4.0, 11.1)	(-9.1, 5.2)				

BCVA, Best-corrected visual acuity; CMH, Cochran-Mantel-Haenszel; PTI, personalised treatment interval (from Q4W up to Q16W).
The weighted estimate is based on CMH test stratified by baseline BCVA score (< 64 letters vs. >= 64 letters), prior Intravitreal anti-VEGF therapy (yes vs. no), and region (U.S. and Canada vs. the rest of the world) and study (GR40349 vs GR40398). Asia and rest of the world regions are combined due to a small number of enrolled patients. Treatment policy strategy and hypothetical strategy were applied to non-COVID-19 related and COVID-19 related intercurrent events, respectively. Missing assessments were not imputed. Invalid BCVA values are excluded from analysis. 95% CI is reported for pooled. 95.04% CI is reported for the individual studies. Estimates below 0% or above 100% are imputed as 0% or 100% respectively. Baseline is defined as the last available measurement obtained on or prior to randomization.

Proportion of patients gaining ≥15 letters in BCVA from baseline over time

In both YOSEMITE and RHINE, comparable adjusted proportions of patients treated with faricimab Q8W or PTI and patients treated with aflibercept Q8W gained ≥15 letters from baseline over time through Week 56. Results were consistent across studies. The proportion of patients who gained ≥15 letters from baseline over time through Week 56 in the pooled ITT population is presented below.

Figure 7: Pooled phase III DMO studies: proportion of patients gaining ≥15 letters in BCVA from baseline in the study eye over time through Week 56: CMH method (primary estimand) (ITT population)

[redacted]

Proportion of patients avoiding a loss of ≥15 letters in BCVA from baseline at Week 48/52/56

In both YOSEMITE and RHINE, comparable adjusted proportions of patients treated with faricimab Q8W or PTI compared with patients treated with aflibercept Q8W avoided a loss of ≥15 letters in BCVA score from baseline at Week 48/52/56. Results were consistent across studies.

In the pooled ITT population, [redacted] of patients in the faricimab Q8W, PTI, and aflibercept Q8W arms, respectively, avoided a loss of ≥15 letters in BCVA score from baseline at Week 48/52/56. The difference between the faricimab Q8W and PTI arms when compared with the aflibercept Q8W arm was [redacted] at Week 48/52/56.

Table 14: Proportion of patients avoiding a loss of ≥15 letters in the study eye BCVA in the individual and pooled phase III DMO studies at Week 48/52/56: CMH method (primary estimand) (ITT population)

	YOSEMITE			RHINE			Pooled YOSEMITE and RHINE		
	Fari 6.0 mg Q8W (n=315)	Fari 6.0 mg PTI (n=313)	Afli 2 mg Q8W (n=312)	Fari 6.0 mg Q8W (n=317)	Fari 6.0 mg PTI (n=319)	Afli 2 mg Q8W (n=315)	Fari 6.0 mg Q8W (n=632)	Fari 6.0 mg PTI (n=632)	Afli 2 mg Q8W (n=627)
Average over week 48, 52, 56									
N	271	276	276	268	293	279	[redacted]	[redacted]	[redacted]
CMH weighted estimate									
%	98.1	98.6	98.9	98.9	98.7	98.6	[redacted]	[redacted]	[redacted]
95% CI	(96.5, 99.7)	(97.2, 100)	(97.6, 100)	(97.6, 100)	(97.4, 100)	(97.2, 99.9)	[redacted]	[redacted]	[redacted]
Difference									
Diff in CMH weighted % vs afli	-0.8	-0.3		0.3	0.0		[redacted]	[redacted]	
95% CI for CMH weighted % diff	(-2.8, 1.3)	(-2.2, 1.5)		(-1.6, 2.1)	(-1.8, 1.9)		[redacted]	[redacted]	

BCVA, Best-corrected visual acuity; CMH, Cochran-Mantel-Haenszel; PTI, personalised treatment interval (from Q4W up to Q16W).
The weighted estimate is based on CMH test stratified by baseline BCVA score (< 64 letters vs. ≥64 letters), prior Intravitreal anti-VEGF therapy (yes vs. no), and region (U.S. and Canada vs. the rest of the world) and study (GR40349 vs GR40398). Asia and rest of the world regions are combined due to a small number of enrolled patients. Treatment policy strategy and hypothetical strategy were applied to non-COVID-19 related and COVID-19 related intercurrent events, respectively. Missing assessments were not imputed. Invalid BCVA values are excluded from analysis. 95% CI is reported for pooled. 95.04% CI is reported for the individual studies. Estimates below 0% or above 100% are imputed as 0% or 100% respectively. Baseline is defined as the last available measurement obtained on or prior to randomization.

Proportion of patients avoiding a loss of ≥15 or ≥10 letters in BCVA from baseline over time

In both YOSEMITE and RHINE, comparable proportions of patients treated with faricimab Q8W or PTI and patients treated with aflibercept Q8W avoided a loss of ≥15 letters from baseline over time through Week 56. Results were consistent across studies.

The proportion of patients who avoided a loss of ≥15 letters from baseline over time through Week 56 in the pooled ITT population is presented below.

[redacted]

Figure 8: Pooled Phase III DMO studies: proportion of patients avoiding a loss of ≥15 letters in BCVA from baseline in the study eye over time through Week 56: CMH method (primary estimand) (ITT population)

[redacted]Faricimab treatment intervals in PTI arm

Proportion of patients in the faricimab PTI arm on Q4W, Q8W, Q12W, or Q16W treatment interval

In YOSEMITE and RHINE, study drug dosing for patients randomised to the PTI arm could be extended, reduced, or maintained at study drug dosing visits using 4-week increments to a maximum of Q16W or a minimum of Q4W based on the relative change of the CST and BCVA compared with the patient's reference CST and reference BCVA.

The proportions of faricimab PTI patients who achieved extended treatment intervals were consistent and reproducible in the two Phase III studies.

In YOSEMITE and RHINE at Week 52, 73.8% and 71.1% of patients, respectively, achieved a Q12W or Q16W dosing regimen. Percentages are based on the number of patients randomised to the faricimab PTI arm who had not discontinued the study at Week 52.

- In YOSEMITE, the proportions of PTI patients on a Q4W, Q8W, Q12W, or Q16W treatment interval at Week 52 were 10.8%, 15.4%, 21.0%, and 52.8%.
- In RHINE, the proportions of PTI patients on a Q4W, Q8W, Q12W, or Q16W treatment interval at Week 52 were 13.3%, 15.6%, 20.1%, and 51.0%.
- In the pooled ITT population at Week 52, 72.4% of patients achieved a Q12W or Q16W dosing regimen.
- Overall, 12.1%, 15.5%, 20.5%, and 51.9% of patients were on a Q4W, Q8W, Q12W, and Q16W treatment interval at Week 52.

Table 15: Proportion of patients in the faricimab PTI arm from the individual and pooled Phase III DMO studies on a Q4W, Q8W, Q12W, or Q16W treatment interval at Week 52

	YOSEMITE	RHINE	Pooled
	Fari 6.0 mg PTI (n=313)	Fari 6.0 mg PTI (n=319)	Fari 6.0 mg PTI (n=632)
Week 52 N	286	308	594
Q4W, n (%) 95% CI	31 (10.8) (7.2, 14.4)	41 (13.3) (9.5, 17.1)	72 (12.1) (9.5, 14.7)

Q8W, n (%) 95% CI	44 (15.4) (11.2, 19.6)	48 (15.6) (11.5, 19.6)	92 (15.5) (12.6, 18.4)
Q12W, n (%) 95% CI	60 (21.0) (16.3, 25.7)	62 (20.1) (15.6, 24.6)	122 (20.5) (17.3, 23.8)
Q16W, n (%) 95% CI	151 (52.8) (47.0, 58.6)	157 (51.0) (45.4, 56.6)	308 (51.9) (47.8, 55.9)

CRC, central reading center; CST, central subfield thickness; PTI, personalised treatment interval (from Q4W up to Q16W); SD-OCT, spectral-domain optical coherence tomography.
Patients randomised to the PTI arm are treated with faricimab on a Q4W dosing interval until at least the patient's Week 12 visit, or a later visit when CST meets the predefined reference CST threshold (CST <325 microns for Spectralis SD-OCT, or <315 microns for Cirrus SD-OCT or Topcon SD-OCT), as determined by the CRC. Treatment interval at a given visit is defined as the treatment interval decision made at that visit.

Proportion of patients in the faricimab PTI arm at Week 52 who achieved a Q12W or Q16W interval without an injection interval decrease below Q12W

YOSEMITE and RHINE had comparable proportions of patients in the faricimab PTI arm (67.8% and 64.3%, respectively) at Week 52 who achieved a dosing interval of Q12W or Q16W, and maintained it without an injection interval decrease below Q12W through Week 52. This was achieved by [redacted] PTI patients in the pooled ITT population.

Anatomic outcome measures using SD-OCT

Change from baseline in CST at Week 48/52/56

In both YOSEMITE and RHINE, patients treated with faricimab Q8W or PTI had numerically greater reductions in CST from baseline at Week 48/52/56 compared with patients treated with aflibercept Q8W. Results were consistent across studies.

In the pooled ITT population, the adjusted mean change in CST from baseline at Week 48/52/56 in the faricimab Q8W, faricimab PTI, and aflibercept arms was -200.9, -192.4, and -170.2 µm, respectively. The difference in adjusted mean change in CST from baseline between the faricimab Q8W and PTI arms when compared with the aflibercept Q8W arm was -30.7 µm (95% CI: -38.9, -22.5) and -22.2 µm (95% CI: -30.3, -14.0) at Week 48/52/56.

Table 16: Change from baseline in CST in the study eye at Week 48/52/56 in individual and pooled Phase III DMO studies: MMRM method (primary estimand) (ITT population)

	YOSEMITE			RHINE			Pooled YOSEMITE and RHINE		
	Fari 6.0 mg Q8W (n=315)	Fari 6.0 mg PTI (n=313)	Afli 2 mg Q8W (n=312)	Fari 6.0 mg Q8W (n=317)	Fari 6.0 mg PTI (n=319)	Afli 2 mg Q8W (n=315)	Fari 6.0 mg Q8W (n=632)	Fari 6.0 mg PTI (n=632)	Afli 2 mg Q8W (n=627)
Average of week 48, 52 and 56									
n	271	275	272	266	291	276	536	566	548
Adjusted mean (SE)	-206.6 (4.15)	-196.5 (4.13)	-170.3 (4.16)	-195.8 (4.22)	-187.6 (4.12)	-170.1 (4.19)	-200.9 (2.96)	-192.4 (2.92)	-170.2 (2.96)
95% CI for adj mean	(-214.7, -198.4)	(-204.7, -188.4)	(-178.5, -162.2)	(-204.1, -187.5)	(-195.8, -179.5)	(-178.3, -161.8)	(-206.7, -195.1)	(-198.1, -186.6)	(176.0, -164.4)
Diff in adj means vs afli (SE)	-36.2 (5.88)	-26.2 (5.86)		-25.7 (5.95)	-17.6 (5.88)		-30.7 (4.19)	-22.2 (4.16)	
95% CI for adj mean diff	(-47.8, -24.7)	(-37.7, -14.7)		(-37.4, -14.0)	(-29.2, -6.0)		(-38.9, -22.5)	(-30.3, -14.0)	

Units: microns. BCVA, best-corrected visual acuity; CRC, central reading center; CST, central subfield thickness; ILM, internal limiting membrane; IVT, intravitreal; MMRM, mixed-model repeated-measures; PTI, personalised treatment interval (from Q4W up to Q16W); VEGF, vascular endothelial growth factor.

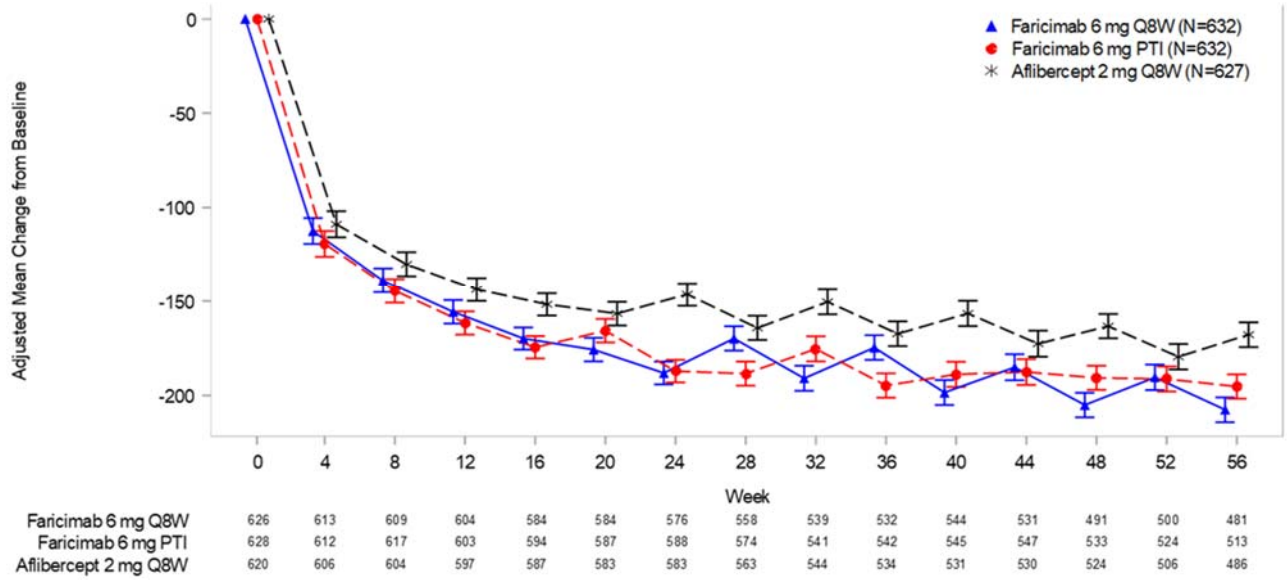
For the MMRM analysis, the model adjusted for treatment group, visit, visit-by-treatment group interaction, baseline BCVA (continuous), baseline BCVA score (< 64 letters vs. >= 64 letters), prior IVT anti-VEGF therapy (yes vs. no), region (U.S. and Canada, Asia, and the rest of the world) and study (GR40349 vs GR40398). An unstructured covariance structure is used. The estimate of the difference between the two groups is using a composite contrast over Weeks 48, 52 and 56.

Observed CST assessments were used regardless of the occurrence of intercurrent events not related to COVID-19. CST assessments were censored at the time of the occurrence of intercurrent events related to COVID-19. Missing post-baseline CST assessments and CST assessments after censoring due to COVID-19 related intercurrent events were implicitly imputed by MMRM. 95% CI is reported for pooled. 95.04% CI is reported for the individual studies. CST will be defined as the distance between ILM and Bruch's membrane (BM), as assessed by CRC

Change from baseline in CST over time

In both YOSEMITE and RHINE, patients in the faricimab Q8W and PTI arms had numerically greater reductions in adjusted mean change from baseline in CST over time through Week 56 compared with the aflibercept arm. In YOSEMITE, this was consistently observed at each post-baseline timepoint. In the pooled ITT population, patients treated with faricimab Q8W or PTI consistently had numerically greater reductions in adjusted mean change from baseline in CST over time through Week 56 compared with patients treated with aflibercept.

Figure 9: Pooled Phase III DMO studies: change from baseline in CST in the study eye over time through Week 56: MMRM method (primary estimand) (ITT population)



Proportion of patients with absence of DMO (CST <325 µm) at weeks 48, 52, and 56

In both YOSEMITE and RHINE, a higher adjusted proportion of patients treated with faricimab Q8W or PTI had an absence of DMO at Week 48, Week 52, and Week 56 compared with patients treated with aflibercept Q8W. Results were consistent across studies.

In the pooled ITT population, the adjusted proportions of patients in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arms with an absence of DMO were, respectively, [redacted]. The difference in the adjusted proportion of patients with an absence of DMO between the faricimab Q8W and PTI dosing arms when compared with the aflibercept Q8W arm was [redacted].

- In YOSEMITE, the adjusted proportion of patients with an absence of DMO (minimum–maximum) at Year 1 (Weeks 48–56) was (77.3%–87.3%) and (79.8%–82.3%) in patients treated with faricimab Q8W and faricimab PTI as compared to (64.1%–70.8%) in aflibercept Q8W patients.
- In RHINE, the adjusted proportion of patients with absence of DMO (minimum–maximum) at Year 1 (Weeks 48–56) was (84.5%–90.2%) and (82.8%-86.6%) in

patients treated with faricimab Q8W and faricimab PTI as compared to (71.4%–77.2%) in aflibercept Q8W patients.

- In the pooled ITT population, the adjusted proportion of patients with absence of DMO (minimum–maximum) at Year 1 (Weeks 48–56) was [redacted] in patients treated with faricimab Q8W and faricimab PTI as compared to [redacted] in aflibercept Q8W patients.

Proportion of patients with absence of DMO (CST <325 µm) over time

In both YOSEMITE and RHINE, the adjusted proportion of patients with an absence of DMO was higher in the faricimab Q8W and faricimab PTI arms compared with the aflibercept Q8W arm over time through Week 56. Results were consistent across studies.

In the pooled ITT population, the adjusted proportion of patients with an absence of DMO [redacted]. By Week 56, DMO was absent in over [redacted] of patients in each of the faricimab arms compared with [redacted] of patients in the aflibercept arm.

Figure 10: Pooled Phase III DMO studies: proportion of patients with an absence of DMO in the study eye over time through Week 56: CMH method (primary estimand) (ITT population)

[redacted]

Proportion of patients with absence of intraretinal fluid in the study eye through Week 56

In both YOSEMITE and RHINE, the adjusted proportion of patients with an absence of intraretinal fluid was higher in the faricimab Q8W and faricimab PTI arms compared with the aflibercept Q8W arm over time through Week 56. Results were consistent across studies

In the pooled ITT population, the adjusted proportion of patients with an absence of intraretinal fluid was consistently higher in the faricimab Q8W and faricimab PTI arms compared with the aflibercept Q8W arm over time through Week 56. At Week 56, intraretinal fluid was absent in [redacted] and [redacted] in the faricimab Q8W and faricimab PTI arms respectively, compared with [redacted] of patients in the aflibercept arm.

Table 17: Proportion of patients with absence of intraretinal fluid in the study eye at Week 56 (ITT population)

	YOSEMITE			RHINE			Pooled YOSEMITE and RHINE		
	Fari 6.0 mg Q8W (n=238)	Fari 6.0 mg PTI (n=245)	Afli 2.0 mg Q8W (n=242)	Fari 6.0 mg Q8W (n=254)	Fari 6.0 mg PTI (n=255)	Afli 2.0 mg Q8W (n=248)	Fari 6.0 mg Q8W (n=492)	Fari 6.0 mg PTI (n=500)	Afli 2.0 mg Q8W (n=490)
Week 56									
N	236	243	245	241	263	247			
Proportion, n (%)	115 (48.7)	103 (42.4)	56 (22.9)	103 (42.7)	108 (41.1)	69 (27.9)			
95% CI for prop	(42.3, 55.1)	(36.2, 48.6)	(17.6, 28.1)	(36.5, 49.0)	(35.1, 47.0))	(22.3, 33.5)			
CMH weighted estimate									
Faricimab Q8W vs Aflibercept, %	48.4		23.0	42.6		27.6			
95% CI	(42.1, 54.6)		(17.8, 28.2)	(36.5, 48.7)		(22.2, 33.1)			
Faricimab PTI vs Aflibercept, %		42.6	22.8		41.0	28.0			
95% CI		(36.4, 48.7)	(17.6, 28.1)		(35.1, 46.9)	(22.5, 33.5)			
Difference									
Diff in proportion (vs. aflibercept)	25.9	19.5		14.8	13.1				
95% CI	(17.6, 34.2)	(11.4, 27.7)		(6.4, 23.2)	(5.0, 21.3)				
Diff in CMH Weighted (vs. aflibercept)	25.4	19.7		15.0	13.0				
95% CI	(17.2, 33.5)	(11.7, 27.8)		(6.8, 23.1)	(4.9, 21.0)				

CMH, Cochran-Mantel-Haenszel; PTI, personalised treatment interval (from Q4W up to Q16W). The weighted estimate is based on CMH test stratified by baseline BCVA score (< 64 letters vs. ≥64 letters), and region (U.S. and Canada vs. the rest of the world). Asia and rest of the world regions are combined due to a small number of enrolled patients. Treatment policy strategy and hypothetical strategy were applied to non-COVID-19 related and COVID-19 related intercurrent events, respectively.
Missing data were not imputed. Estimates below 0% or above 100% are imputed as 0% or 100% respectively. Intraretinal fluid and subretinal fluid is as measured in the central subfield (centrer 1 mm).

B.3.6.3. Patient-reported outcomes

Change from baseline in NEI VFQ-25 composite score at Week 52

In both YOSEMITE and RHINE, patients treated with faricimab Q8W or PTI had similar clinically meaningful mean changes from baseline in the NEI VFQ-25 composite score at Week 24 and Week 52 compared with patients treated with aflibercept Q8W. Results were consistent across studies.

In the pooled ITT population, the adjusted mean change from baseline in the NEI VFQ 25 composite score at Week 52 was [redacted] in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arms, respectively; the difference between the faricimab Q8W and PTI dosing arms when compared with the aflibercept Q8W arm was [redacted] (92).

Table 18: Change from baseline in NEI VFQ-25 composite score at Week 52 in individual and pooled Phase III DMO studies: MMRM method (primary estimand) (ITT population)

	YOSEMITE			RHINE			Pooled YOSEMITE and RHINE		
	Fari 6.0 mg Q8W (n=315)	Fari 6.0 mg PTI (n=313)	Afli 2 mg Q8W (n=312)	Fari 6.0 mg Q8W (n=317)	Fari 6.0 mg PTI (n=319)	Afli 2 mg Q8W (n=315)	Fari 6.0 mg Q8W (n=632)	Fari 6.0 mg PTI (n=632)	Afli 2 mg Q8W (n=627)
Week 52									
n	253	256	248	249	274	259			
Adjusted mean (SE)	7.6 (0.69)	7.9 (0.69)	7.8 (0.70)	6.9 (0.68)	7.0 (0.65)	7.6 (0.67)			
95% CI for adj mean	(6.3, 9.0)	(6.6, 9.3)	(6.4, 9.2)	(5.5, 8.2)	(5.7, 8.2)	(6.3, 8.9)			
Diff in adj means vs afli (SE)	-0.2 (0.98)	0.1 (0.98)		-0.7 (0.95)	-0.6 (0.93)				
95% CI for adj mean diff[a]	(-2.1, 1.7)	(-1.8, 2.1)		(-2.6, 1.1)	(-2.5, 1.2)				

BCVA, best corrected visual acuity; MMRM, mixed-model repeated-measures; NEI VFQ-25, National Eye Institute Visual Function Questionnaire-25; PTI, personalised treatment interval (from Q4W up to Q16W).

For the MMRM analysis, the model adjusted for treatment group, visit, visit-by-treatment group interaction, baseline NEI VFQ-25 Composite Score (continuous), baseline BCVA (< 64 letters vs. >= 64 letters), prior Intravitreal anti-VEGF therapy (yes vs. no), region (U.S. and Canada, Asia, and the rest of the world) and study (GR40349 vs GR40398). An unstructured covariance structure is used. Treatment policy strategy and hypothetical strategy were applied to non-COVID-19 related and COVID-19 related intercurrent events, respectively. Missing data were implicitly imputed by MMRM. 95% CI is reported for pooled. 95.04% CI is reported for the individual studies

Change from baseline in the NEI VFQ-25 near activities, distance activities, and driving subscales over time

In both YOSEMITE and RHINE, patients treated with faricimab Q8W or PTI had similar mean changes from baseline in the NEI VFQ-25 near activities, distance activities, and driving subscale scores at Week 24 and Week 52 compared with patients treated with aflibercept Q8W. Results were consistent across studies.

In the pooled ITT population, the mean change from baseline in NEI VFQ-25 near activities score at Week 52 was [redacted] in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arms, respectively.

The mean change from baseline in NEI VFQ-25 distance activities score at Week 52 was [redacted] and [redacted] points in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arms, respectively.

The mean change from baseline in NEI VFQ-25 driving score at Week 52 was [redacted] in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arms, respectively.

Proportion of patients with a ≥4-point improvement from baseline in NEI VFQ-25 composite score at Week 52

In both YOSEMITE and RHINE, a comparable proportion of patients treated with faricimab Q8W or PTI had a ≥4-point improvement from baseline in NEI VFQ-25 composite score at Week 24 and Week 52 compared with patients treated with aflibercept Q8W. Results were consistent across studies.

In the pooled ITT population, [redacted] of patients had a ≥4-point improvement from baseline in NEI VFQ composite score in the faricimab Q8W, PTI, and aflibercept Q8W arms, respectively, at Week 52; the difference between the faricimab Q8W and PTI dosing arms when compared with the aflibercept Q8W arm was [redacted].

B.3.7 Subgroup analysis

The primary endpoint of the change from baseline in BCVA at Week 48/52/56 was analysed across various baseline demographic subgroups (e.g. by age, gender, race, baseline HbA1c, baseline visual acuity, prior intravitreal anti VEGF therapy). In the pooled ITT population, the differences in adjusted mean change in BCVA at Week 48/52/56 between treatment groups were [redacted]. Please refer to Appendix E for details.

B.3.8 Meta-analysis

As no further Phase III RCTs studying the efficacy and safety of faricimab for DMO were found, no meta-analysis was conducted.

B.3.9 Indirect and mixed treatment comparisons

YOSEMITE and RHINE compared the efficacy and safety of faricimab and aflibercept. Randomised phase III trial data comparing faricimab with ranibizumab was not available at the time of submission. To inform this comparison and explore estimates of relative effects and safety, a systematic literature review (SLR) of clinical evidence was conducted to identify relevant studies for use in the indirect comparison with faricimab. Indirect treatment comparison results are used to assess whether faricimab provides similar health benefits with comparable safety to aflibercept and ranibizumab. The data from the eligible studies was extracted and compared in a network meta-analysis. Full details are presented in Appendix D.

B.3.9.1 Identification and selection of relevant studies

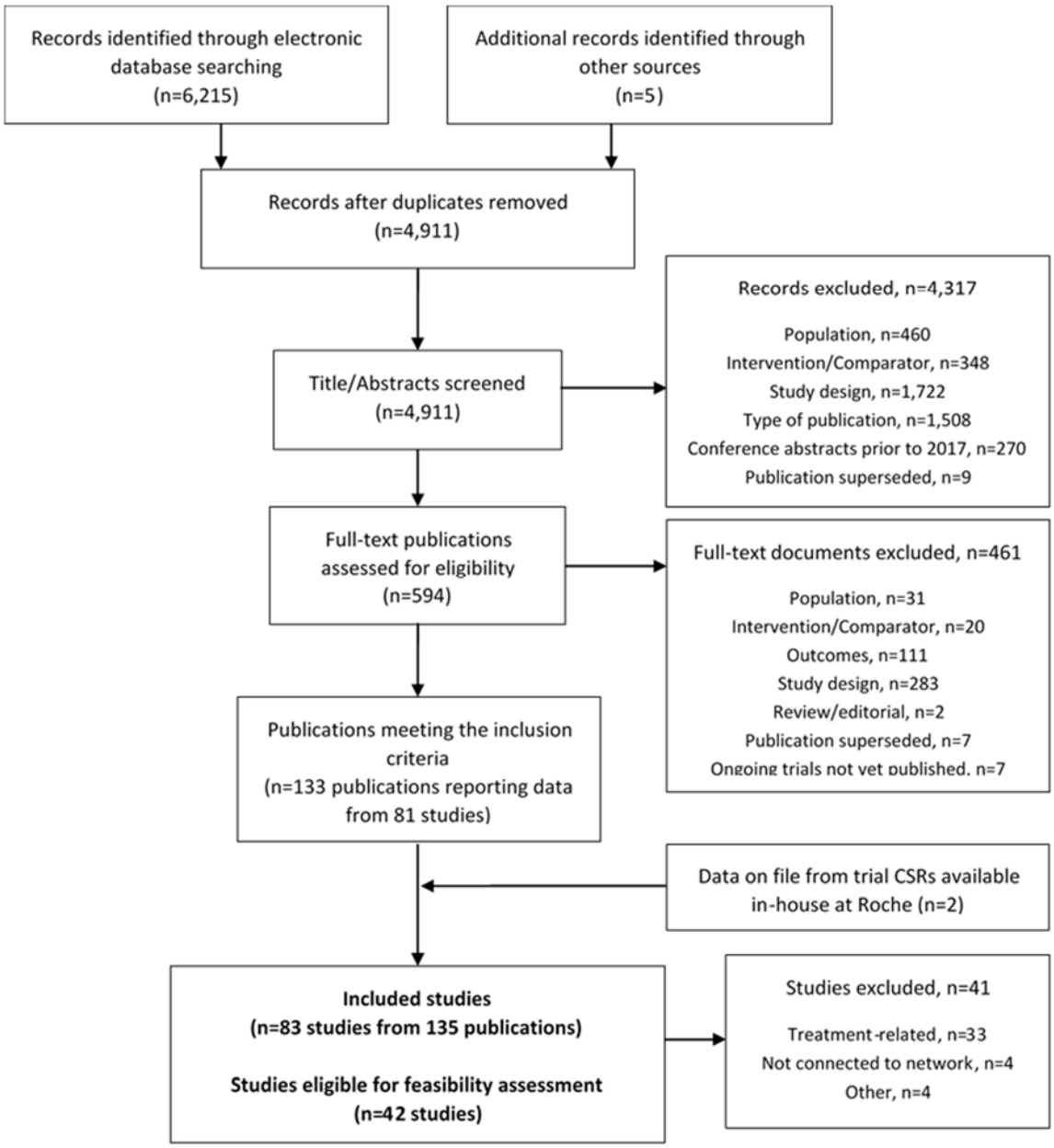
As described in section B.3.1, a systematic literature review (SLR) was conducted to identify relevant randomised controlled trial (RCT) evidence of the efficacy, safety, and HRQoL of pharmacological interventions for the treatment of DMO. In total, 6,215 publications were screened, of which 594 were reviewed at the full-text stage. After exclusion of publications not meeting the criteria, a total of 135 publications reporting 83 studies were deemed eligible for inclusion in the SLR, of which 129 were full publications and four were conference abstracts (see Figure 11). Of those, 42 studies, including YOSEMITE and RHINE (4) which were included via hand searching, were eligible for feasibility assessment (see Figure 11). Another study identified in the searches was Protocol T, which was conducted by the Diabetic Retinopathy Clinical Research Network (DRCR.net) to compare the efficacy and safety for people receiving aflibercept, bevacizumab or ranibizumab (93). Protocol T, YOSEMITE and RHINE studies were the main sources of clinical data incorporated in the cost-comparison model (see B.4.2.3) (4, 93).

Following the identification of relevant studies from the clinical SLR, a network meta-analysis (NMA) was performed to assess the efficacy and safety of faricimab compared with the relevant comparators to this appraisal: aflibercept and ranibizumab. The SLR and NMA were conducted in line with the NICE guide to the methods of technology appraisal (94). Full details are presented in Appendix D.

September 2021 update

The primary systematic literature review was completed in October 2020. Cochrane guidance states searches should be rerun if conducted more than 6 months before publication. To align with this guidance and to ensure all crucial study information had been captured in the ITC, literature searches were re-run in September 2021 following the approach taken for the original searches. After screening and full text review, four new studies were identified. None of these studies were deemed large enough, if incorporated in the ITC, to influence results in a meaningful way. Therefore, the decision was taken not to update the ITC following the re-running of the searches.

Figure 11: PRISMA Flow Chart of Included and Excluded Publications



CSR, clinical study report; NMA, network meta-analysis; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SLR, systematic literature review.

B.3.9.2 Feasibility assessment

Following identification of relevant studies from the clinical SLR, an assessment was conducted to determine the feasibility of performing a network meta-analysis (NMA) to estimate the relative effectiveness of faricimab and the relevant comparators. The eligibility criteria for the NMA were based on the population, intervention, comparator, and outcome (PICO) criteria reported in Table 19.

To improve the strength of the network, studies including treatments outside the scope of the cost-comparison analysis were included. Only results pertaining to the comparison of faricimab to aflibercept or ranibizumab are considered relevant to this appraisal.

Table 19: PICO framework for NMA

Criteria	Inclusion
Population	Patients >18 years old with DMO
Intervention	Faricimab
Comparators	Licensed and / or standard doses only (Table 20) of • Ranibizumab • Aflibercept • Bevacizumab • Dexamethasone intravitreal implants • Laser therapy • Placebo/sham
Outcomes	Timepoints for all outcomes: 12 and 24 months Vision outcomes: • Mean change from baseline in BCVA score • Proportion of patients gaining letters: o at least 15 letters o at least 10 letters • Proportion of patients avoiding loss of letters: o at least 15 letters o at least 10 letters Anatomic outcomes: • Mean change in CST Other: • Treatment frequency: o Number of injections • Overall treatment discontinuation/withdrawal Safety outcomes: • Treatment discontinuation/withdrawal due to AEs • Mortality (total number of deaths) • Overall ocular AEs rate • Overall ocular SAE rate • Overall systemic AE rate • Overall systemic SAE rate • Arterial and venous thromboembolic events • Intraocular inflammation • Glaucoma • Cataract • Endophthalmitis • Retinal detachment • Retinal pigment epithelial tear • Retinal tear • Vitreous hemorrhage • Increased Intraocular pressure

AE, adverse event; BCVA , best corrected visual acuity; CST, central subfield thickness; DMO, diabetic macular oedema; PICO, population, intervention, control, and outcomes; SAE, serious adverse event

All potential treatment strategies / dosing regimens were included:

- Fixed interval: injections are administered on a fixed schedule every X-weeks, for example, Q4W (monthly treatment); Q8W (every eight weeks), etc.
- PRN (pro re nata): injections are administered as needed, following a PRN definition pre-specified in the study protocol
- T&E (treat-and-extend): treat with the potential to extend the treatment interval, for example, +/- 2-week adjustment between treatment timings.

An overview of the treatment regimens included in the NMA is presented in Table 20. All regimens could either include or exclude a loading dose.

Table 20: Treatment doses and regimens included in the NMA

Treatment	Dose	Regimen
Aflibercept	2 mg IVT	• PRN • Q4W • Q8W
Bevacizumab	1.25 mg	• PRN • T&E
Dexamethasone	0.7 mg	• PRN
Faricimab	6.0 mg	• Q8W • PTI/T&E Q4W-Q16W
Laser	Any	• Deferred • Early • PRN
Ranibizumab	• 0.3 mg IVT • 0.5 mg IVT	• PRN • Q4W • T&E
Sham / placebo	N/A	• Treatment schedule as per active treatment

IVT, intravitreal; MG, milligram; PBO, placebo; PRN, treatment as needed (pro re nata); Q4/8/16W, every 4/8/16 weeks; RAN, ranibizumab; T&E, treat and extend

The following considerations were made when developing the networks:

- The 0.3 mg and 0.5 mg ranibizumab doses were merged into one group in the network as there is evidence to suggest that no difference exists between them when used monthly (95).
- It was also noted that the MEAD studies only permitted treatment with IVT dexamethasone no more than every six months in the 0.7 mg treatment groups and this may represent under treatment compared with clinical practice (14).
- Different approaches were taken to PRN dosing across the studies, with some studies including a loading dose regimen with more injections (range: 0 to 6) before entering the PRN stage of dosing. These variations were not considered clinically relevant, so have not been treated as separate nodes in the network.
- Patients in some studies receive laser therapy on the same day as IVT therapy, or a week later (81, 96-99). However, patients in other studies received laser therapy 3 months or more after baseline IVT therapy (100, 101). Given previous precedent of comparing the 2 approaches separately (82), early and later laser therapies have been treated as separate nodes.

- The time interval between IVT injection varied between studies, with some studies assessing for treatment and/or treating patients on a monthly basis, whilst others assessed or treated the patients on an 8-weekly basis. These differing treatment schedules have been treated as separate nodes.
- Different approaches were taken during the PRN phase of studies, with some patients receiving the same treatments as they did before PRN started, and others receiving different treatments (99, 102). These differing approaches to PRN dosing have been treated as separate nodes in the network diagram.
- Treatment regimens that have been pooled for each treatment node or are only a single study but described as PRN or T&E, are detailed in Appendix D (Tables 12–15).
- Twelve of the 42 studies included in the base case network permitted the use of rescue therapy if required by patients, including 11 studies permitting rescue with laser treatment. It was considered that this additional treatment could have a significant impact on patient outcome, particularly for efficacy outcomes. Studies are grouped by those that reported an adjustment for patient data following rescue and those that did not. Details of these studies can be seen in Appendix D, table 16.
- A large quantity of data is available for the outcomes of interest at approximately 12-month follow-up to allow comparisons between faricimab and comparators. Outcome-specific evidence networks are feasible for the majority of outcomes at 12-months.
- Fewer studies reported data at 24-month follow-up, with no 24-month data available for faricimab at the time of submission.

Results of the feasibility assessment showed that it was possible to develop a connected network of trials which assessed various treatments for DMO (see Table 20) and were similar in design to YOSEMITE and RHINE (4).

B.3.9.3 Network meta-analysis methodology

General considerations

Given the high likelihood of heterogeneity between trials, random effects models were used in the base-case analysis for all endpoints. A Bayesian framework was used when developing the network as it captures and characterises uncertainty.

Statistical models

Change from baseline in BCVA score, CST, and number of injections were modelled as continuous data, using the arm level mean change from baseline (or for number of injections, the mean number of injections since baseline) as the outcome. Both the outcome and its variance are needed. If not reported explicitly, the variance was derived from the confidence interval using standard methods based on the normal distribution. The mean change can be calculated simply as: value at follow-up – value at baseline (see Equation 1). The variance of the change can be calculated as:

Equation 1: Variance of mean change

$$Var_{base} + Var_{follow-up} - 2\rho\sqrt{Var_{base}Var_{follow-up}}$$

VAR, variance

To estimate the variance of the change, it is necessary to specify the coefficient ρ representing within-patient correlation between baseline and follow-up. In the absence of other data, a correlation coefficient of 0.5 was used, which is commonly considered conservative (103).

If the mean change was not reported or able to be derived using the above methods, the median change was used where reported. If the variance of the change was not reported or able to be derived using the above methods, it was estimated using the pooled variance (pooled standard deviation squared) of the change across all studies and arms with values in the relevant network.

Other endpoints were modelled as ordered categorical data (proportion of patients gaining/losing ETDRS letters), or as binary data (adverse events and discontinuation).

To assess whether treatment effects were influenced by patient characteristics, meta-regressions were conducted to determine the best fit for each NMA model.

B.3.9.4 NMA results

The results of the NMA models are presented in the following sections. The results of the NMA models for BCVA and injection frequency were incorporated in the economic model (see section B.4.2). The NMA results for other outcomes are presented to demonstrate the comparable efficacy and safety of faricimab to the comparators, and support the case for faricimab being appraised using the cost-comparison framework in the fast track appraisal process.

Results comparing faricimab with aflibercept or ranibizumab regimens are presented below. To strength the networks other studies that assessed different treatment regimens were included, but are not within the scope of this cost-comparison analysis, so the results of these comparisons are not presented.

BCVA

The indirect comparisons obtained through the NMA are reported in Figure 12 for faricimab (6.0 mg Q4-16W: faricimab administered in T&E regimen allowing treatment free intervals of up to 16 weeks) versus each comparator.

Figure 12: Network for mean change in BCVA from baseline to one year

AFL, aflibercept; BEV, bevacizumab; DEX, dexamethasone; FAR, faricimab; IVT, intravitreal; PBO, placebo; PRN, treatment as needed (pro re nata); Q4/8/16W, every 4/8/16 weeks; RAN, ranibizumab; T&E, treat and extend

The indirect comparisons for mean change in BCVA from baseline to one year obtained through the NMA are reported in Figure 13. The forest plot presents the differences in mean change in BCVA for faricimab (6.0 mg Q4-16W) compared with each comparator. The base-case NMA demonstrated faricimab to be associated with comparable efficacy to all comparators in terms of mean change in BCVA score from baseline to one year. Additionally, results indicate that faricimab may be favourable to ranibizumab regimens (credible intervals not crossing zero).

Figure 13: Forest plot of differences and 95% credible intervals of faricimab (6.0 mg Q4-16w) compared with other comparators: BCVA score mean change from baseline at 12m (base-case, random-effects model)

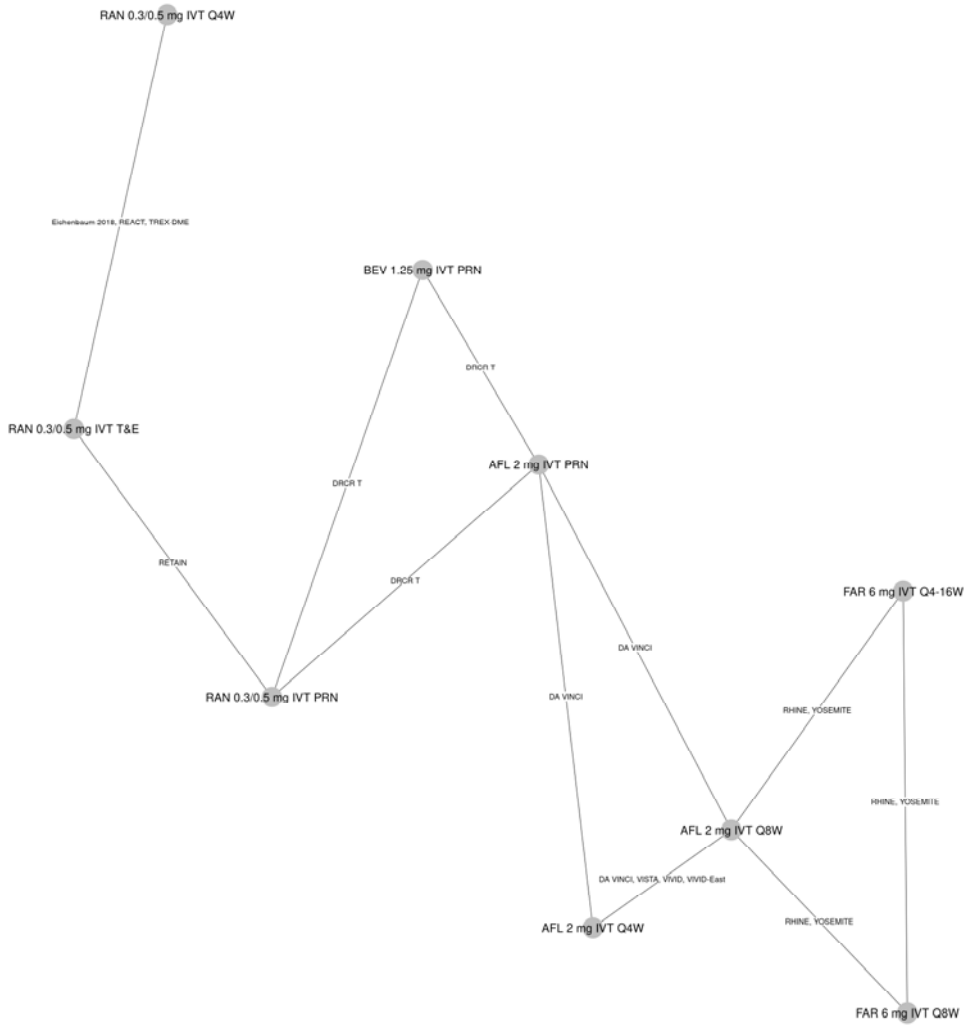
[redacted]

AFL, aflibercept; BCVA, best-corrected visual acuity; BEV, bevacizumab; DEX, dexamethasone; FAR, faricimab; IVT, intravitreal; PBO, placebo; PRN, treatment as needed (pro re nata); Q4/8/16W, every 4/8/16 weeks; RAN, ranibizumab; T&E, treat and extend

Injection frequency

The network for mean number of injections from baseline to one year is displayed in Figure 14.

Figure 14: Network diagram: Mean number of administration injections at 12 months



AFL, aflibercept; BEV, bevacizumab; DEX, dexamethasone; FAR, faricimab; IVT, intravitreal; PRN, treatment as needed (pro re nata); Q4/8/16W, every 4/8/16 weeks; RAN, ranibizumab; T&E, treat and extend

The indirect comparisons for injection administration frequency estimates obtained through the NMA are reported in Figure 15. The forest plot presents the differences in injection administration frequency for faricimab (6.0 mg Q4-16W) compared with each comparator. They demonstrate that faricimab is associated with comparable or less frequent dosing to all comparators in terms of mean number of injections at one year.

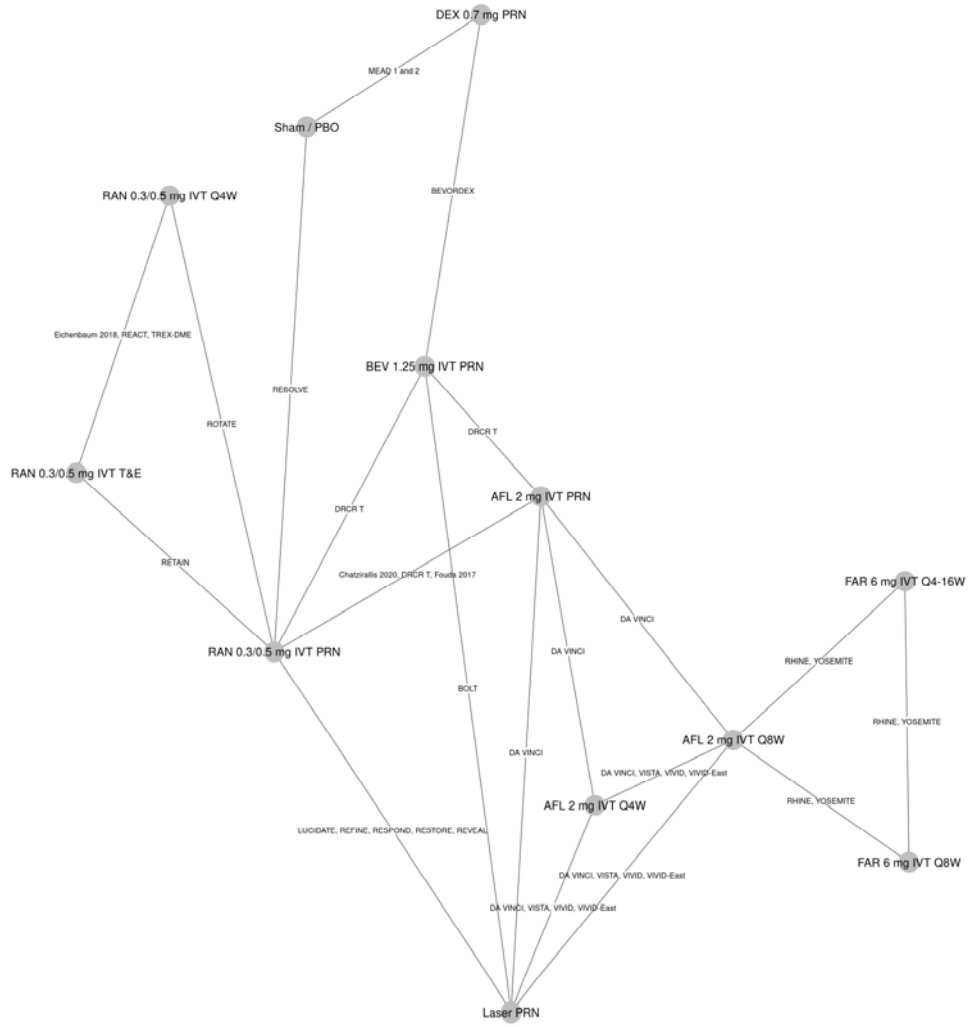
Figure 15: Forest plot of differences and 95% credible intervals of faricimab (6.0 mg Q4-16W) compared with other comparators: Mean number of injections at 12 months (base-case, random-effects model)

AFL, aflibercept; BCVA, best-corrected visual acuity; BEV, bevacizumab; DEX, dexamethasone; FAR, faricimab; IVT, intravitreal; PRN, treatment as needed (pro re nata); Q4/8/16W, every 4/8/16 weeks; RAN, ranibizumab; T&E, treat and extend

Central subfield thickness (CST)

The network for mean change in CST from baseline to one year is displayed in Figure 16.

Figure 16: Network diagram: CST mean change from baseline at 12 months



AFL, aflibercept; BEV, bevacizumab; CST; Central subfield thickness; DEX, dexamethasone; FAR, faricimab; IVT, intravitreal; PBO, placebo; PRN, treatment as needed (pro re nata); Q4/8/16W, every 4/8/16 weeks; RAN, ranibizumab; T&E, treat and extend

The indirect comparisons for CST obtained through the NMA are reported in Figure 17. The forest plot presents the differences in CST for faricimab (6.0 mg Q4-16W) compared with each comparator. Faricimab shows comparable anatomic changes to all comparators for mean change in CST from baseline to one year. The NMA results also suggest that faricimab (Q4-16W) may be favourable to all comparators.

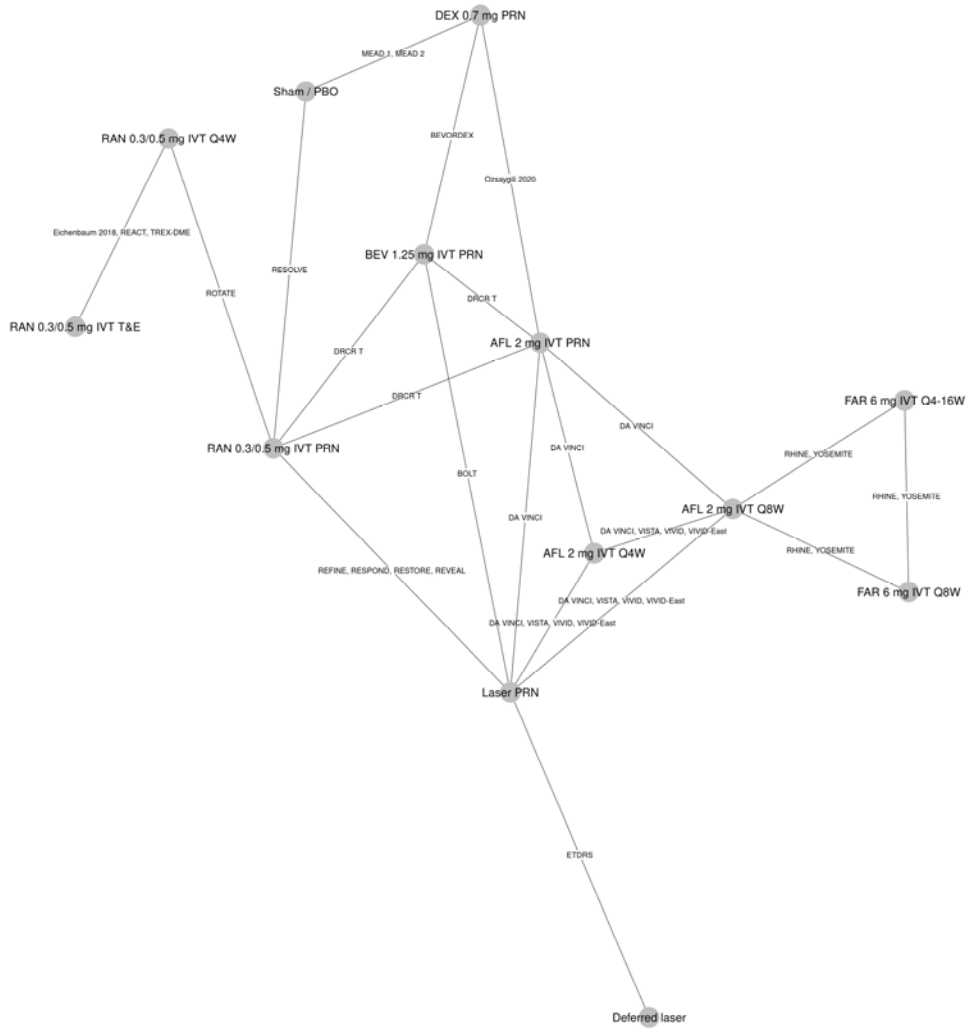
Figure 17: Forest plot of differences and 95% credible intervals of faricimab (6.0 mg Q4-16W) compared with other comparators: CST mean change from baseline at 12m (base case, RE model)

AFL, aflibercept; CST; Central subfield thickness; BEV, bevacizumab; DEX, dexamethasone; FAR, faricimab; IVT, intravitreal; PBO, placebo; PRN, treatment as needed (pro re nata); Q4/8/16W, every 4/8/16 weeks; RAN, ranibizumab; T&E, treat and extend

Proportion of patients gaining or losing ≥10/15 letters from baseline

The network for mean change in proportion of patients gaining or losing ≥10/15 letters from baseline to one year is displayed in Figure 18.

Figure 18: Network diagram: ETDRS letters categories at 12 month



AFL, aflibercept; BEV, bevacizumab; DEX, dexamethasone; ETDRS, Early Treatment Diabetic Retinopathy Study; FAR, faricimab; IVT, intravitreal; PBO, placebo; PRN, treatment as needed (pro re nata); Q4/8/16W, every 4/8/16 weeks; RAN, ranibizumab; T&E, treat and extend

The indirect comparisons for the proportion of patients gaining or losing ≥10/15 letters (assessed by ETDRS) obtained through the NMA are reported in Figure 19. The forest plot presents the differences for faricimab (6.0 mg Q4-16W) compared with each comparator.

Faricimab shows comparable vision changes to all comparators from baseline to one year. Assessment of the model suggested that there may be insufficient data to estimate the between study heterogeneity. Therefore, this result presented in Figure 19 should be interpreted with caution.

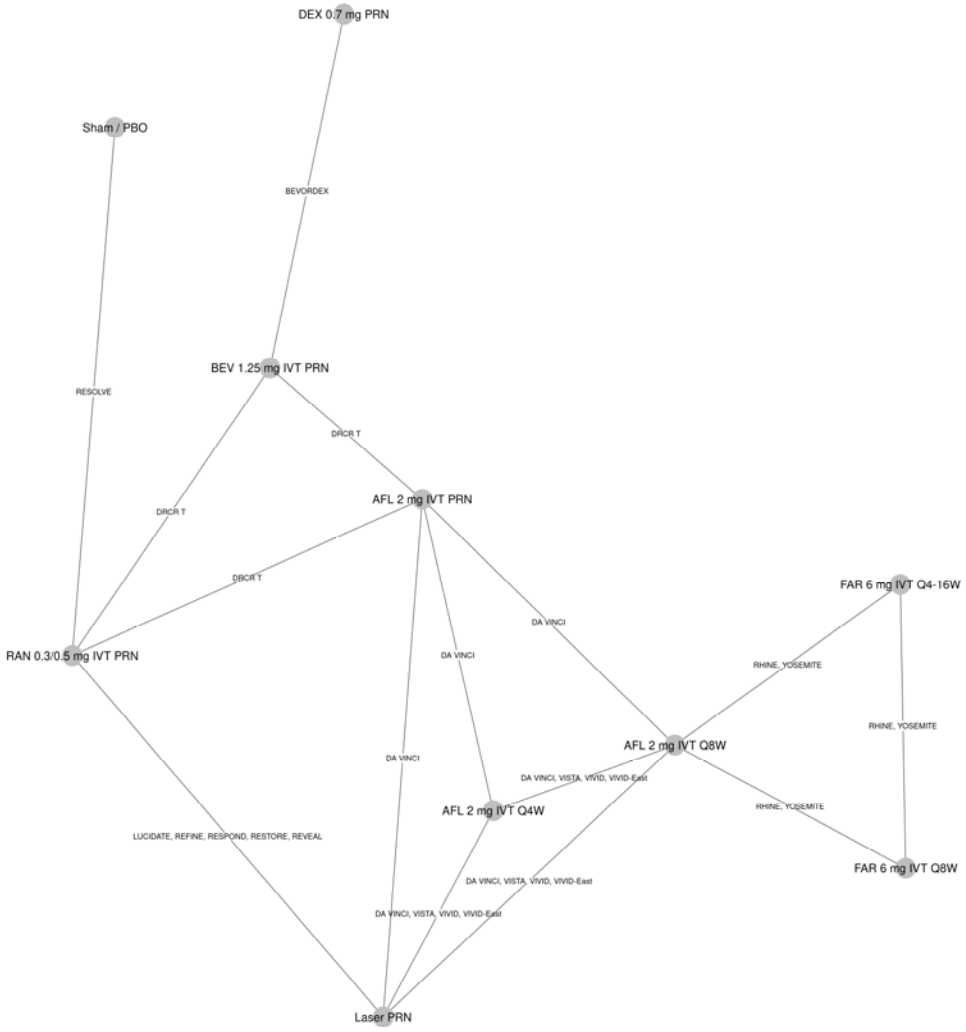
Figure 19: Forest plot of probit scale treatment differences and 95% credible intervals of faricimab (6.0 mg Q4-16W) versus other comparators: ETDRS letters categories at 12m (base case, RE model)

AFL, aflibercept; BEV, bevacizumab; DEX, dexamethasone; ETDRS, Early Treatment Diabetic Retinopathy Study; FAR, faricimab; IVT, intravitreal; PBO, placebo; PRN, treatment as needed (pro re nata); Q4/8/16W, every 4/8/16 weeks; RAN, ranibizumab; T&E, treat and extend

Discontinuation

The network for all-cause discontinuation from baseline to one year is displayed in Figure 20.

Figure 20: Network diagram: All cause discontinuation at 12 months



AFL, aflibercept; BEV, bevacizumab; DEX, dexamethasone; FAR, faricimab; IVT, intravitreal; PBO, placebo; PRN, treatment as needed (pro re nata); Q4/8/16W, every 4/8/16 weeks; RAN, ranibizumab; T&E, treat and extend

The indirect comparisons for all-cause discontinuation obtained through the NMA is reported in Figure 10 for faricimab (Q4-16W) compared with each comparator. The forest plots show that the probability of discontinuation was comparable for faricimab and all comparators from baseline to one year. A significant share of discontinuation events in YOSEMITE and RHINE are due to the death of patients, which are not considered treatment related. Given the low absolute likelihood for the occurrence of a patient's death, these are unlikely to be completely balanced across trials. This can also be seen e.g. in YOSEMITE (8 and 9 events in faricimab arms vs. 4 in aflibercept arm). Therefore, these results should be interpreted with caution.

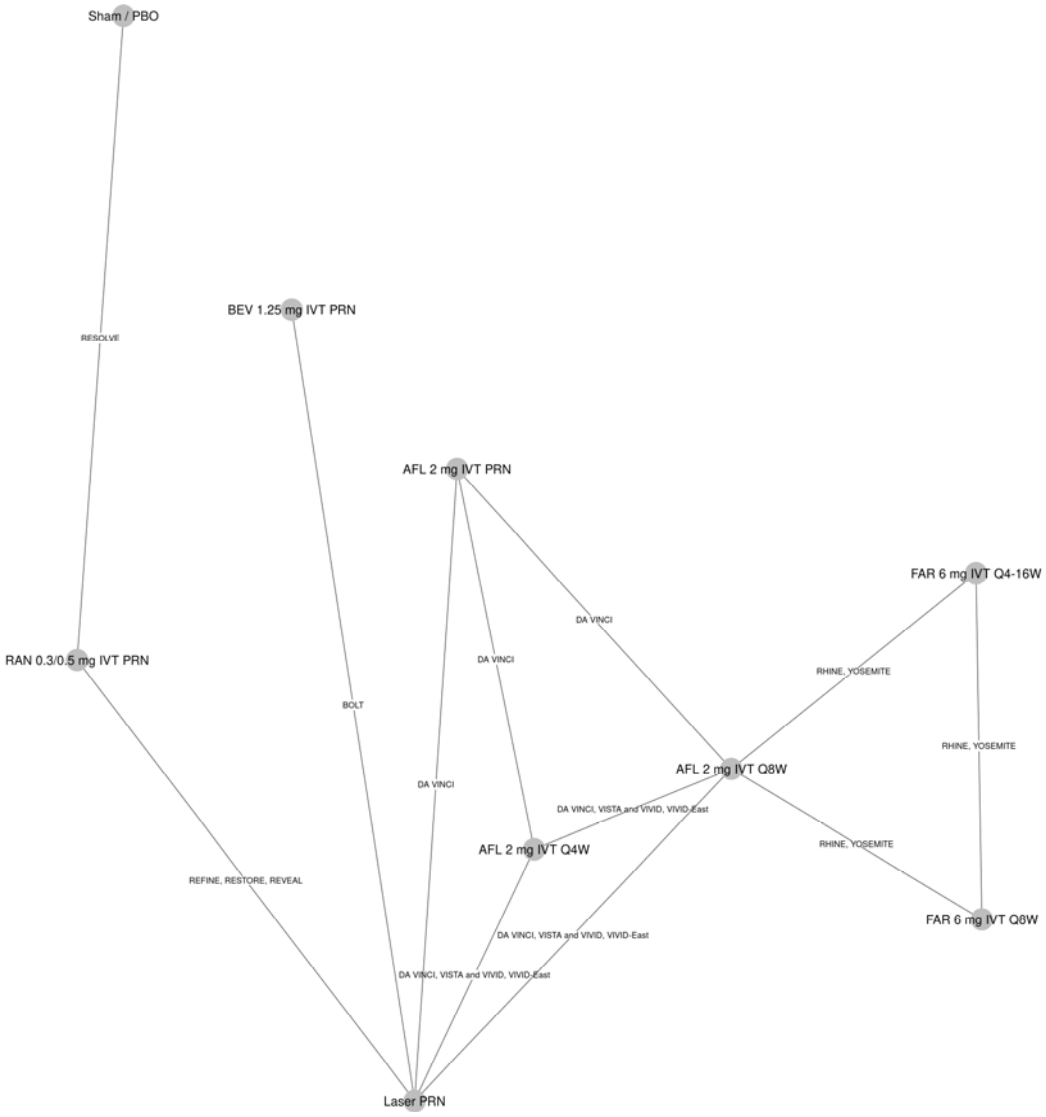
Figure 21: Forest plot of odds ratios and 95% credible intervals of faricimab (6.0 mg Q4-16W) versus other comparators: All cause discontinuation at 12 months (sensitivity, fixed-effects model)

AFL, aflibercept; BEV, bevacizumab; DEX, dexamethasone; ETDRS, Early Treatment Diabetic Retinopathy Study; FAR, faricimab; IVT, intravitreal; PBO, placebo; PRN, treatment as needed (pro re nata); Q4/8/16W, every 4/8/16 weeks; RAN, ranibizumab; T&E, treat and extend

Adverse events

The network for ocular adverse events from baseline to one year is displayed in Figure 22.

Figure 22: Network diagram: ocular adverse events at 12 months



AFL, aflibercept; BEV, bevacizumab; DEX, dexamethasone; FAR, faricimab; IVT, intravitreal; PBO, placebo; PRN, treatment as needed (pro re nata); Q4/8/16W, every 4/8/16 weeks; RAN, ranibizumab; T&E, treat and extend

The indirect comparisons for adverse events obtained through the NMA are reported in Figure 23 for faricimab (6.0 mg Q4-16W) compared with each comparator. The results demonstrate that faricimab is associated with a comparable or favourable safety profile to all comparators in terms of ocular adverse events. The NMA results for adverse events were estimated using a fixed-effects model as it was a better fit than the random-effects model (assessed by deviance information criterion [DIC]).

Additional NMA results exploring serious ocular adverse events and serious systemic adverse events support the finding that the overall safety profile of faricimab is comparable to other IVTs (see appendix D). However, given the rare occurrence of serious ocular

adverse events and the limited available evidence, the results should be interpreted with caution.

Figure 23: Forest plot of odds ratios and 95% credible intervals of faricimab (Q4-16W) compared with other comparators: Ocular adverse events at 12 months (sensitivity, fixed-effects model)

AFL, aflibercept; BEV, bevacizumab; DEX, dexamethasone; FAR, faricimab; IVT, intravitreal; PBO, placebo; PRN, treatment as needed (pro re nata); Q4/8/16W, every 4/8/16 weeks; RAN, ranibizumab; T&E, treat and extend

B.3.9.5 Uncertainties in the indirect and mixed treatment comparisons

It is acknowledged that there are some limitations associated with the NMA. In order to include all available evidence for treatments of interest, time equivalence was assumed between 48 - 56 weeks, 12 months and for one-year outcomes. Several trials, including YOSEMITE and RHINE, demonstrate that gains in visual acuity in DMO are usually achieved within the first months of treatment with anti-VEGF therapy. Further therapy beyond that point typically preserves early visual gains, with lessening amounts of improvements, therefore the assumption of equivalence across similar time points is not anticipated to affect results.

Another limitation relates to the assumption that different approaches to PRN dosing, with varying numbers of injections in a loading phase (range: 0 to 6), were grouped for the purposes of the ITC. No consensus was reached with clinical experts to determine whether the number of injections in the loading phase would influence visual outcomes. Given the absence of a clinically relevant way to categorise PRN studies, it was decided that grouping all PRN studies together was reasonable. Further to this, one clinical expert consulted by Roche noted that any differences in visual outcomes resulting from different treatment loading phases would not be significant if assessing outcomes after 1 year of treatment, the same time point considered in the NMA results.

A further limitation relates to the outcome of retinal thickness. Aspiring to include as much relevant evidence as possible, other definitions of retinal thickness (CST, central retinal thickness [CRT], central foveal thickness [CFT], central macular thickness [CMT], in that order) are used if CST values were not reported. These definitions are often used interchangeably, and previous NMAs have used similar approaches (104).

A final limitation of the NMA was that in particular for sensitivity analysis and adverse events, limited evidence was available, making these networks less robust.

Despite the above limitations, the results of the NMA are considered to be robust and represent the most recent analysis of comparative efficacy between faricimab and relevant comparators. Results of the NMA demonstrated faricimab to be associated with superior or comparable visual outcomes in terms of BCVA and superior or comparable anatomical outcomes in terms of decreasing retinal thickness with a similar or lower injection frequency than current standard of care.

B.3.10 Adverse reactions

Results of the pooled safety analysis are presented below, based on data up to Week 56 (the timepoint of the primary analysis), and all safety data up to the clinical cut-off date (CCOD) of 20 October 2020 for YOSEMITE and 19 October 2020 for RHINE (105).

B.3.10.1 Treatment exposure

Overall, treatment exposure in all treatment arms was balanced between the individual Phase III studies. The majority of the randomised patients received at least one dose of study treatment in each treatment arm of the pooled dataset through Week 56 ([redacted]); 2 patients randomised to the faricimab Q8W arm and 2 patients randomised to the aflibercept Q8W arm did not receive a dose of study drug and are, therefore, excluded in the safety-evaluable population.

The mean number of study drug administrations through Week 56 was comparable between the faricimab Q8W and the aflibercept Q8W arms and lower in the faricimab PTI arm ([redacted] in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arms, respectively), with the total number of injections in the study eye of [redacted] in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arms, respectively.

At the time of the primary analysis, the Phase III trials continue to be ongoing. Therefore, cumulative exposure data available as of the CCOD associated with the primary endpoint was also assessed (i.e., the subset of patients with follow-up data beyond Week 56). After Week 56, an additional [redacted] (median) of treatment duration for 1031 patients (out of 1262 patients) in the combined faricimab arms and [redacted] (median) of treatment duration for [redacted] (out of 625 patients) in the aflibercept Q8W arm are available up to the CCOD. As the study was ongoing at the time of the CCOD, not all patients had the same treatment duration at the time of the CCOD with some patients not having any additional treatment duration beyond Week 56.

Table 21: Summary of study treatment exposure in the study eye through Week 56 from individual and pooled Phase III DMO studies (pooled safety-evaluable population)

	YOSEMITE			RHINE			Pooled YOSEMITE and RHINE		
	Fari 6.0 mg Q8W (n=313)	Fari 6.0 mg PTI (n=313)	Afli 2 mg Q8W (n=311)	Fari 6.0 mg Q8W (n=317)	Fari 6.0 mg PTI (n=319)	Afli 2 mg Q8W (n=314)	Fari 6.0 mg Q8W (n=630)	Fari 6.0 mg PTI (n=632)	Afli 2 mg Q8W (n=625)
Mean treatment duration, weeks (SD)	53.1 (9.75)	52.9 (10.43)	53.2 (9.54)	53.1 (10.00)	54.5 (7.45)	53.7 (8.65)	[redacted]	[redacted]	[redacted]
Mean no. of administrations (SD)	9.5 (1.41)	8.4 (2.45)	9.2 (1.47)	9.3 (1.52)	8.7 (2.50)	9.3 (1.36)	[redacted]	[redacted]	[redacted]
Dose interruptions, n (%)									
n	38	54	38	60	37	42	[redacted]	[redacted]	[redacted]
At least one interrupted dose	29 (9.3)	33 (10.5)	29 (9.3)	40 (12.6)	31 (9.7)	34 (10.8)			
Intraocular inflammation	5 (1.6)	6 (1.9)	2 (0.6)	2 (0.6)	1 (0.3)	1 (0.3)			
BCVA decrease	1 (0.3)	0	1 (0.3)	0	0	1 (0.3)			
Elevated intraocular pressure	4 (1.3)	2 (0.6)	1 (0.3)	0	3 (0.9)	1 (0.3)			
Rhegmatogenous retinal detachment or macular hole	1 (0.3)	0	0	0	0	0			
Active or suspected infection	6 (1.9)	7 (2.2)	4 (1.3)	12 (3.8)	2 (0.6)	6 (1.9)			
Cataract surgery (study eye)	2 (0.6)	1 (0.3)	8 (2.6)	6 (1.9)	6 (1.9)	2 (0.6)			
On-study prohibited medications	1 (0.3)	0	0	0	0	0			
Other	16 (5.1)	20 (6.4)	18 (5.8)	26 (8.2)	21 (6.6)	24 (7.6)			
Interruptions per patient									
n	29	33	29	40	31	34	[redacted]	[redacted]	[redacted]
1	24 (7.7)	26 (8.3)	23 (7.4)	28 (8.8)	26 (8.2)	29 (9.2)			
2	2 (0.6)	3 (1.0)	3 (1.0)	7 (2.2)	4 (1.3)	4 (1.3)			
3	2 (0.6)	1 (0.3)	3 (1.0)	3 (0.9)	1 (0.3)	0			

4	1 (0.3)	1 (0.3)	0	1 (0.3)	0	0	[redacted]	[redacted]	[redacted]
5	0	1 (0.3)	0	1 (0.3)	0	1 (0.3)			
10	0	1 (0.3)	0	0	0	0			

Study drug: faricimab (Fari) or aflibercept (Afli). Study treatment: faricimab, aflibercept or sham. Treatment duration: (max date of the last dose of study treatment and date of the last treatment dose hold) minus date of the first dose plus one day. Includes study treatment received and dose hold on or prior to Day 405

B.3.10.2 Overview of safety profile

Overall, based on the pooled safety data from 1887 patients from the YOSEMITE and RHINE studies, the safety data indicate that faricimab has a comparable safety profile to aflibercept. Faricimab was well tolerated as evidenced by the low incidence of AEs leading to treatment withdrawal, and AEs were generally manageable. No new safety signals were identified.

Table 22: Overview of safety through Week 56 in pooled analysis (pooled safety-evaluable patients)

	Fari 6.0 mg Q8W (n=630)	Fari 6.0 mg PTI (n=632)	Afli 2 mg Q8W (n=625)
Total no. of patients with at least one AE	[redacted]	[redacted]	[redacted]
Total no. of AEs	2169	1891	1852
Total no. of patients with at least one SAE	[redacted]	[redacted]	[redacted]
Total no. of SAEs	272	193	191
Total no. of deaths	[redacted]	[redacted]	[redacted]
Total no. of patients withdrawn from study due to AE	[redacted]	[redacted]	[redacted]
Total no. of patients withdrawn from study treatment due to AE	[redacted]	[redacted]	[redacted]
Total no. of patients with at least one AESI	[redacted]	[redacted]	[redacted]
Ocular events: study eye			
Total no. of patients with at least one:			
AE	235 (37.3)	225 (35.6)	215 (34.4)
SAE	15 (2.4)	19 (3.0)	8 (1.3)
AE leading to study treatment withdrawal	[redacted]	[redacted]	[redacted]
Treatment related AE	[redacted]	[redacted]	[redacted]
Treatment related SAE	[redacted]	[redacted]	[redacted]
AE of special interest	15 (2.4)	17 (2.7)	6 (1.0)
Drop in VA score ≥30	[redacted]	[redacted]	[redacted]
Associated with severe IOI	[redacted]	[redacted]	[redacted]
Intervention req to prevent permanent vision loss	[redacted]	[redacted]	[redacted]
Suspected transmission of infectious agent by study drug	[redacted]	[redacted]	[redacted]
Ocular events: fellow eye			
Total no. of patients with at least one:			
AE	[redacted]	[redacted]	[redacted]
SAE	[redacted]	[redacted]	[redacted]
AE of special interest	[redacted]	[redacted]	[redacted]
Drop in VA score ≥30	[redacted]	[redacted]	[redacted]
Associated with severe IOI	[redacted]	[redacted]	[redacted]
Intervention req to prevent permanent vision loss	[redacted]	[redacted]	[redacted]
Suspected transmission of infectious agent by study drug	[redacted]	[redacted]	[redacted]
Non-ocular events			
Total no. of patients with at least one:			
AE	[redacted]	[redacted]	[redacted]
SAE	[redacted]	[redacted]	[redacted]
AE leading to study treatment withdrawal	[redacted]	[redacted]	[redacted]
AE of special interest	[redacted]	[redacted]	[redacted]

Elevated ALT or AST with either elevated bilirubin or clinical jaundice	[redacted]	[redacted]	[redacted]
Adjudicated APTC events	13 (2.1)	12 (1.9)	14 (2.2)
Non-fatal MI	[redacted]	[redacted]	[redacted]
Non-fatal stroke	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]

AE, adverse event, AESI, adverse event of special interest; Afli, aflibercept; ALT, alanine aminotransferase; APTC, Antiplatelet Trialists' Collaboration; AST, aspartate aminotransferase; Fari, faricimab; IOI, Intraocular Inflammation, MedDRA, Medical Dictionary for Regulatory Activities; PTI, personalised treatment interval (from Q4W up to Q16W), SAE, serious adverse event, VA, visual acuity.
APTC events are defined as non-fatal strokes or non-fatal myocardial infarctions or vascular deaths (including deaths of unknown cause).
Drop in VA score ≥30 is defined as causing a decrease of ≥30 VA score lasting more than 1 hour.
Intervention req. to prevent permanent vision loss is defined as required surgical or medical intervention to prevent permanent loss of sight.
Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once except for the "Total number of AEs" row in which multiple occurrences of the same AE are counted separately. Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

B.3.10.3 Ocular AEs in the study eye from the pooled Phase III DMO studies

AE by frequency through Week 56

Through Week 56, the incidence of ocular AEs occurring in the study eye was comparable across treatment arms ([redacted] in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arms, respectively), with the exception (≥2% difference in any treatment arms) of vitreous floaters ([redacted] in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arms, respectively), which were mainly mild and all non-serious.

Ocular AEs in the study eye occurring in ≥1% in any treatment arm through Week 56 are summarised below.

Table 23: Ocular adverse events in the study eye occurring in ≥1% in any treatment arm through Week 56 from pooled Phase III DMO Studies (pooled safety evaluable population)

n (%)	Fari 6.0 mg Q8W (n=630)	Fari 6.0 mg PTI (n=632)	Afli 2 mg Q8W (n=625)
Total no. of patients with at least one AE	[redacted]	[redacted]	[redacted]
Total no. of events, n	[redacted]	[redacted]	[redacted]
Conjunctival haemorrhage	[redacted]	[redacted]	[redacted]
Cataract	[redacted]	[redacted]	[redacted]
Vitreous detachment	[redacted]	[redacted]	[redacted]
Vitreous floaters	[redacted]	[redacted]	[redacted]
Intraocular pressure increased	[redacted]	[redacted]	[redacted]
Dry eye	[redacted]	[redacted]	[redacted]
Eye pain	[redacted]	[redacted]	[redacted]
Conjunctivitis	[redacted]	[redacted]	[redacted]
Cataract cortical	[redacted]	[redacted]	[redacted]

Diabetic retinal oedema	[redacted]	[redacted]	[redacted]
Medication error	[redacted]	[redacted]	[redacted]
Punctate keratitis	[redacted]	[redacted]	[redacted]
Posterior capsule opacification	[redacted]	[redacted]	[redacted]
Blepharitis	[redacted]	[redacted]	[redacted]
Vision blurred	[redacted]	[redacted]	[redacted]
Vitreous haemorrhage	[redacted]	[redacted]	[redacted]
Cataract nuclear	[redacted]	[redacted]	[redacted]
Diabetic retinopathy	[redacted]	[redacted]	[redacted]
Cataract subcapsular	[redacted]	[redacted]	[redacted]
Macular fibrosis	[redacted]	[redacted]	[redacted]
Sensation of foreign body	[redacted]	[redacted]	[redacted]
Ocular hypertension	[redacted]	[redacted]	[redacted]

MedDRA, Medical Dictionary for Regulatory Activities; Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. PTI, personalised treatment interval (from Q4W up to Q16W). For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately. Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

Through Week 56, [redacted] of patients experienced at least one ocular AE in the fellow eye in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arms, respectively. The most common ocular AEs in the fellow eye (≥2% incidence in any treatment arm: faricimab Q8W, faricimab PTI, and aflibercept Q8W arm, respectively) by PT were [redacted]

Ocular AEs suspected to be related to faricimab by the Investigator

Through Week 56, the incidence of ocular AEs suspected by the investigator to be related to faricimab [redacted]

The most common treatment-related ocular AEs in the study eye (≥0.5% incidence in either of the faricimab arms) were [redacted].

Ocular AEs suspected to be related to aflibercept by the Investigator

Through Week 56, the incidence of ocular AEs suspected by the investigator to be related to aflibercept was low [redacted]

The most common treatment-related ocular AEs in the study eye (≥0.5%) were [redacted]

Ocular AEs in study eye by severity through Week 56

The majority of ocular AEs in the study eye through Week 56 were mild or moderate in severity in the combined faricimab arms and aflibercept Q8W arms.

Through Week 56, [redacted] experienced at least one severe ocular AE in the study eye in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arm, respectively. The severe ocular AEs in the study eye suspected by the investigator to be related to study treatment were [redacted].

After Week 56 to the CCOD, [redacted] experienced at least one severe ocular AE in the study eye in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arm, respectively.

Deaths

Through Week 56, death was reported [redacted] None of the deaths were suspected by the investigator to be related to study treatment.

From baseline to the CCOD, death was reported in [redacted] of patients in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arms, respectively. None of the deaths were suspected by the investigator to be related to study treatment.

Table 24: Patient deaths through Week 56 from pooled Phase III DMO Studies (pooled safety evaluable population)

n (%)	Fari 6.0 mg Q8W (n=630)	Fari 6.0 mg PTI (n=632)	Afli 2 mg Q8W (n=625)
Total no. of deaths	[redacted]	[redacted]	[redacted]
Primary cause of death			
Death	[redacted]	[redacted]	[redacted]
Acute myocardial infarction	[redacted]	[redacted]	[redacted]
Myocardial infarction	[redacted]	[redacted]	[redacted]
Bladder cancer	[redacted]	[redacted]	[redacted]
Cardiac arrest	[redacted]	[redacted]	[redacted]
Cardiac failure	[redacted]	[redacted]	[redacted]
Adenocarcinoma of colon	[redacted]	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]	[redacted]
Cerebral haemorrhage	[redacted]	[redacted]	[redacted]
Completed suicide	[redacted]	[redacted]	[redacted]
Coronary artery disease	[redacted]	[redacted]	[redacted]
Diabetic complication	[redacted]	[redacted]	[redacted]
Diabetic gangrene	[redacted]	[redacted]	[redacted]
Embolism	[redacted]	[redacted]	[redacted]
General physical health deterioration	[redacted]	[redacted]	[redacted]
Hypotension	[redacted]	[redacted]	[redacted]

Left atrial dilation	[redacted]	[redacted]	[redacted]
Leukaemia	[redacted]	[redacted]	[redacted]
Pneumonia aspiration	[redacted]	[redacted]	[redacted]
Sepsis	[redacted]	[redacted]	[redacted]
Type 1 diabetes mellitus	[redacted]	[redacted]	[redacted]

PTI, personalised treatment interval (from Q4W up to Q16W). Percentages for Total Number of Deaths are relative to total N. All other percentages are relative to n within each module. Includes death occurred on or prior to Day 405 (last day of Week 56 analysis visit window.

Serious ocular AEs in the study eye

Through Week 56, [redacted] However, the incidence was [redacted].

From baseline to the CCOD, [redacted] of patients experienced at least one serious ocular AE in the study eye in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arms, respectively.

Table 25: Serious ocular adverse events in the study eye through Week 56 from pooled Phase III DMO Studies (pooled safety evaluable population)

n (%)	Fari 6.0 mg Q8W (n=630)	Fari 6.0 mg PTI (n=632)	Afli 2 mg Q8W (n=625)
Total no. of patients with at least one AE	[redacted]	[redacted]	[redacted]
Total no. of events, n	[redacted]	[redacted]	[redacted]
Diabetic retinal oedema	[redacted]	[redacted]	[redacted]
Endophthalmitis	[redacted]	[redacted]	[redacted]
Cataract	[redacted]	[redacted]	[redacted]
Vitreous haemorrhage	[redacted]	[redacted]	[redacted]
Uveitis	[redacted]	[redacted]	[redacted]
Visual acuity reduced transiently	[redacted]	[redacted]	[redacted]
Ocular hypertension	[redacted]	[redacted]	[redacted]
Retinal tear	[redacted]	[redacted]	[redacted]
Cataract subcapsular	[redacted]	[redacted]	[redacted]
Chemical burns of eye	[redacted]	[redacted]	[redacted]
Chorioretinitis	[redacted]	[redacted]	[redacted]
Device dislocation	[redacted]	[redacted]	[redacted]
Diabetic retinopathy	[redacted]	[redacted]	[redacted]
Dry eye	[redacted]	[redacted]	[redacted]
Glaucoma	[redacted]	[redacted]	[redacted]
Influenza	[redacted]	[redacted]	[redacted]
Intraocular pressure increased	[redacted]	[redacted]	[redacted]
Keratouveitis	[redacted]	[redacted]	[redacted]
Macular fibrosis	[redacted]	[redacted]	[redacted]
Narrow anterior chamber angle	[redacted]	[redacted]	[redacted]
Retinal artery occlusion	[redacted]	[redacted]	[redacted]

Retinal neovascularisation	[redacted]	[redacted]	[redacted]
Retinal vein occlusion	[redacted]	[redacted]	[redacted]
Rhegmatogenous retinal detachment	[redacted]	[redacted]	[redacted]
Uveitic glaucoma	[redacted]	[redacted]	[redacted]
Viral keratouveitis	[redacted]	[redacted]	[redacted]
Visual impairment	[redacted]	[redacted]	[redacted]

MedDRA, Medical Dictionary for Regulatory Activities; Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. PTI, personalised treatment interval (from Q4W up to Q16W). For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately. Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

Adverse events that led to withdrawal of study treatment or study discontinuation

Through Week 56, the incidence of ocular AEs leading to study treatment discontinuation was [redacted] Similarly, the incidence of ocular AEs leading to study discontinuation was [redacted].

From baseline to the CCOD, [redacted] experienced at least one ocular AE that led to study treatment discontinuation in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arms, respectively. After Week 56 to the CCOD, [redacted].

Adverse events that led to dose interruption

Overall through Week 56, the incidence of ocular AEs leading to dose [redacted] (Table 82).

From baseline to the CCOD, 3[redacted] experienced at least one ocular AE that led to dose interruption in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arms, respectively.

Ocular selected adverse events

Intraocular inflammation

Through Week 56, the incidence of IOI events in the study eye was low and generally comparable across all treatment arms ([redacted] in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arms, respectively. In assessing cumulative data from baseline to the CCOD, [redacted] experienced at least one IOI event in the study eye in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arm, respectively.

Retinal vascular occlusive disease

Through Week 56, [redacted] experienced a retinal vascular occlusive disease AE in the study eye in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arms, respectively. After Week 56 to the CCOD, there was

[redacted]

B.3.11 Conclusions about comparable health benefits and safety

Despite the proven efficacy of anti-VEGF monotherapies for the treatment of DMO in controlled clinical trial settings, many patients fail to achieve and maintain similar outcomes in clinical practice (64-66). Furthermore, the frequent injections needed to maintain efficacy is a cause of stress and anxiety for patients (48), with the requirement for multiple clinic visits for treatment and/or monitoring to achieve optimal long-term outcomes results in a high burden for patients, caregivers, and healthcare professionals (14, 67). Therefore, there is a need for novel treatment options beyond anti-VEGF monotherapy that can extend treatment intervals for longer, without compromising efficacy and safety.

Faricimab is a first-in-class dual-pathway inhibitor for ocular use of Ang-2 and VEGF, two key drivers of DMO. The unique dual inhibition of two distinct ligands with faricimab, mediated through two distinct receptors (the VEGF receptor and the Tie2 receptor), reduces vascular permeability and inflammation, inhibits pathological angiogenesis, and restores vascular stability. Hence, faricimab's approach of targeting two very distinct and separate pathways is crucially different to the broad binding of aflibercept to multiple members of the VEGF family of growth factors.

The Phase 3 YOSEMITE and RHINE trials for DMO were designed to primarily show noninferiority of faricimab compared with aflibercept in the ITT population, which included both anti-VEGF treatment-naïve and previously treated patients. An additional objective was to assess extended durability of faricimab compared with a fixed-interval aflibercept regimen dosed per the prescribing information (106). Clinical experts concurred that the enrolled populations are reflective of patients seen in UK clinical practice, although they noted that generalisability of the study population to UK patients is not important for DMO since patients are treated irrespective of age and gender (69).

To address heterogeneity of treatment response in DMO, the studies incorporated an innovative PTI dosing regimen based on the widely used treat-and extend (T&E) concept, which allowed for incremental changes by 4 weeks up to a maximum of Q16W, with reductions by 4 and 8 weeks if needed. The PTI design was informed by the Phase 2 BOULEVARD trial, which demonstrated superior VA gains with faricimab compared to ranibizumab monotherapy at week 24, and suggested that faricimab patients experienced greater durability of effect, with greater average times to disease reactivation in the off-treatment period (79). Compared to previous T&E regimens, PTI extensions of 4 weeks (compared to 2 weeks) and to a maximum Q16W interval (compared Q12W) could help reduce the frequency of scheduled visits, with a reduced treatment burden helping to improve real-world outcomes.

In YOSEMITE and RHINE, the pre-specified primary endpoint was met; both the faricimab Q8W and up to Q16W PTI treatment regimens demonstrated non-inferiority in mean change from baseline in BCVA at Week 48/52/56 compared with aflibercept Q8W in patients with DMO. The non-inferiority of the faricimab PTI regimen compared with the aflibercept Q8W regimen on the primary endpoint in these analyses highlights the durability of faricimab whereby, at Week 52, [redacted] of patients were on a faricimab ≥Q12W or Q16W dosing

regimen, and [redacted] of patients were on a Q16W regimen, therefore [redacted] Furthermore, [redacted] represents a clinically meaningful reduction in the treatment burden in patients with DMO. Similar results to the aflibercept Q8W treatment regimen were also demonstrated for faricimab Q8W and Q16W via multiple secondary outcomes based on VA and patient-reported quality of life.

The results of the anatomical outcomes, namely a [redacted]. In totality, the improved anatomic outcomes observed with faricimab offer signficiant benefits to both physicians and patients in UK clinical practice given that [redacted] are strong drivers for deciding when to treat. As such, the anatomical benefits observed with faricimab will allow physicians to extend treatment intervals for this regimen, thereby reducing the frequency of injections and alleviating the burden on patients and caregivers. Despite patients having attended monthly in YOSEMITE and RHINE to maintain masking during treatment, the PTI algorithm only utilised data collected at dosing visits to guide changes to the treatment interval. Thus, in real-world practice there may be no requirement for monthly monitoring between treatment visits.

Safety data from YOSEMITE and RHINE indicate that faricimab was generally well tolerated and has a comparable safety profile to aflibercept, as evidenced by the low incidence of serious ocular AEs, ocular AESIs and AEs leading to treatment withdrawal. No new or unexpected safety signals were identified in the clinical trial program compared with aflibercept.

Overall, UK clinical experts were encouraged by the efficacy, druability and anatomical benefits associated with faricimab, adding that the Q12W and Q16W dosing would correspond well with routine monitoring for diabetic retinopathy, thereby foregoing the need for additional monitoring and treatment appointments (69).

A NMA was conducted to provide a robust and current analysis of comparative efficacy between faricimab and relevant comparators. Results of the NMA demonstrated faricimab to be associated with superior or comparable visual outcomes in terms of BCVA and superior or comparable anatomical outcomes in terms of decreasing retinal thickness with a similar or lower injection frequency than current standard of care. Adverse events were also found to be comparable for faricimab and relevant comparators.

A limitation of the current available evidence is that only 1-year data for YOSEMITE and RHINE are currently reported. However, 2-year outcomes are expected in [redacted] and will provide further robust evidence for the potential for faricimab to improve retinal stability and deliver sustained efficacy, in addition to the potential for the PTI approach to reduce the burden of frequent visits and injections while maintaining vision outcomes through individual optimisation of treatment intervals. The prespecified and automatically assigned interval

adjustments (with potential for dosing intervals of up to Q16W) based on CST and BCVA at dosing visits, and regardless of the CST and BCVA measurements at sham visits, are key features of the study design that will support this evaluation.

Conclusion

The results of the Phase III clinical trials provide strong evidence of the efficacy, safety, and optimal treatment frequency of faricimab in patients with DMO. The pivotal studies YOSEMITE and RHINE demonstrate that patients receiving faricimab up to Q16W via a PTI regimen can maintain vision gains equivalent to aflibercept Q8W. Together with the improved anatomical outcomes such as the absence of DMO and IRF observed, faricimab offers signficant benefits to both physicians and patients in UK clinical practice as the regimen allows for extended injection intervals and fewer injections without compromising vision gains or safety.

With its unique dual mechanism of action, which supports the increased durability of effect, faricimab brings innovation to DMO, providing patients with a much needed opportunity to alleviate the substantial treatment burden associated with current anti-VEGF therapies while optimising disease control for those living with DMO. Moreover, an additional longer-acting treatment option that reduces the need for future treatment and monitoring visits will also help to alleviate the burden on the healthcare system, particularly in the context of the COVID-19 pandemic, while ensuring patients retain continuity of treatment and ultimately maintain their vision.

B.3.12 Ongoing studies

Two-year data for YOSEMITE and RHINE will be available in [redacted].

RHONE-X is a 2-year, global, single-arm, open-label extension study to evaluate the long-term safety and tolerability of faricimab in patients with DMO who have completed YOSEMITE or RHINE. Timelines for availability of the one-year data (i.e. 3 years from start of YOSEMITE/RHINE) from RHONE-X are to be confirmed.

B.4 Cost-comparison analysis

B.4.1 Changes in service provision and management

Faricimab is anticipated to be used in the hospital setting, in line with the currently licensed anti-VEGF therapies used for DMO, aflibercept and ranibizumab. No additional requirements in terms of service provision or disease management are expected.

Treatment with faricimab stabilises DMO such that the majority of patients are anticipated to receive faricimab q16w after the initial loading dose phase. Model estimates suggest that patients receiving faricimab have a lower total number of injection and monitoring visits than those on aflibercept or ranibizumab. Details of the resource use associated with the use of faricimab are provided in Section B.4.2.8 below.

B.4.2 Cost-comparison analysis inputs and assumptions

B.4.2.1 Features of the cost-comparison analysis

The objective of this analysis was to evaluate the costs associated with faricimab versus aflibercept and ranibizumab for the treatment of DMO from a UK (England and Wales) healthcare system perspective. A cost-comparison model was developed to capture the lifetime costs of people with DMO treated with faricimab, aflibercept or ranibizumab.

Results from the YOSEMITE and RHINE trials found faricimab to be non-inferior to aflibercept in terms of change from baseline to year 1 in best-corrected visual acuity (see section B.3.6). In the trials, faricimab demonstrated superiority to aflibercept in terms of several anatomical outcomes: change from baseline in CST, absence of DMO and absence of IRF (see section B.3.6). The results of a network meta-analysis study also demonstrated that faricimab was non-inferior to aflibercept and ranibizumab in terms of change in BCVA, and had a comparable safety profile (see section B.3.8). The NMA results also found favourable results for faricimab in terms of BCVA gains compared with ranibizumab regimens, and in terms of change in CST compared with all comparators. Clinical expert opinion, trial evidence and network meta-analysis results all suggest that adverse events are comparable across the treatments, occur rarely and are generally mild in severity. The observed discontinuation rates in YOSEMITE and RHINE were similar for faricimab and aflibercept, and the results of the network meta-analysis found that the annual probability of discontinuation was comparable and low for faricimab, aflibercept and ranibizumab.

As such, a cost comparison whereby treatment efficacy, treatment safety and treatment discontinuation were all set equal was deemed appropriate and the preferred model framework.

An overview of the features of the cost-comparison analysis are presented in Table 26 below:

Table 26: Features of the cost-comparison analysis

Component	Approach
Population	Adults aged ≥ 18 years with visual impairments caused by DMO (reflecting the populations in the YOSEMITE and RHINE trials)
Intervention	Faricimab (6 LP → q16w/q12w [T&E] → PRN)
Comparator	Aflibercept (2 LP → PRN) Ranibizumab (0.5 LP → PRN)
Outcome	Incremental cost per patient and total cost per patient
Perspective	NHS and Personal Social Services (PSS) in England and Wales
Time horizon	Lifetime - 25 years
Discounting	Costs discounted at 3.5% per annum

DMO: diabetic macular oedema; LP: loading phase; NHS: National Health Service; PSS: Personal Social Services; PRN: pro re nata; qXw: one injection every X weeks; T&E: treat and extend

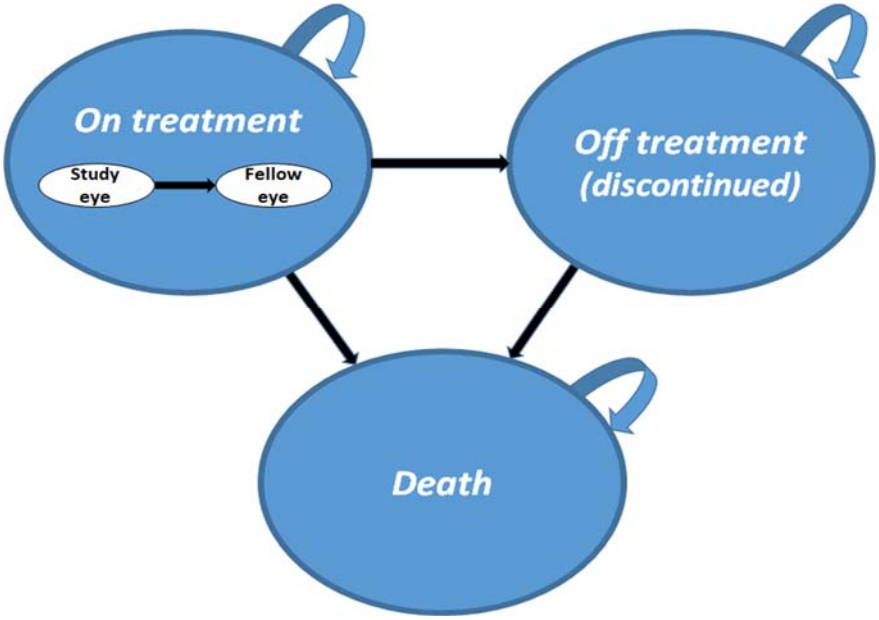
B.4.2.2 Model structure

A cost-comparison model was developed in Microsoft Excel ® 2016 using a Markov cohort approach to calculate the proportion of patients across three health states over time: On treatment (unilateral “study eye” or bilateral “fellow eye” treatment); Discontinued treatment (off treatment) and Death (Figure 24). Patients could enter the model with either unilateral or bilateral disease. Patients with unilateral disease could develop bilateral disease over time according to an annual probability of developing fellow eye DMO involvement. Once patients developed bilateral disease, they could not revert to having unilateral disease. The general modelling approach and inputs were cross referenced with previous technology appraisals and subsequently validated by external health economists and UK clinical experts.

A lifetime time horizon (25 years) was adopted in line with the NICE reference case (94). The time horizon was considered to be sufficiently long to reflect any differences in costs between the technologies being compared. A cycle length of 4-weeks was adopted, reflecting the shortest treatment period (q4w) which could be applied in the model. In line with the NICE reference case (94) a discount rate of 3.5% was applied to costs and benefits in the model. The impact of applying a discount rate of 1.5%, in-line with the proposals included in the ongoing NICE methods consultation (107), was explored in a scenario analysis (see section B.4.4).

To assess the plausibility and robustness of the model predictions, the impact of varying certain assumptions and parameter values were explored in sensitivity and scenario analyses (see section B.4.4).

Figure 24: Cost-comparison model structure



B.4.2.3 Patient population

The patient population considered in the analysis was reflective of the anticipated marketing authorisation for faricimab and the populations evaluated in the YOSEMITE and RHINE trials: adults aged ≥ 18 years with diabetes mellitus (type 1 or 2) and decreased visual acuity attributable primarily to DMO (4).

YOSEMITE and RHINE are identical in design, were conducted in parallel, and there are no relevant imbalances in key baseline characteristics between the patient populations (see section B.3.6). The main data sources used in the model are the pooled data covering the patient populations of YOSEMITE and RHINE (4), the population from Protocol T (93, 108, 109) who received either aflibercept or ranibizumab, and the populations of studies included in the network meta-analysis (see sections B.3.6 and B.3.8).

A restriction of the FTA process is that the appraised population must align with that covered by the NICE recommendations for the comparator technologies. That is, adults with visual impairment caused by DMO with a central retinal thickness of 400µm or more. Given that stratification of CRT </> 400µm was not pre-specified in YOSEMITE and RHINE, it was not possible to align the model population with the restricted appraisal population. To consider these data, post-hoc analyses breaking randomisation would be required, which would represent a limitation when interpreting the results. Consultation with UK clinical experts supported the view that relative efficacy and safety for faricimab and the comparators in the group of with CRT > 400µm would be consistent with the overall population (any CRT). Further to this, similar challenges and arguments were accepted by the appraisal committee in TA346 (3) when considering the comparison of aflibercept and ranibizumab.

In the base case analysis, baseline characteristics, including age and gender, were derived from the ITT populations of the YOSEMITE and RHINE trials (Table 27). Estimates of the proportion of patients with unilateral or bilateral DMO at baseline, were informed by values used in the appraisal of aflibercept for DMO (TA346) (3). Feedback from UK clinical experts

agreed that the baseline characteristics of the model were generalisable to UK clinical practice.

Bilateral disease was assumed to require bilateral treatment. Patients with unilateral disease were also assumed to be at risk of developing DMO in the fellow eye (bilateral disease) over time. In the base case analysis, the annual probability of developing wAMD in the fellow eye (10%) was informed from estimates provided by clinical experts in the appraisal of aflibercept in DMO (TA346) (3). These figures were also validated during consultation with UK clinical experts undertaken by Roche (see section B.4.2.11). A scenario analysis was conducted to explore the impact of varying bi-lateral prevalence and incidence.

Table 27: Modelled population baseline characteristics

Characteristic	Value	Source
Age, mean (SD) at baseline	62 years (3.1)	YOSEMITE and RHINE trials
Percentage male	60%	YOSEMITE and RHINE trials
Prevalence of DMO in second eye at baseline	46.5%	TA346 assumption and clinical expert opinion
Monthly incidence of DMO in second eye	0.81%	TA346 assumption and clinical expert opinion

SE; standard error: SD; standard deviation

B.4.2.4 Mortality

Mortality was modelled by applying general population all-cause mortality data obtained from England and Wales National Life Tables published by the Office for National Statistics (2019) based on 2017−2019 mortality data (110). To reflect the patient population in the model, age- and gender-specific mortality rates were combined into a single rate using the proportion of males and mean age set in the model to reflect the patient population in the YOSEMITE and RHINE trials. In line with the approach used in the appraisal of aflibercept for DMO, mortality was further adjusted by applying a diabetes specific hazard (111) for the entire population as well as health state mortality risks from being blind and visually impaired.

The results of the network meta-analysis and consultation with UK clinical experts supported the view that faricimab was similar in efficacy and safety to aflibercept and ranibizumab. As such, given there was no evidence to suggest that mortality rates would differ across treatments, the annual rate of mortality was assumed to be equivalent for faricimab, aflibercept and ranibizumab.

B.4.2.5 Intervention and comparators' acquisition costs

A summary of the acquisition costs for faricimab, aflibercept and ranibizumab is presented in Table 28 below. The drug acquisition costs for aflibercept and ranibizumab were based on the list price stated in the British National Formulary (112). Whilst confidential patient access scheme (PAS) discounts have been agreed with the Department of Health for aflibercept and ranibizumab, the size of these discounts is unknown to Roche and therefore the list price for each treatment was used in the base case cost comparison analyses. Scenario

analyses exploring the impact of varying the discounts applied to the list price of aflibercept and ranibizumab have been conducted (see section B.4.4).

If recommended, faricimab will be available at a simple confidential discount PAS price of [redacted] ([redacted] to list price £857). This net price has been used in the base case cost comparison analysis.

Table 28: Acquisition costs of the intervention and comparator technologies

	Faricimab	Aflibercept	Ranibizumab
Pharmaceutical formulation	120 mg/mL solution for injection vial	2 mg/50 µL solution for injection vial	1.65 mg/0.165 mL solution for injection in pre-filled syringe
(Anticipated) care setting	Hospital	Hospital	Hospital
Acquisition cost (excluding VAT) *	**Net price*** [redacted]	**NHS list price (112)** £816.00	**NHS list price (112)** £551.00
Method of administration	Intravitreal injection	Intravitreal injection	Intravitreal injection
Dose	6 mg	2 mg	0.5 mg
Dosing regimen	6 LP → q16/12w (T&E) → PRN	2 LP→ PRN	0.5 LP → PRN
Dosing frequency	Year 1: 8.40 Year 2: 4.70 Year 3+: 1.90	Year 1: 9.20 Year 2: 5.00 Year 3+: 2.37	Year 1: 9.40 Year 2: 5.40 Year 3+: 2.17
Separate monitoring visits	Year 1: 0.00 Year 2: 0.00 Year 3+: 2.10	Year 1: 3.75 Year 2: 4.40 Year 3+: 1.63	Year 1: 3.26 Year 2: 3.90 Year 3+: 1.83

* Price listed includes an approved patient access scheme.

LP: loading phase; PRN: pro re nata; PRNX: pro re nata and extend dosing regimen; qXw: one injection every X weeks; T&E: treat-and-extend dosing regimen; VAT: value added tax.

B.4.2.6 Dosing regimens

For faricimab, a 6 mg LP→ T&E → PRN dosing regimen was included in the base case analysis. This is in line with the faricimab personalised treatment interval (PTI) arm in YOSEMITE and RHINE which included a loading phase of four injections (one a month for 4 months). PTI is a protocol-driven treat-and-extend regimen in which treatment intervals are adjusted based on individualised treatment response, as measured by central subfield thickness (CST) and visual acuity. Dosing intervals in the PTI arm could be extended up to every 16 weeks (q16w), in increments of 4 weeks. This is also in line with the anticipated marketing authorisation for faricimab (5). The PTI approach was developed by taking into account key learnings from previous studies that evaluated treat and extend approaches in treating patients with DMO (113, 114). Consultation with UK clinical experts confirmed that the PTI arm was reflective of T&E regimens, and if administering faricimab in clinical practice they would expect to follow a T&E regimen in the first years of treatment.

A range of dosing schedules are available for aflibercept and ranibizumab. In the base case analysis, it is assumed that aflibercept and ranibizumab are administered using a pro re nata (PRN) regimen. In PRN (as needed) regimens, patients receive treatment in response to disease activity. Prior to commencing the PRN regimen, it is assumed that patients receiving aflibercept or ranibizumab would receive five injections (one per month for 5 months) in a treatment loading phase (aflibercept 2 mg LP → PRN, ranibizumab 0.5 mg LP → PRN). This is in line with the treatment and monitoring schedule in Protocol T, a trial comparing visual acuity loss for people receiving aflibercept, bevacizumab or ranibizumab (93). No consensus was reached with UK clinical experts regarding a preferred treatment regimen for alfibercept and ranibizumab, however it was agreed that PRN regimens are regularly used in clinical practice for administering anti-VEGF therapies.

Alternative dosing regimens for the comparator treatments can be applied in the model. Estimates of the dosing and monitoring frequencies associated with alternative regimens are informed by YOSEMITE and RHINE and the outputs of the network meta-analysis (see section B.3.8).

B.4.2.7 Treatment discontinuation

Observed discontinuation rates in YOSEMITE and RHINE (4) and the results of the network meta-analysis found that the annual probability of discontinuation for people treated with faricimab, aflibercept and ranibizumab was low and comparable across treatments (see sections B.3.6 and B.3.8). This finding was reflected in the base-case analysis where the annual probability of treatment discontinuation to year 5 was assumed to be equivalent for faricimab, aflibercept and ranibizumab. This assumption was supported by clinical expert opinion (see section B.4.2.11).

The annual probability of discontinuation from years 1 to 5 was based on pooled data from the faricimab PTI arms from YOSEMITE and RHINE. A separate rate of discontinuation is assumed in year 1 based on discontinuation probabilities observed in the pooled year 1 data from YOSEMITE and RHINE. The probability of discontinuation was assumed to be constant from years 2 to 5 based on the annualised probability of discontinuation derived from patients' part way through the second year of YOSEMITE and RHINE (4).

UK clinical experts consulted by Roche suggested that in the majority of cases DMO could be well controlled with treatment, and in 80 to 90% of cases people would no longer receive anti-VEGF injections after 5 years of treatment (see section B.4.2.11). To reflect this, a maximum treatment duration of 5 years from baseline was applied for the study eye in the base case analysis. After this point, 85% of those who were alive and on treatment were assumed to discontinue treatment. The assumption that a proportion of people (15%) will remain on treatment beyond year 5 aligns with findings in the literature (115) and expert opinion (see section B.4.2.11). For people who develop DMO in their second eye (bilateral or fellow eye involvement), a maximum treatment duration of 5 years is started from the point that DMO develops in the second eye. UK clinical experts agreed with the approach and assumptions in the base case analysis to model discontinuation.

A number of scenario analyses exploring alternative discontinuation assumptions were conducted (see section B.4.4). The following scenario analyses were conducted:

- Varying the maximum treatment duration to 3 years or 10 years.
- Varying the proportion of people who discontinued treatment after year 5 (0%, 50% 70%, or 100%). In these scenarios, for the proportion of people remaining on treatment, the same model assumptions in terms of, injection and monitoring frequency, costs, discontinuation and mortality risk were applied from year 5 until discontinuation or death.
- Varying positive discontinuation probabilities differently for faricimab, aflibercept and ranibizumab after year 1. Differential year 1 discontinuation proportions were informed by the proportions of people who achieved absence of DMO (CST < 325 µm) at week 56 in YOSEMITE and RHINE. It was assumed a treatment specific (faricimab [redacted] than aflibercept [redacted]) proportion would stop treatment after 1 year in the model equivalent to that which achieve the outcome in YOSEMITE and RHINE. The discontinuation proportion for ranibizumab was assumed equivalent to that applied for aflibercept. After discontinuation, no further injection or monitoring visits take place.

B.4.2.8 Intervention and comparators' healthcare resource use and associated costs

In current UK clinical practice, patients are diagnosed with DMO using optical coherence tomography (OCT). In the model, the cost of an OCT is applied across all patients at cycle one. It is also applied in the first model cycle after when patients develop DMO in their second (fellow) eye. The cost of OCT was sourced from the 2019/2020 NHS reference schedule (Table 29) (116). The assumption that OCT is used to diagnose DMO was validated in consultation with UK clinical experts (see section B.4.2.11).

OCT costs are also applied in subsequent injection administration and monitoring visits – (see 'injection administration visits' and 'monitoring visits').

Table 29: Optical coherence tomography cost

Item	Unit cost	Source
OCT	£125.88	NHSE reference schedule 2019/20. Outpatient Procedure code for Retinal Tomography: BZ88A (ophthalmology) (116)

OCT: optical coherence tomography

Injection administration visits

In the base case analysis, the frequency of injection administrations for faricimab in years 1 and 2 is derived from data pooled across the YOSEMITE and RHINE studies (see sections B.3.6, B.4.2.1 and B.4.2.6) (4). In year 1, injection administration frequency is derived as the annualised mean number of faricimab treatments administered in the PTI arms at week 52. This is calculated as mean number of treatments multiplied by the mean duration on treatment. This frequency is annualised to take account of anyone who discontinued treatment or died before the end of week 52. Faricimab injection administration frequency in year 2 is estimated using the same approach, but is derived using data from patients' in the second year of YOSEMITE and RHINE (4). Given the lack of long-term data to derive injection administration frequency after year 2, alternative approaches and assumptions are used to estimate injection administration frequencies in year 3 and beyond. The injection administration frequency for faricimab in year 3 is estimated by applying the relative difference in year 2 between faricimab and ranibizumab to a year 3 administration frequency for ranibizumab taken from Protocol T (93). It is assumed that the frequency of injections in years 3 to 5 is consistent.

The modelled frequency of injection administration visits for aflibercept in year 1 is informed by the results of the NMA assuming it is administered using a PRN regimen. In year 2, aflibercept injection frequency is informed by the mean number of injections received by patients in the aflibercept PRN arm of Protocol T (93). The frequency of aflibercept injection administration visits in year 3 and beyond is estimated using the same approach as used for faricimab.

The modelled frequency of injection administration visits for ranibizumab in year 1 is informed by the results of the NMA assuming it is administered using a PRN regimen. The frequency of injection administration visits for ranibizumab in years 2 to 3 is informed by the number of injections received by patients in the ranibizumab PRN arm of Protocol T (93). Injection administration frequency for each year (2 and 3) was derived separately from the mean number of injections in each year of Protocol T (93). It is assumed that the number of ranibizumab injections administered in years 4 and 5 would be consistent with the frequency injection administration in year 3.

UK clinical experts consulted by Roche were aligned with the approach taken in the base case analysis, and agreed that they expected to be able to extend treatment intervals more with faricimab than aflibercept and ranibizumab (see section B.4.2.11).

The annual mean number of injection administration visits applied in the base case analysis can be seen in Table 30.

Table 30: Annual mean number of injection administration visits (base-case assumptions)

Dosing regimen	Injection administration visits		
	Year 1	Year 2	Year 3+
Faricimab 6 LP → q16/12w (T&E) → PRN	8.42	4.73	1.90
Aflibercept 2 LP → PRN	9.20	5.00	2.37
Ranibizumab 0.5 LP → PRN	9.40	5.40	2.17

LP: loading phase; PRN: pro re nata; T&E: treat and extend

Alternative estimates of injection administration frequencies associated with different treatment regimens (q4w, q8w [aflibercept only], T&E [ranibizumab only]) have been explored as scenario analyses (see section B.4.4 and Table 39). The injection administration frequencies assumed for each regimen explored in the scenario analyses was informed by YOSEMITE and RHINE or the results of the network meta-analysis (section B.3.8). The NMA results were estimated by pooling data from different treatment arms across different studies for each treatment and regimens, using a random-effects approach taking account of between-trial heterogeneity.

The unit costs for injection administration visits were obtained from the NHS Reference Schedule 2019/2020 and the appraisal of aflibercept for DMO (TA346) (3, 116). It was assumed that IVT injections would be administered in consultant led outpatient appointments, following an assessment of retinal fluid using OCT. It was also assumed that there would be an additional resource use and cost associated with IVT injections which would apply at each injection administration visit. The cost of an IVT injection was estimated as the difference in costs between an injection administration visit and a monitoring visit as calculated by the evidence review group (ERG) in the appraisal of aflibercept for DMO (TA346) (3). In the base case analysis, in addition to treatment acquisition cost (see Table 28), the cost of an injection administration visit was assumed to comprise of an outpatient consultant-led visit (£101.80), an injection administration cost (£54.54), and an OCT procedure (£125.88) – see Table 29 and Table 31 (116). UK clinical experts agreed with this approach and the cost and resource use estimates (see B.4.2.11).

The proportion of outpatient consultant or non-consultant led (£89.13) and day case visits (£660.84) were explored in scenario analyses – see Table 31 (116).

Table 31: Resource use unit costs

Item	Unit cost	Source
Consultant led outpatient visit	£101.80	NHS reference costs 19/20: Consultant led non-admitted follow-up (ophthalmology) WF01A, service code 130
IVT injection	£54.54	Estimated from aflibercept for DMO ERG report (TA346)
Scenario analysis only		
Day case	£660.84	NHS reference costs 19/20. Day case: Minor Vitreous Retinal Procedures, 19 years and over BZ87A

Non-consultant led outpatient visit	£89.13	NHS reference costs 19/20: non-Consultant led, face-to-face, non-admitted follow-up (ophthalmology) WF01A, service code 130, WF01A

OCT: Ocular Retinal Tomography; NHS: National Health Service; IVT: intravitreal injection

Monitoring visits

In the model, the number of monitoring visits that a person received in addition to injection administration visits is determined by treatment regimen.

The PTI arm of YOSEMITE and RHINE was developed to reflect treat and extend (T&E) approaches for DMO (see section B.4.2.6). Treat and extend is a proactive regimen that allows extension of treatment intervals in the absence of disease activity. If a sufficient number of injections administration visits are taking place, separate monitoring visits may not be required if following a T&E regimen. PRN, or "as required", regimens are considered reactive and involve frequent, often monthly visits where an injection is given only after the reoccurrence of disease activity.

As faricimab was administered using a regimen which reflects T&E, it is assumed that no additional monitoring visits are required in years 1 and 2. In year 3 and beyond it is assumed that everyone treated with faricimab would move to a PRN type regimen where separate monitoring visits to evaluate disease activity could occur. In the base case it is assumed that when injection administration visits are less than 4 in year 3 and beyond, people will attend separate monitoring visits until a minimum number of 4 total visits is reached (see Table 32). This assumption applies in the model until discontinuation or death. The total number of visits in year 3 and beyond (4) is based on total visit numbers observed for patients treated with aflibercept and ranibizumab in years 3-5 of the protocol T study (108). These assumptions are consistent with the views of clinical experts consulted by Roche and in line with faricimab's anticipated marketing authorisation (5). Clinical experts agreed that the aim is to reduce additional monitoring visits whenever possible and that this could be achieved using T&E (see B.4.2.11).

In the base-case analysis, it is assumed that aflibercept and ranibizumab are administered using a PRN regimen, so additional monitoring visits are applied in all years of the model (see Table 32). This assumption was supported by the views of clinical experts who said that although the aim is to avoid additional monitoring visits, additional visits could occur for people on PRN regimens (see B.4.2.11). A minimum number of total (injection and monitoring) visits for aflibercept and ranibizumab was derived from the average number of visits observed in Protocol T (93, 108, 109). In the model, the minimum number of total visits for aflibercept and ranibizumab is assumed in years 1 (12.95 and 12.66 visits respectively) and 2 (9.40 and 9.30 respectively). In year 3 and beyond a minimum of 4 total visits, in line with the assumptions made for faricimab, it is assumed until treatment discontinuation or death. If the modelled number of injection administration visits for aflibercept or ranibizumab is less than this minimum, it is assumed that patients will attend separate monitoring visits until the minimum number of total visits is reached (see Table 32).

In the scenario analyses where alternative dosing regimens are explored, the minimum annual number of total injection and monitoring visits also applied for continuous fixed regimens (q4w and q8w).

Table 32: Separate monitoring visits for faricimab, aflibercept and ranibizumab

Dosing regimen	Year 1	Year 2	Year 3+
Faricimab 6 LP → q16/12w (T&E) → PRN	0.00	0.00	2.10
Aflibercept 2 LP → PRN	3.75	4.40	1.63
Ranibizumab 0.5 LP → PRN	3.26	3.90	1.83

LP: loading phase; PRN: pro re nata; T&E, treat and extend

In the model, it is assumed that at each monitoring visit, retinal fluid would be assessed using OCT in a consultant led outpatient appointment. So, the cost of a separate monitoring visit comprised of an outpatient consultant-led visit and an OCT procedure (see Table 29 and Table 31). Feedback from UK clinical experts was aligned with the cost and resource assumptions adopted in the base case analysis.

Bilateral treatment multipliers

In the base case analysis, multipliers have been utilised to illustrate the additional costs incurred through treating two eyes rather than just one.

With respect to drug costs, because the unit cost of treatment does not vary according to number of eyes treated, it is assumed that drug costs would double in cases of bilateral treatment. This is in line with the approach adopted in the NICE clinical guideline for AMD NG82 (117) and has been judged broadly reflective of UK clinical practice by clinical experts.

In terms of administration and monitoring costs, it is assumed that the treatment of bilateral DMO comprises '1-stop' appointments (i.e. the cost of administration and monitoring is shared between eyes). In the model, the cost of administration and monitoring was therefore assumed to increase by 87.7% (cost multiplier of 1.877 i.e. costs doubled in 87.7% of the cases, but are shared (no additional costs) in the remaining 12.3% of cases). This aligns with assumptions use in the appraisal of aflibercept for DMO (TA346) (3), and is consistent with the views of UK clinical experts who agreed that cost and time savings occurred in 1-stop appointments.

The impact of assuming an alternative multiplier for administration and monitoring costs (multiplier of 1.5) taken from the appraisal of brolucizumab for treating wet age-related macular degeneration (AMD) has been explored as a scenario analysis (see section B.4.4) (118).

Bilateral cost multipliers for drug costs and administration and monitoring costs are presented in Table 33.

Table 33: Cost multipliers for bilateral treatment

Cost multiplier	Value	Assumption	Source
Drug cost multiplier	2.000	Assumed drug costs will double	NICE clinical guideline for AMD NG82 (117)
Administration and monitoring cost multiplier	1.877	Assumed that administration and monitoring costs would double in 87.7% of the cases and are shared (no extra cost) in other case	NICE appraisal of aflibercept for DMO (TA346) (3)
Scenario analysis only			

Administration and monitoring cost multiplier	1.500	Assumed that administration and monitoring costs would double in 50% of the cases and are shared (no extra cost) in other case	NICE appraisal of brolucizumab for AMD (TA672) (118)

AMD: age-related macular degeneration; DMO: diabetic macular oedema; NG: NICE guideline; TA: technology appraisal

B.4.2.9 Adverse reaction unit costs and resource use

The relative safety of faricimab and aflibercept was assessed in the safety-evaluable population (defined as all patients in either study who received at least one injection of active study drug, grouped according to the actual treatment received) which was pooled across YOSEMITE and RHINE (4). The safety results found that the incidence of AEs was generally comparable across treatment arms (81.4%, 76.9%, and 78.1% of patients in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arms, respectively). The incidence of ocular AEs occurring in the study eye was also found to be comparable across treatment arms, with the exception of vitreous floaters (4.8%, 2.1%, and 1.6% in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arms, respectively), which were mainly mild in severity and all were non-serious. There was a higher incidence of serious AEs in the study eye in both faricimab arms (2.4% and 3.0%, in the faricimab Q8W and PTI arms respectively), compared with aflibercept arm (1.3%). However, the overall frequency was low, and no consistent patterns were observed at an individual patient level across the different treatment arms. Additionally, the differences in serious adverse events were not statistically significant at week 56 (95% confidence interval crossing zero).

In line with the safety results from YOSEMITE and RHINE, the results of the network meta-analysis, presented in B.3.8, demonstrated that safety events associated with faricimab, aflibercept and ranibizumab were comparable and occurred rarely across all treatments. In the model, it is assumed that the safety of faricimab, aflibercept and ranibizumab is equivalent (see B.3.8). As such, cost and resource use related to adverse events have not been included in the base case analysis. The omission of these costs from the base case analysis does not have a significant impact on the overall results.

B.4.2.10 Miscellaneous unit costs and resource use

No further costs or resource use were included within the base case cost-comparison analysis that have not been described elsewhere.

As the onset of DMO typically occurs during working age, the associated vision loss and anti-VEGF treatment burden can lead to an inability to work or work at full capacity, reduced workplace productivity (119), and may lead to early retirement (47). These costs will not be taken into consideration in a cost minimisation analysis, so the wider societal benefits of faricimab will not be fully considered. To reflect this, the wider societal impact of visual impairment and anti-VEGF treatment burden have been explored in scenario analyses (B.4.4).

Frequent IVT injections, such as anti-VEGF injections, can represent a burden to patients in terms of anxiety associated with injections and the need for frequent and sometimes inconvenient interactions with the health service. These factors can contribute to

absenteeism in the workplace for both patients and those who care for them. This was consistent with the views of clinical experts consulted by Roche who explained that injection days cause disruption to patients and carers. To capture this, two scenarios have been explored which assess the impact of IVT injections on patients and carers:

- Caregiver scenario: Assuming carers take patients to DMO appointments and miss one day of work costed at the average UK wage (120).
- Productivity gains scenario: Assuming 1-day of zero productivity, costed at the UK average wage (ONS) (120), following IVT injections until retirement (66 years: UK state pension age). Estimated as a relative productivity gain compared to a person with visual impairment who is untreated.

B.4.2.11 Clinical expert validation

Given the precedents available from the previous appraisals of aflibercept and ranibizumab in this indication, the majority of assumptions adopted in the base case analysis have been informed by existing precedents (3).

Clinical data have been incorporated into the model from YOSEMITE and RHINE (4) studies, as well as other published clinical trials (see section B.3.9). The general modelling approach and inputs were cross referenced with previous technology appraisals and subsequently validated by external health economists and UK clinical experts. To assess the generalisability of the evidence and plausibility of the model assumptions and predictions, clinical expert validation of the assumptions applied in the base case cost-comparison analysis was sought from 3 leading UK clinical experts. A summary of the areas of feedback provided by the experts is below:

- Generalisability of the trial population to UK clinical practice (see section B.4.2.3)
- Treatment injection frequencies and dosing regimens (see section B.4.2.6)
- Treatment discontinuation patterns (see section B.4.2.7)
- Healthcare resource use and costs (see section B.4.2.8)
- Patient and carer productivity losses (see section B.4.2.10).

B.4.2.12 Uncertainties in the inputs and assumptions

A summary of the assumptions adopted in the base case cost-comparison analysis is presented in Table 34.

Table 34: Assumptions adopted in the base case cost-comparison analysis

Assumption	Description
Equivalent efficacy across treatments and regimens	The cost-comparison model assumes that the different treatments have equivalent efficacy (non-inferior in terms of change in BCVA) and safety, regardless of the treatment regimens or injection frequencies. YOSEMITE and RHINE demonstrate that faricimab is non-inferior to aflibercept in terms of BCVA outcomes and safety (B.3.6). Results from the NMA (B.3.8) also demonstrated that faricimab is associated with comparable efficacy in terms of BCVA and safety versus both aflibercept and ranibizumab.

Mortality	The cohort followed the age- and gender-adjusted mortality probabilities from published by the Office for National Statistics (2019) based on 2017−2019 mortality data (110). Mortality was further adjusted by applying a diabetes specific hazard (111) for the entire population as well as health state mortality risks from being blind and visually impaired (121). An increase in mortality from bilateral disease or adverse events was not assumed, and mortality rates were the same regardless of DMO treatment.
Discontinuation probability	The annual probability of discontinuation from years 1 to 5 was based on data pooled across the faricimab PTI arms of YOSEMITE and RHINE. The probability of discontinuation in year 1 is based on observed discontinuations up to week 52 across YOSEMITE and RHINE. In years 2 to 5, the probability of discontinuation is assumed to be constant, and was based on the annualised probability of discontinuation from patients' part way through the second year of YOSEMITE and RHINE (4).
Maximum treatment duration	In the base case analysis, a maximum treatment duration of 5 years from baseline was applied for the study eye. After this point, if patients in the model have not developed DMO in their second eye, 85% of those who were alive and on treatment were assumed to discontinue treatment. 15% of people remain on treatment beyond year 5 to reflect the fact that some people with DMO require long-term treatment. Patients who develop bilateral disease are treated in their second (fellow) eye for a maximum of 5 years after bilateral disease develops.
Treatment switching	Patients were either on or off treatment and did not switch treatments.
Injection administration visits	Treatment frequency for faricimab in years 1 and 2 is derived from data pooled across the YOSEMITE and RHINE studies (see sections B.3.6 and B.4.2.6) (4). Year 1 frequency is derived as the annualised mean number of faricimab treatments for patients at week 52 in the PTI arms of YOSEMITE and RHINE. Year 2 frequency is derived using the same approach but annualising the injection frequency of patients' part way through the second year of YOSEMITE and RHINE (4). The modelled frequency of injection administration visits for aflibercept and ranibizumab in year 1 and 2 is informed by the mean number of injections received by patients in the PRN arms in years 1 and 2 of Protocol T (93, 109) Injection administration frequencies in year 3 were estimated by applying the relative difference in year 2 frequencies across faricimab, aflibercept and ranibizumab to a year 3 injection administration frequency for ranibizumab taken from Protocol T (93, 108, 109). Given the absence of long-term RCT evidence, it was assumed that the number of injections in years 4 and 5 would reflect the mean number of injections received in Year 3 for faricimab, aflibercept and ranibizumab.
Monitoring visits	In years 1 and 2 in the model, it is assumed that people treated with faricimab follow a T&E strategy and no monitoring visits in addition to administration injection visits are required. In year 3 and beyond it is assumed that everyone treated with faricimab would move to a PRN type regimen where separate monitoring visits to evaluate disease activity could

	occur. In the base case it is assumed that when injection administration visits are less than 4 in year 3 and beyond, people will attend separate monitoring visits until a minimum number of 4 total visits is reached. This assumption applies in the model until discontinuation or death. The total number of visits in year 3 and beyond (4) is based on total visit numbers observed for patients treated with aflibercept and ranibizumab in years 3-5 of the protocol T study (108). These assumptions are consistent with the views of clinical experts consulted by Roche and in line with faricimab's anticipated marketing authorisation (5). Clinical experts agreed that the aim is to reduce additional monitoring visits whenever possible and that this could be achieved using T&E (see B.4.2.11). In the base-case analysis, it is assumed that aflibercept and ranibizumab are administered using a PRN regimen, so additional monitoring visits are applied in all years of the model (see Table 32). This assumption was supported by the views of clinical experts who said that although the aim is to avoid additional monitoring visits, additional visits could occur for people on PRN regimens (see B.4.2.11). A minimum number of total (injection and monitoring) visits for aflibercept and ranibizumab was derived from the average number of visits observed in Protocol T (93, 108, 109). In the model, the minimum number of total visits for aflibercept and ranibizumab is assumed in years 1 (12.95 and 12.66 visits respectively) and 2 (9.40 and 9.30 respectively). In year 3 and beyond a minimum of 4 total visits, in line with the assumptions made for faricimab, is assumed until treatment discontinuation or death. If the modelled number of injection administration visits for aflibercept or ranibizumab is less than this minimum, it is assumed that patients will attend separate monitoring visits until the minimum number of total visits is reached (see Table 32).
Adverse event probability	The cost minimisation model assumes that the probability of adverse events was the same across all treatments and regimens, so safety is assumed to be equivalent. No adverse events are modelled in the base-case analysis.
Probability of developing bi-lateral disease	Patients with unilateral disease had a fixed annual probability of developing bilateral disease (10%). The probability of developing bi-lateral disease aligns with the figure applied in the appraisal of aflibercept for DMO (TA346) (3).
Cost for bi-lateral disease	In the base case analysis, patients with bilateral disease incurred twice the treatment costs, and 1.877 times the administration and monitoring cost of people with unilateral disease. These assumptions align to those applied in the appraisal of aflibercept for DMO (TA346) (3).
OCT	OCT is assumed to be undertaken at diagnosis (cycle one for treatment naive patients and in the first cycle after people develop bi-lateral disease), and at every injection administration and monitoring visit.
Consultant led appointments	It is assumed that all injection administration and monitoring visits are led by a consultant in an outpatient setting.

AMD: age-related macular degeneration; BCVA: best-corrected visual acuity; DMO: diabetic macular oedema; OCT: Optical coherence tomography; PRN: pro re nata; PTI: personalised treatment interval; TA: technology appraisal

B.4.3 Base-case results

The results of the base case cost-comparison analysis are presented in Table 35. The results presented do not account for the patient access scheme discounts for aflibercept and ranibizumab as these net prices are confidential. Therefore, the base case results presented in Table 35 assume aflibercept and ranibizumab are provided at list price (112), while faricimab is provided at its confidential net price (see section B.4.2.5).

Assuming faricimab, aflibercept and ranibizumab have equal efficacy in terms of BCVA outcomes and safety, the use of faricimab is estimated to result in a per-patient [redacted] compared with aflibercept and [redacted] compared with ranibizumab over a lifetime time horizon (see section B.4.2.1).

Table 35: Base case cost-comparison results (faricimab at net price; aflibercept and ranibizumab at list price)

Cost	Faricimab 6 mg LP → q16w/q12w	Aflibercept 2 LP → PRN	Ranibizumab 0.5 LP → PRN
Drug cost	[redacted]	£29,607	£19,954
Administration cost	[redacted]	£9.854	£9,832
Monitoring cost	[redacted]	£4,820	£4,694
Diagnostic cost	£195	£195	£195
Mean total cost	[redacted]	£44,476	£34,675
Incremental cost vs faricimab	N/A	[redacted]	[redacted]

LP: loading phase; PRN: pro re nata;

With similar results in BCVA outcomes, comparable safety, and improved treatment durability compared with aflibercept and ranibizumab, faricimab represents a cost-effective alternative to currently licensed and NICE recommended anti-VEGF therapies.

Acknowledging that aflibercept and ranibizumab are available to the NHS at a discounted price, the impact of varying the level of discount to list price for aflibercept and ranibizumab was explored in a threshold analysis presented in Table 36. When adopting the base case cost-comparison assumption, this analysis demonstrated that at its net price faricimab remains [redacted] compared with aflibercept and ranibizumab up to a discount level of [redacted] and [redacted] respectively.

Table 36: threshold analysis: incremental cost of faricimab compared with aflibercept and ranibizumab at varying list price discount levels

Discount	Aflibercept		Ranibizumab	
	Discounted aflibercept price	Incremental cost vs faricimab	Discounted ranibizumab price	Incremental cost vs faricimab
0%	£816.00	[redacted]	£551.00	[redacted]
5%	£775.20	[redacted]	£523.50	[redacted]

10%	£734.40	[redacted]	£495.90	[redacted]
15%	£693.60	[redacted]	£468.40	[redacted]
20%	£652.80	[redacted]	£440.80	[redacted]
25%	£612.00	[redacted]	£413.30	[redacted]
30%	£571.20	[redacted]	£385.70	[redacted]
35%	£530.40	[redacted]	£358.20	[redacted]
40%	£489.60	[redacted]	£330.60	[redacted]
45%	£448.80	[redacted]	£303.10	[redacted]
50%	£408.00	[redacted]	£275.50	[redacted]
55%	£367.20	[redacted]	£248.00	[redacted]
60%	£326.40	[redacted]	£220.40	[redacted]
65%	£285.60	[redacted]	£192.90	[redacted]

B.4.4 Sensitivity and scenario analyses

B.4.4.1 Deterministic sensitivity analysis

A univariate deterministic sensitivity analysis (DSA) was conducted to assess which parameters have the greatest impact on incremental cost. In the absence of data on the variability around parameter values, each was varied by ±20%. The parameter values used in the deterministic sensitivity analyses are presented in Table 37. Results of the DSA are displayed in **Error! Reference source not found.** and **Error! Reference source not found.**, where the 10 parameters that had the greatest impact on incremental costs are presented.

The results of the DSA (see Figure 25 and Figure 26) show that drug costs, model starting age, maximum treatment duration, and the share of people who discontinue treatment at 5 years have the biggest impact on incremental costs.

Table 37: Parameter values used for DSA

Parameter	Base-case value	Lower value	Higher value	Variation
Maximum treatment duration (months)	60	48	72	± 20%
Drug cost for aflibercept (£)	816	653	979	± 20%
Drug cost for ranibizumab (£)	551	441	661	± 20%
Drug cost for faricimab (£)	[redacted]	[redacted]	[redacted]	± 20%
Share of patients which discontinue treatment after 5 years (%)	85	68	100	± 20%
Starting age of cohort (years)	62	50	74	± 20%

Cost of separate monitoring visits to evaluate response (£)	228	182	273	± 20%
Administration cost multiplier for second eye treatment (%)	1.877	1.702	2.000	± 20%
Administration cost for IVT injections	282	226	338	± 20%
Time horizon (years)	25	20	30	± 20%
Discount rate costs (%)	3.5	2.8	4.2	± 20%
Prevalence of DMO in second eye at baseline (%)	46.5	37.2	55.8	± 20%
Monthly incidence of DMO in second eye (%)	8.04	6.44	9.65	± 20%

DMO, diabetic macular oedema; DSA, deterministic sensitivity analysis; IVT, intravitreal injection

Figure 25: Tornado plot (faricimab net price compared with aflibercept list price)

DMO, diabetic macular oedema; IVT, intravitreal injection

Figure 26: Tornado plot (faricimab net price compared with ranibizumab list price)

DMO, diabetic macular oedema; IVT, intravitreal injection

B.4.4.2 Scenario analysis

Scenario analyses were conducted to assess uncertainty around model structure and parameters. The table below outlines the areas of the model that were evaluated and describes each scenario.

Table 38: Parameters varied in the scenario analysis

Parameter	Description
Age	Varying base-line age of the model population
Discount rate	Adjusting the discount rate for costs to 1.5% in line with the proposals of the ongoing NICE methods review consultation (107)
Bi-lateral cost multiplier	Applying the multiplier of 1.5 applied in the appraisal brolucizumab for AMD
Aflibercept dosing regimen	Applying different dosing regimens for aflibercept (see Table 39)
Ranibizumab dosing regimen	Applying different dosing regimens for ranibizumab (see Table 39)
Maximum treatment duration	Varying the time-point in the model when the majority of people on treatment discontinue
Proportion discontinuing after 5 years	Varying the proportion of people who remain on treatment or discontinue beyond year 5
Absence of DMO positive discontinuation	To reflect the positive results for the absence of DMO (CST < 325 μm) secondary outcome from YOSEMITE and RHINE, a positive discontinuation scenario was explored. This scenario assumes that those who achieve absence of DMO (CST <325 μm) in the model at week 56 would positively discontinue treatment and have no further injection or monitoring visits. In the absence of ranibizumab data for this outcome, it is assumed that positive discontinuation would be achieved in the same proportion of the population as aflibercept. It was also assumed that week 56 outcome results could be considered equivalent to year 1 (week 52) results.
Treatment and monitoring setting costs	Changing from 100% consultant led appointments (£101.80) to assume 36.8% of day case admissions (£660.84: NHS reference costs 19/20, day case: BZ787A) - per NG82
	Assuming all appointments are non-consultant led (£89.13: NHS reference costs 19/20: non-Consultant led, face-to-face, non-admitted follow-up, service code 130, WF01A) (116)
Carer costs at injection and monitoring visits	Assuming carers take patients to DMO appointments and miss 1 day of work costed at the average UK wage (ONS: AWE: Whole Economy Level (£): Seasonally Adjusted Total Pay Excluding Arrears - £576 /week) (120)
Productivity impairment following IVT injections	Assuming 1-day of zero productivity, costed at the UK average wage (ONS), following IVT injections until retirement (66 years: UK state pension age (122))

AMD, wet age-related macular degeneration; AWE, average weekly earnings; DMO, diabetic macular oedema; IVT, intravitreal; LP, loading phase; NG, NICE guideline; NHS, national health service; ONS, office for national statistics; T&E, treat and extend; QXW, one injection every X weeks; UK, United Kingdom

For the scenarios exploring alternative dosing regimens, the frequency of injection and monitoring visits varied. A summary of the injection and monitoring frequencies applied in the base-case analysis and in each scenario can be seen in Table 39.

Table 39: Annual mean number of injections and total visits per dosing regimen

Dosing regimen	Injections			Separate monitoring visits		
	Year 1	Year 2	Year 3+	Year 1	Year 2	Year 3+
Base-case						
Faricimab (6 LP → q16w/q12w [T&E] → PRN)	8.42	4.73	1.90	0	0	2.10
Aflibercept (2 LP → PRN)	9.20	5.00	2.37	3.75	4.40	1.63
Ranibizumab (0.5 LP → PRN)	9.40	5.40	2.17	3.26	3.90	1.83
Scenario analyses						
Aflibercept (2 LP → q4w)	12.73	5.00	2.37	0.22	4.40	1.63
Aflibercept (2 LP → q8w)	8.86	6.17	2.48	4.09	3.23	1.52
Ranibizumab (0.5 LP → q4w)	11.02	5.40	2.17	1.64	3.90	1.83
Ranibizumab (0.5 LP → T&E)	9.53	5.40	2.17	3.13	3.90	1.83

LP, loading phase; PRN, pro re nata; T&E, treat and extend; QXW, one injection every X weeks; UK, United Kingdom

The results of the scenario analyses are presented below. Across all of the scenarios conducted, faricimab remained [redacted] versus both aflibercept and ranibizumab.

Table 40: Scenario analyses results (with faricimab at net prices; aflibercept and ranibizumab at list price)

Scenario	Base-case	Scenario	Incremental cost vs aflibercept	% change from base case incremental cost	Incremental cost vs ranibizumab	% change from base case incremental cost
Base-case	-	-	[redacted]	N/A	[redacted]	N/A
Model starting age	62 years	50 years	[redacted]	[redacted]	[redacted]	[redacted]
		75 years	[redacted]	[redacted]	[redacted]	[redacted]
Discount rate	3.5%	1.5%	[redacted]	[redacted]	[redacted]	[redacted]
Bi-lateral cost multiplier	1.877	1.500	[redacted]	[redacted]	[redacted]	[redacted]
Aflibercept dosing regimen	LP → PRN	LP → q4w	[redacted]	[redacted]	N/A	N/A
		LP → q8w	[redacted]	[redacted]	N/A	N/A
Ranibizumab dosing regimen	LP → PRN	LP → q4w	N/A	N/A	[redacted]	[redacted]
		LP → T&E	N/A	N/A	[redacted]	[redacted]
Maximum treatment duration	5 years	3 years	[redacted]	[redacted]	[redacted]	[redacted]
		10 years	[redacted]	[redacted]	[redacted]	[redacted]
Proportion discontinuing after 5 years	85%	0%	[redacted]	[redacted]	[redacted]	[redacted]
		50%	[redacted]	[redacted]	[redacted]	[redacted]
		70%	[redacted]	[redacted]	[redacted]	[redacted]
		100%	[redacted]	[redacted]	[redacted]	[redacted]
Absence of DME / positive discontinuation proportions at year 1	Not applied	[redacted] discontinue on faricimab [redacted] discontinue comparators	[redacted]	[redacted]	[redacted]	[redacted]
Treatment and monitoring setting costs	£101.80	£307.53	[redacted]	[redacted]	[redacted]	[redacted]
		£89.13	[redacted]	[redacted]	[redacted]	[redacted]
Carer costs at injection and monitoring visits	£0	£82 (per visit)	[redacted]	[redacted]	[redacted]	[redacted]
Productivity impairment following IVT injections	None	1-day	[redacted]	[redacted]	[redacted]	[redacted]

IVT, intravitreal; LP, loading phase; NG, NICE guideline, T&E, treat and extend; QXW, one injection every X weeks

The scenario analyses were limited by the availability of relevant data. Where possible, evidence or results from the network meta-analysis, clinical expert opinion, or the literature were used to inform the alternative assumptions applied in each scenario. The implications of this limitation are limited as for the purposes of the cost-comparison analysis the scenarios analyses are illustrative, with the most plausible assumptions, reflecting current UK practice, adopted in the base-case.

Of the scenario analyses conducted, assuming different treatment regimens for the comparators, adjusting the maximum treatment duration or the proportion of people continuing treatment beyond 5 years had the greatest impact on incremental costs.

B.4.5 Subgroup analysis

No economic subgroup analyses have been conducted for the purposes of this appraisal.

B.4.6 Interpretation and conclusions of economic evidence

This economic evaluation focused on comparing the cost of faricimab with aflibercept and ranibizumab for the treatment of patients with visual impairment caused by DMO with a central retinal thickness of 400 micrometres or more, from a UK health system perspective.

The model draws upon clinical data from the YOSEMITE and RHINE studies: ongoing, Phase III, randomised, placebo-controlled studies in patients with DMO. The baseline characteristics of the patients in YOSEMITE and RHINE have been validated by clinical experts and can be considered broadly representative of the corresponding population in the UK. This evaluation can therefore be considered relevant to clinical practice in England and Wales.

In-line with the fast track appraisal framework set out in the cost comparison addendum to the guide to the methods of technology appraisal (123) evidence was presented to demonstrate that faricimab provides similar or greater health benefits to NICE recommended technologies (ranibizumab and aflibercept) (2, 3). As demonstrated in the results from YOSEMITE and RHINE and the network meta-analysis (see sections B.3.6 and B.3.9.4) the efficacy of faricimab is similar or greater than aflibercept and ranibizumab, and safety is comparable. Furthermore, the results demonstrate that faricimab is a more durable treatment than aflibercept and ranibizumab, with greater intervals between injections being possible on faricimab.

A UK NHS perspective was taken with respect to the costs and resource use quantified in the model. All costs were taken from published UK sources or previous NICE technology appraisals in this disease area. This methodology is in accordance with that of the NICE Reference Case (94).

The base case results from the cost comparison show that faricimab is [redacted] compared to aflibercept ([redacted]) and ranibizumab ([redacted]) – see Table 35. The results of this cost-comparison analysis support the fact that the introduction of faricimab would have [redacted] on NHS expenditure. However, the results presented in this submission compare faricimab PAS price, to aflibercept and ranibizumab at list price, so should be interpretted with caution. Nevertheless, when varying the prices of

aflibercept and ranibizumab, faricimab remains a cost effective option up to a discount of [redacted] and [redacted] respectively.

Extensive sensitivity and scenario analyses have been conducted to test the robustness of model results when parameter values were manipulated, alternative approaches implemented, and different data sources utilised. Complete results of these analyses can be found in section B.4.4. Drug costs, model starting age, maximum treatment duration, and the share of people who discontinue treatment at 5 years have the biggest impact on incremental costs.

COVID-19 has brought the requirement for more efficient use of healthcare resources into urgent focus. Patients with DMO are highly vulnerable to vision loss with even short lapses in care. The need for longer-acting treatments for patients with DMO has perhaps never been more evident as people who cannot or do not feel comfortable leaving their homes, may be at risk for vision loss due to missed treatment. Furthermore, with health service capacity stretched, improved treatment durability and extensions to treatment intervals that are possible with faricimab, are of significant value, not only to patients and carers, but clinicians and the health service as a whole.

The key strengths associated with the presented cost-comparison analysis surround its use of the best available evidence to inform the model:

- Clinical effectiveness data taken from a randomised placebo-controlled trials (YOSEMITE and RHINE) in which all patients had been assessed for the primary endpoint (mean change in BCVA). Faricimab demonstrated non-inferiority to aflibercept in terms of mean change in BCVA with fewer injections.
- The results from the meta-analysis show that faricimab provides similar or greater health benefits to aflibercept and ranibizumab with comparable safety across all treatments
- Costs and resource use data taken from well-established UK sources and previous NICE technology appraisals
- Extensive sensitivity and scenario analyses conducted to quantify uncertainty and identify major drivers of cost-effectiveness results

There are no significant limitations associated with the cost-comparison analysis. Uncertainties stemming from the immaturity of trial evidence and the extrapolation of short-term trial evidence are not unique to this analysis and are regularly observed in technology appraisals.

With similar efficacy in terms of improvement in BCVA, similar impact on vision-related HRQoL, superior treatment durability and less frequent injections, the results of the economic analysis indicate that faricimab is the most cost-effective treatment option for DMO versus currently licensed anti-VEGF therapies and results in cost savings to the NHS over a lifetime time horizon up to discounts of [redacted] (vs aflibercept) and [redacted] (vs ranibizumab). Therefore, faricimab meets the cost-comparison criteria to be recommended as an option for the treatment of DMO.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Faricimab for treating diabetic macular oedema [ID3899] Clarification questions

November 2021

File name	Version	Contains confidential information	Date
ID3899_Faricimab for DMO_CQ Response_REDACTED_RPL151121	1.0	No	15.11.2021

Tables

Figures

Section A: Clarification on effectiveness data

Decision problem

A1. The NICE scope and the company decision problem include the outcomes "BVCA affected eye" and "BVCA both eyes". The clinical efficacy outcomes reported appear to be for the affected eye only. Please clarify whether this is the case and whether any evidence is available to assess these outcomes separately.

Clinical efficacy outcomes were analysed for the affected eye only. No BCVA data are available for the fellow (contralateral) eye.

A2. The NICE scope specifies cataract surgery and disease severity as outcomes. Please explain why these outcomes are not included in the decision problem.

Ocular adverse events, including cataracts, were captured in YOSEMITE and RHINE (1). Although the need for cataract surgery was not captured, results from YOSEMITE and RHINE and the network meta-analysis suggest that adverse events are comparable across faricimab, aflibercept and ranibizumab. Concluding that including adverse events would not affect results, all adverse events, including cataracts were excluded from the cost-comparison analysis.

In the absence of a specific scale measuring disease severity in DMO, change in Diabetic Retinopathy Severity Score (DRSS) was presented. The results of the secondary endpoint "Table 12: Proportion of patients with ≥2-step DRSS Improvement in the study eye from baseline on the ETDRS DRSS in the individual and pooled phase III DMO studies at Week 52: CMH method (primary estimand) (ITT population)" demonstrate changes in disease severity of diabetic retinopathy captured in YOSEMITE and RHINE (1).

Results for change in retinal thickness (CST) and visual acuity (BCVA) have also been provided. These measures are commonly used to determine the progression of diabetic macular oedema, and could therefore reflect the severity of the DMO.

Company trials

A3. Company Submission (CS) section B.3.3.2 states that in the YOSEMITE and RHINE trials, the primary endpoint was change from baseline in BCVA at 1 year, with 1 year defined as the average of the Week 48, 52 and 56 visits.

(a) Please clarify why this average was used instead of the Week 52 visit date.

In the YOSEMITE and RHINE trials (1), the schedule of treatments were not synchronised across the 3 arms of the trials.

- *Subjects in Arm A were scheduled to receive 6 mg IVT faricimab injections every 4 weeks (Q4W) to Week 20, followed by 6 mg IVT faricimab injections Q8W to Week 96.*
- *Subjects in Arm B were scheduled to receive 6-mg IVT faricimab injections Q4W to at least Week 12, followed by PTI dosing of 6 mg IVT faricimab injections to Week 96.*
- *Subjects in Arm C were scheduled to receive 2 mg IVT aflibercept injections Q4W to Week 16, followed by 2 mg IVT aflibercept injections Q8W to Week 96.*

The primary endpoint assessment was therefore based on averaging the BCVA over 3 timepoints (the average of the Week 48, 52 and 56 visits, defined in the studies as "1 year"), thus reducing the impact of BCVA measurement variability and the impact of time from the last dose received by patients across treatment arms and on different dosing intervals. This measurement is a more robust measure of the true treatment effect on BCVA than measurement at a single time-point. This approach was endorsed by [redacted] health authority feedback.

(b) Please clarify why the averaging approach for weeks 48, 52 and 56 for BCVA was not also applied to other outcomes.

The approach where data from the week 48, 52 and 56 was averaged (listed as "1 year") was indeed applied to other secondary efficacy endpoints. These are:

- *Proportion of patients gaining ≥15 or ≥10 letters in BCVA from baseline over time and at 1 year*
- *Proportion of patients avoiding a loss of ≥15 or ≥10 letters in BCVA from baseline over time and at 1 year*
- *Proportion of patients gaining ≥15 letters from baseline or achieving BCVA of ≥84 letters over time and at 1 year*
- *Change from baseline in CST at 1 year*
- *Proportion of patients with absence of DMO (CST <325 µm for Spectralis SD-OCT) over time and at 1 year*

Other secondary endpoints where the averaging approach was either not possible or not appropriate were reported at week 52. These endpoints include:-

- *Proportion of patients with a ≥2-step DRSS improvement from baseline on the ETDRS DRSS at Week 52*
- *Change from baseline in BCVA (as measured on the ETDRS chart at a starting distance of 4 metres) over time*
- *Proportion of patients in the PTI arm on a Q4W, Q8W, Q12W, or Q16W treatment interval at Week 52, and over time*
- *Proportion of patients in the PTI arm at Week 52 who achieved a Q12W or Q16W treatment interval without an injection interval decrease below Q12W*
- *Change from baseline in CST over time*
- *Proportion of patients with absence of intraretinal fluid and subretinal fluid over time and at Week 52*
- *Change from baseline in NEI VFQ-25 composite score over time and at Week 52*

Endpoints relating to changes in DRSS or NEI VFQ-25 could not be averaged, as these were not part of the routine measurements taken at each study visit (DRSS, weeks 16 and 52; NEI VFQ-25, weeks 24 and 52). Similarly, for endpoints which require description of the actual injection intervals, and outcomes such as absence of intra- or subretinal fluid, it is more meaningful to approach these as a cross-sectional measurement at 1 year (week 52).

A4. Please clarify why a non-inferiority margin of >- 4 letters was used for BCVA (CS section B.3.4.2)

Non-inferiority hypothesis testing for the primary endpoint of the change from baseline in BCVA averaged over Weeks 48, 52, and 56 was performed using a 4-letter non-inferiority margin based on the VISTA and VIVID aflibercept pivotal DME studies (2). These studies compared aflibercept to laser control. The 4-letter non-inferiority margin also preserves approximately 50% of the least estimated benefit of aflibercept over control in both VISTA and VIVID studies individually (2). The VISTA study randomized 466 patients in the United States and the VIVID study randomized 406 patients in Europe, Japan, and Australia (2). At Week 52, in VISTA, patients receiving 2 mg of aflibercept Q8W gained 10.7 letters from baseline compared with 0.2 letters for patients in the control arm. The corresponding results from the VIVID study were a gain of 10.7 letters for aflibercept versus 1.2 letters for the control arm (2).

The non-inferiority margin should be small enough to allow a conclusion that the new treatment is not inferior to the active control to an unacceptable extent on the basis of a combination of clinical judgment and statistical reasoning. From a clinical perspective, the non-inferiority margin should be fewer than 5 letters given that a loss of 5 letters (one ETDRS line) between treatments would be considered clinically relevant and therefore a non-inferiority margin of 4 letters provides assurance that there would be no important loss of efficacy if the new treatment is used instead of the reference product.

A5. PRIORITY QUESTION. CS section 3.4.5 states “Efficacy analyses were based on the ITT population and the Treatment naïve population, unless otherwise specified” and “Patients with missing baseline assessments were not imputed”. The CS also states that “Non-standard BCVA data and invalid BCVA data were excluded from the analyses” (CS section 3.4.5 and footnote to CS Table 9).

(a) Please clarify how the ITT analysis of change from baseline was conducted if there were missing baseline data.

In all efficacy analyses, baseline is defined as the last value on or prior to the randomization date. If a patient does not have a valid baseline value, then change from baseline cannot be calculated. While this patient is included in the ITT

population, the baseline value will be missing and the patient will not contribute values to the change from baseline analyses.

(b) Please clarify how invalid BCVA data were defined and how many of these data were missing for each trial arm.

Invalid BCVA data were defined as BCVA data obtained when the BCVA testing was performed incorrectly. BCVA testing was considered to be performed incorrectly if any of the following occurred:

- *4m Test stopped too early: Stopping rule not followed (last line tested >=4 letters)*
- *4m Test stopped too early: Total at 4m <=19 but 1m test not done*
- *1m test stopped too early: Stopping rule not followed: last line tested >=4 letters*

In YOSEMITE, through Week 56 there were a total of 7 invalid BCVA values observed in the study eye (total 6 patients; 3 patients in Faricimab Q8W, 2 patients in Faricimab PTI, and 1 patient in Aflibercept Q8W). In RHINE, there were a total of 18 invalid BCVA values in the study eye (total 12 patients; 5 patients in Faricimab Q8W, 5 patients in Faricimab PTI, and 2 patients in Aflibercept Q8W) through Week 56 (1).

A6. CS section B.3.4.5 reports the statistical adjustment for multiplicity which encompasses both assessments of non-inferiority and superiority. This analysis is not very intuitive to follow. Please explain what the likelihood of falsely accepting/rejecting each non-inferiority/superiority hypothesis would be based on the stated overall experiment-wise error rate.

A nominal type I error penalty of 0.0001 was taken each time the independent Data Monitoring Committee (iDMC) reviewed unmasked data prior to the formal analysis of the primary efficacy endpoint. At the time of the primary analysis, four safety interim data reviews were conducted by the iDMC for YOSEMITE/RHINE (Ref); therefore, efficacy analyses were be performed with a family-wise significance level of 0.0496 (0.05 – [0.0001 x 4]).

Given the study design of the YOSEMITE and RHINE studies (1), with two faricimab arms (Q8W and PTI) and active comparator (aflibercept Q8W), and three hypothesis tests for the primary endpoint, to control for the overall type I error rate, a graph-

based testing procedure (3, 4) was followed for both YOSEMITE and RHINE at this overall significance level of α = 0.0496. The graph based approach is illustrated in Figure 5 (section B.3.4.5) where each treatment sequence (Q8W and PTI) is initially tested at half the overall significance level of α/2 (=0.0248).

The first hypothesis test conducted was non-inferiority of faricimab (Q8W and PTI) compared with aflibercept Q8W in the ITT population with a non-inferiority margin of 4 letters. Since this is a non-inferiority test, it was conducted one-sided at half of the designated significance level (half of α/2 [=0.0124]) for each faricimab comparison. This test was successful for each treatment sequence and so the full α/2 was propagated to the next hypothesis test (Superiority of faricimab compared with aflibercept Q8W in the treatment-naive population) within each treatment sequence. Therefore, a significance level of 0.0248 was used for each superiority comparison (Q8W and PTI) separately against the active comparator (aflibercept Q8W). This test was not positive for either comparison and therefore no further propagation of α/2 occurred for either treatment sequence.

A7. Please clarify whether non-inferiority margins were assumed for changes in central subfield thickness, absence of DMO and intraretinal and subretinal fluid (CS section B.4.2.1) and if so the rationale for these.

Continuous secondary endpoints were analysed using the estimand, analysis method and data handling rules following those for the primary endpoint as well as using descriptive statistics after censoring observations following COVID-19 related intercurrent events as described.

Binary secondary endpoints were analysed using the estimand, analysis method and data handling rules following those for the key secondary endpoint, as well as using descriptive statistics after censoring observations following COVID-19 related intercurrent events.

The primary endpoint (Change in BCVA score from baseline averaged over Weeks 48, 52, and 56) assessed non-inferiority of faricimab compared with aflibercept Q8W in the ITT population with a non-inferiority margin of 4 letters.

The key secondary endpoint (Patient with 2-step DRS improvement from baseline on the ETDRS DRSS at Week 52) assessed non-inferiority of faricimab compared with aflibercept Q8W in the ITT population with a non-inferiority margin of 10%.

Non-inferiority margins were not assumed for other secondary endpoints, including central subfield thickness, absence of DMO and intraretinal and subretinal fluid. Non-inferiority comparisons were therefore not made for these endpoints.

A8. Please clarify the rationale for the assumption of a standard deviation of 11 letters and a dropout rate of 10% used in the sample size calculation (CS section B.3.4.3).

The standard deviation and dropout rate used in the sample size determination were informed by previous studies conducted in DME patients, together with the anticipated rates based on the study design for YOSEMITE and RHINE (1). The historical studies considered included the pivotal Phase III DME studies for both ranibizumab and aflibercept.

A9. CS section B.3.6.2 states descriptively that results for the analysis in the pooled TN population were consistent with the results in the pooled ITT population. Please provide the quantitative data supporting this assertion.

As noted in section B.3.6.2, in the pooled ITT population, the adjusted proportion of patients who had a ≥2-step DRSS improvement from baseline at Week 52 was comparable across the faricimab Q8W, faricimab PTI, and aflibercept Q8W arms [redacted]. The difference in adjusted proportions between the faricimab Q8W and PTI arms when compared with the aflibercept Q8W arm was [redacted].

Results from the analysis demonstrated that in the pooled TN population, the adjusted proportion of patients who had a ≥2-step DRSS improvement from baseline at Week 52 was [redacted]. The difference in adjusted proportions between the faricimab Q8W and PTI arms when compared with the aflibercept Q8W arm was [redacted].

Network meta-analyses

The information provided by the company is insufficient for the ERG to validate the NMA methods and results. Please provide the information requested in the following questions (A10 to A28), noting that the ERG will have limited time between receiving company clarification responses (16th November) and submitting our draft scrutiny opinion (26th November). Therefore, we kindly request that all responses are as concise and transparent as possible and that all data provided can be readily traced to and checked against the published sources.

A10. The PRISMA chart (CS Figure 11) states that 461 documents were excluded at full-text screening, for the general reasons stated in the chart. Please provide a list of these 461 excluded references with a more precise reason for exclusion (i.e., if an article was excluded on population, intervention, comparator or outcome please specify which specific aspect of the population, intervention, comparator or outcome precluded including the study).

The list of excluded studies and justifications for their exclusion can be seen in "List of excluded studies" spreadsheet.

A11. The PRISMA chart states that 83 studies were included in the review but CS Appendix D Table 11 lists 84 studies. Please explain this discrepancy.

Appendix D Table 11 contains 84 rows, including 83 unique studies. This discrepancy could be explained by:

- *ENDURANCE, which is an open label extension of the VISTA-DME study (5, 6)(refs) and RESTORE open label extension, which is an open label extension of RESTORE trial (7, 8), being listed in separate rows of Table 11. Although listed separately, open label extension studies were considered a continuation of the original studies, therefore not considered as separate studies.*
- *Mead 1 and Mead 2 being included on a single row but considered as 2 studies (9).*

A12. PRIORITY QUESTION. The PRISMA chart indicates that 41 of the 83 included studies were then excluded leaving 42 studies for "feasibility assessment" and these

formed the “base case network”. Please provide a list of these 41 excluded studies with the specific reason(s) for excluding each study.

The below tables contain the list of excluded studies and the rationale for their exclusion. Most studies were excluded for treatment related reasons (n=33), others were excluded as they did not connect to the faricimab network (n=4), and the remaining studies were excluded for a variety of different reasons.

Table 1: Studies Excluded For A Treatment-Related Reason (n=33)

Trial name / Author	Reason for study exclusion
ADDENDUM (10)	Insufficient distinction between randomized arms for the purpose of the current proposed NMA · All patients received AFL 2 mg Q4W loading then PRN, plus either · Laser (navigated focal grid laser) or · Laser (conventional focal grid laser)
Akduman 1997 (11)	Insufficient distinction between randomized arms for the purpose of the current proposed NMA · Laser (argon green (514nm) session 1 then PRN) · Laser (diode laser (810nm) session 1 then PRN)
Bandello 2005 (12)	Insufficient distinction between randomized arms for the purpose of the current proposed NMA · Laser (Classic Nd:Yag 532nm) PRN · Laser (Light Nd:Yag 532nm) PRN
Blankenship 1979 (13)	Observation arm not of interest for the NMA
Casswell 1990 (14)	Insufficient distinction between randomized arms for the purpose of the current proposed NMA · Laser (Grid with argon blue/green 488/514nm) PRN · Laser (Grid with argon blue/green 488/514nm) PRN
DEGAS (NCT00701181) (15)	Comparator arms PF-04523655 0.4 mg, 1 mg and 3 mg IVT not of interest for the NMA
Doga 2017 (16)	Insufficient distinction between randomized arms for the purpose of the current proposed NMA · Laser (mETDRS + SMYL) · Laser (mETDRS)
DRCR Network Protocol A (NCT00071773) (17, 18)	Insufficient distinction between randomized arms for the purpose of the current proposed NMA · Laser (mETDRS direct/grid) PRN

	· Laser (mild macular grid) PRN
DRCR Network Protocol B (NCT00367133) (19-21) (refs)	Comparator arms TA 1 mg and TA 4 mg IVT not of interest for the NMA
DRCR Network Protocol V (22)	Treatment regimen during follow-up differs from other studies and was not of specific interest for the NMA. In the AFL arm, patients received an injection at baseline and were evaluated for repeat injections up to every 4 weeks as needed until 24 weeks into the study. In this study, if an eye with 5- to 9-letter VA decrease did not have a decrease from baseline by ≥5 letters at the subsequent 4-week visit, follow-up was extended to 8 weeks and then every 16 weeks
Ekinci 2014 (23)	Unlicensed comparator arm RAN 0.05mg PRN not of interest for the NMA
Figueira 2009 (24)	Insufficient distinction between randomized arms for the purpose of the current proposed NMA · Laser (micro-pulse diode) PRN · Laser (Conventional green) PRN
Freyler 1990 (25)	Insufficient distinction between randomized arms for the purpose of the current proposed NMA · Laser (red 630 nm) · Laser (argon green 514 nm)
IBERA-DME (Nepomuceno 2013) (26)	Unlicensed comparator arm BEV 1.5mg IVT PRN not of interest for the NMA
Karacorlu 1993 (27)	Insufficient distinction between randomized arms for the purpose of the current proposed NMA · Laser (argon green) · Laser (dye yellow grid)
Khairallah 1996 (28)	Insufficient distinction between randomized arms for the purpose of the current proposed NMA · Laser (argon green) PRN · Laser (Krypton red) PRN
Ladas 1993 (29)	Observation arm not of interest for the NMA
Lafuente 2017 (30)	Comparator arm RAN 0.5 mg IVT + DHA 1.5 mg QD then PRN not of interest for the NMA
NCT00148265 (31)	Comparator arm TA 4 mg IVT + Laser not of interest for the NMA
NCT00370669 Soheilian 2012 (32)	Treatment regimen during follow-up differs from other studies and was not of specific interest for the NMA. In the BEV arm, patients received an injection every 12 weeks on an as-needed basis, with retreatment performed on the basis of visual acuity response (persistent clinically significant macular edema based on ETDRS criteria, if visual acuity was not better than 20/40) rather than

	OCT findings. This would likely underestimate DME recurrence and in turn have an impact on the number of treatments given.
NCT00440609 (Ferrone 2016) (33)	Unlicensed comparator arm RAN 1.0mg IVT PRN not of interest for the NMA
NCT00552435 (34)	Insufficient distinction between randomized arms for the purpose of the current proposed NMA · Laser (normal-density SDM) PRN · Laser (high-density SDM) PRN · Laser (mETDRS focal/grid) PRN
NCT01342159 (Lim 2012) (35)	Comparator arms not of interest for the NMA · BEV 1.25 mg IVT + TA 2 mg IVT PRN · TA 2 mg PRN (BEV)
NCT02448446 (36)	Insufficient distinction between randomized arms for the purpose of the current proposed NMA · RAN 0.3 mg then PRN until macular edema resolved · RAN 0.3 mg then PRN until macular edema and hard exudates resolved
NCT02645734 (37)	Comparator arms not of interest for the NMA · ZIV AFL 1.25 mg IVT PRN · ZIV AFL 2.5 mg IVT PRN
Ockrim 2008 (38)	Comparator arm TA 4 mg IVT not of interest for the NMA
Olk 1986 (39)	No treatment arm not of interest for the NMA
Olk 1990 (40)	Insufficient distinction between randomized arms for the purpose of the current proposed NMA · Laser (Argon green 514nm) PRN · Laser (Krypton red Laser 647nm) PRN
OZDRY (Ramu 2015) (41)	Insufficient distinction between randomized arms for the purpose of the current proposed NMA: · DEX 0.7 mg IVT baseline→PRN every 5 months · DEX 0.7 mg IVT→PRN Q4W monitoring + every 4 months treatment
READ-3 (Sepah 2016) (42)	Unlicensed comparator arm RAN 2.0 mg IVT PRN not of interest for the NMA
Rutllan 1994 (43)	Insufficient distinction between randomized arms for the purpose of the current proposed NMA · Laser (argon green [514nm]) · Laser (dye-yellow laser [577 nm])
TRIASTIN (Kriechbaum	Comparator arms not of interest for the NMA

2014, Prager 2018) (44, 45)	· BEV 2.5 mg IVT PRN (unlicensed) · TA 8 mg IVT PRN
Vujosevic 2010 (46)	Insufficient distinction between randomized arms for the purpose of the current proposed NMA · Laser (Diode) PRN · Laser (ETDRS) PRN

Abbreviations: ETDRS, Early Treatment Diabetic Retinopathy Study protocol; IVT, intravitreal injections; mETDRS, modified ETDRS; NMA, network meta-analysis; OCT, optical coherence tomography; OLE, open label extension; PRN, Pro re nata (as needed); QD, once daily; RAN, ranibizumab; SDM, subthreshold micropulse diode-laser; SMPL, subthreshold micropulse laser; TA, Triamcinolone acetonide; VA, visual acuity

Table 2: Studies Not Connected To The Faricimab Network (n=4)

Trial name / Author	Randomized treatment arms
NCT01492400 (47-49)	· RAN 0.5 mg IVT ± Laser PRN Q4W · 3 doses DEX 0.7 mg IVT Q20W +/- Laser
RELATION	Premature termination of trial, maximum follow-up time was 11 months, with mean follow-up of 6.2 ± 2.8 months in the ranibizumab plus laser arm and mean follow-up of 6.2 ± 2.5 months in the laser arm. LOCF was then used to extrapolate outcome data to 12 months
Weingessel 2018 (50)	· RAN 0.5 mg IVT PRN + Prompt Laser · RAN 0.5 mg IVT PRN + Deferred Laser
Yang 2018 (51)	· RAN 0.5mg IVT Q4W→PRN · RAN 0.5 mg IVT Q4W + Laser 1st week→PRN · Laser baseline

Abbreviations: BEV, bevacizumab; DEX, dexamethasone; IVT, intravitreal injections; PRN, Pro re nata (as needed); Q4W, every 4 weeks; Q6W, every 6 weeks; Q20W, every 20 weeks; RAN, ranibizumab

Table 3: Studies Excluded For Other Reasons (n=4)

Trial name / Author	Reason for study exclusion
COMET / Ishibashi 2020 (52)	Only protocol available
DIME / McKee 2019 (53) (ref)	Intervention arm comprised mixed anti-VEGF treatment: ranibizumab, bevacizumab, or aflibercept
EVADE (NCT02392364) (54)	Treatment doses not stated in publication. Authors were contacted but no reply received at the time of writing this report.
RDP study (ISRCTN84503751) (55)	Treatment doses not stated in publication. Authors were contacted but no reply received at the time of writing this report.

Abbreviations: VEGF, vascular endothelial growth factor

A13. PRIORITY QUESTION. According to the network diagrams reported in CS Figures 12, 14, 16, 20 and 22 the NMAs together contain 25 studies in total, meaning that a further 16 studies have been excluded from the “feasibility

assessment" set of 42 which made up the "base case network". Please provide a list of the specific reasons for excluding each of these 16 studies.

There are 26 studies included in the networks presented in figures 12, 14, 16, 20, 22 of the company submission (see list of studies below). These 26 studies form the base-case network for the NMA.

Table 4: Studies included in base-case network for outcomes presented in company submission

#	Study name	#	Study name	#	Study name
1	BEVORDEX (56)	**10**	REFINE (57)	**19**	VISTA (58)
2	BOLT (59)	**11**	RESOLVE (60)	**20**	VIVID (58)
3	Chatzirallis 2020 (61)	**12**	RESPOND (62)	**21**	VIVID-East (63)
4	DA VINCI (64)	**13**	RESTORE (7)	**22**	YOSEMITE (1)
5	DRCR T (65)	**14**	RETAIN (66)	**23**	Fouda 2017 (67)
6	Eichenbaum 2018 (68)	**15**	REVEAL (69)	**24**	ETDRS (70)
7	LUCIDATE (71)	**16**	RHINE (1)	**25**	MEAD 1 (9)
8	Ozsaygili 2020 (72)	**17**	ROTATE (73)	**26**	MEAD 2 (9)
9	REACT (74)	**18**	TREX-DME (75)		

The discrepancy of 16 studies between the feasibility assessment and the base-case network for the NMA, can be explained by:

- *13 studies being excluded for investigating unlicensed combination regimens*
- *3 studies (RISE, RIDE (76),, and NCT00370422 (77)), did not report any relevant data for outcomes of interest at 12-months.*

A14. CS Appendix D Tables 12 to 16 list some further characteristics of "included" studies. However:

- 14 of the studies in CS Appendix Table 12 are not included in any network diagrams.
- 3 of the studies in CS Appendix Table 13 are not included in any network diagrams.

- 3 of the studies in CS Appendix Table 14 are not included in any network diagrams.
- 2 of the studies CS Appendix Table 16 are not included in any network diagrams.

Please explain the purpose of these tables, as they do not appear to align fully with the sets of studies that were included for analysis.

The list of studies included in Tables 12-16 of the submission appendices aligns to those included after the systematic literature review feasibility assessment. The discrepancy between the studies included in the feasibility assessment and those in the base-case network has been described in the response to question A13.

The reason for including Tables 12-16 in the submission appendices was to provide the ERG with complete information regarding Roche's feasibility assessment of the studies identified in the systematic literature review.

A15. PRIORITY QUESTION. No rationale is provided for each of the risk of bias judgements reported in CS Appendix D1.3. Moreover, the risk of bias judgements do not inform the NMAs.

(a) Please provide a clear rationale for each risk of bias judgement for each study included in the NMAs.

Justifications for the judgement of bias in each study included in the NMAs can be seen in the "Critical Appraisal NICE" sheet of the data extraction table.

(b) Please conduct a sensitivity analysis for each NMA to determine the impact of high risk of bias studies on the efficacy and safety outcomes.

The risk of bias of each study identified in the SLR feasibility assessment was assessed across 7 criteria:

- *Was randomisation carried out appropriately?*
- *Was the concealment of treatment allocation adequate?*
- *Were the groups similar at the outset of the study in terms of prognostic factors?*

- *Were the care providers, participants and outcome assessors blind to treatment allocation?*
- *Were there any unexpected imbalances in drop-outs between groups?*
- *Is there any evidence to suggest that the authors measured more outcomes than they reported?*
- *Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?*

Each study judged to be high risk in any of the above criteria was excluded for the purpose of the sensitivity analysis. For each outcome, data extraction tables, network diagrams and forest plots have been provided.

Figure 1: Network Diagram: BCVA score mean change from baseline at 12m excluding high risk of bias studies (Base case, RE model)

Abbreviations: AFL, aflibercept; FAR, faricimab; IVT, intravitreal; PBO, placebo; PRN, treatment as needed (pro re nata); Q4/8/16W, every 4/8/16 weeks; RAN, ranibizumab; T&E, treat and extend

Table 5: Original extracted data: BCVA score mean change from baseline at 12m excluding high risk of bias studies (Base case, RE model)

Study	Treatment	Patients	Mean	SE
BOLT	BEV 1.25 mg IVT PRN	42	5.599999999	1.554
BOLT	Laser PRN	38	-4.6	2.333
DA VINCI	AFL 2 mg IVT PRN	45	12	1.653
DA VINCI	AFL 2 mg IVT Q4W	44	13.1	1.589
DA VINCI	AFL 2 mg IVT Q8W	42	9.7	1.378
DA VINCI	Laser PRN	44	-1.3	3.124

DRCR T	AFL 2 mg IVT PRN	208	13.3	0.77
DRCR T	BEV 1.25 mg IVT PRN	206	9.7	0.704
DRCR T	RAN 0.3/0.5 mg IVT PRN	206	11.2	0.655
Eichenbaum 2018	RAN 0.3/0.5 mg IVT Q4W	10	8.2	1.992
Eichenbaum 2018	RAN 0.3/0.5 mg IVT T&E	10	7	2.72
RESOLVE	RAN 0.3/0.5 mg IVT PRN	204	10.3	0.636
RESOLVE	Sham / PBO	49	-1.4	2.029
RESTORE	Laser PRN	110	0.9	1.087
RESTORE	RAN 0.3/0.5 mg IVT PRN	115	6.8	0.774
RETAIN	RAN 0.3/0.5 mg IVT PRN	117	7.44	0.782
RETAIN	RAN 0.3/0.5 mg IVT T&E	125	6.8	0.78
REVEAL	Laser PRN	128	1.8	0.731
REVEAL	RAN 0.3/0.5 mg IVT PRN	133	6.6	0.666
RHINE	AFL 2 mg IVT Q8W	315	10.3	0.52
RHINE	FAR 6 mg IVT Q4-16W	319	10.8	0.51
RHINE	FAR 6 mg IVT Q8W	317	11.8	0.52
VIVID-East	AFL 2 mg IVT Q4W	127	13.6	0.9
VIVID-East	AFL 2 mg IVT Q8W	127	13.1	1
VIVID-East	Laser PRN	124	-0.5	1.4
YOSEMITE	AFL 2 mg IVT Q8W	276	10.9	0.56
YOSEMITE	FAR 6 mg IVT Q4-16W	276	11.6	0.56
YOSEMITE	FAR 6 mg IVT Q8W	271	10.7	0.56

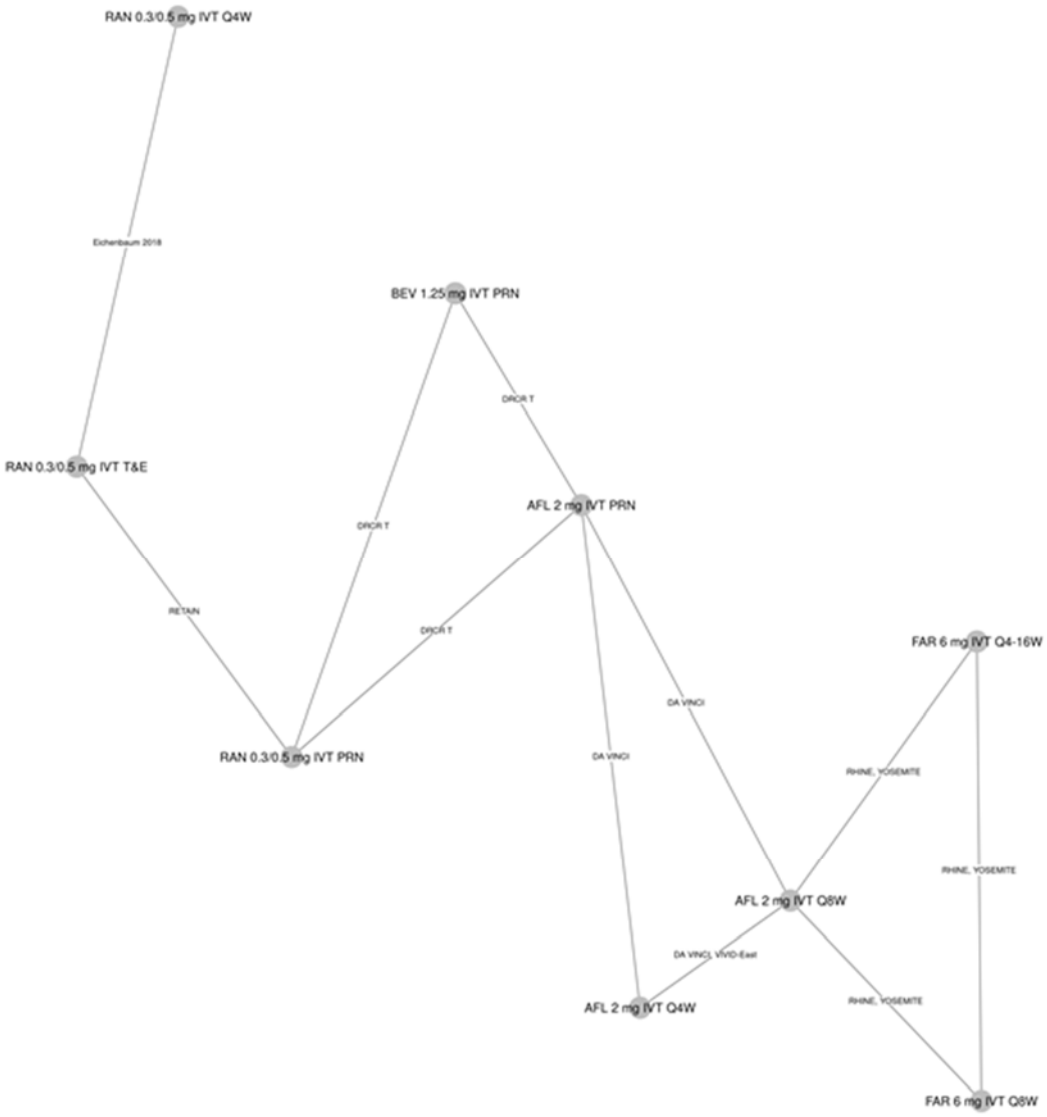
Abbreviations: AFL, aflibercept; FAR, faricimab; IVT, intravitreal; PBO, placebo; PRN, treatment as needed (pro re nata); Q4/8/16W, every 4/8/16 weeks; RAN, ranibizumab; T&E, treat and extend

Figure 2: Forest plot of differences and 95% credible intervals of faricimab (6.0 mg Q4-16w) compared with other comparators: BCVA score mean change from baseline at 12m excluding high risk of bias studies (base-case, random-effects model)

[redacted] *Figure redacted*

Abbreviations: AFL, aflibercept; FAR, faricimab; IVT, intravitreal; PBO, placebo; PRN, treatment as needed (pro re nata); Q4/8/16W, every 4/8/16 weeks; RAN, ranibizumab; T&E, treat and extend

Figure 3: Network Diagram: Mean number of injections at 12m (excluding Laser PRN node) excluding high risk of bias studies (Base case, RE model)



Abbreviations: AFL, aflibercept; FAR, faricimab; IVT, intravitreal; PBO, placebo; PRN, treatment as needed (pro re nata); Q4/8/16W, every 4/8/16 weeks; RAN, ranibizumab; T&E, treat and extend

Table 6: Original extracted data: Mean number of injections at 12m excluding high risk of bias studies (Base case, RE model)

Study	Treatment	Patients	Mean	SE

DA VINCI	AFL 2 mg IVT PRN	44	7.4	0.481
DA VINCI	AFL 2 mg IVT Q4W	42	10.8	0.443
DA VINCI	AFL 2 mg IVT Q8W	45	7.2	0.259
DRCR T	AFL 2 mg IVT PRN	208	9.2	0.139
DRCR T	BEV 1.25 mg IVT PRN	206	9.7	0.16
DRCR T	RAN 0.3/0.5 mg IVT PRN	206	9.4	0.146
Eichenbaum 2018	RAN 0.3/0.5 mg IVT Q4W	10	10.9	0.601
Eichenbaum 2018	RAN 0.3/0.5 mg IVT T&E	10	10.7	0.506
RETAIN	RAN 0.3/0.5 mg IVT PRN	118	7	0.179
RETAIN	RAN 0.3/0.5 mg IVT T&E	126	7	0.174
RHINE	AFL 2 mg IVT Q8W	314	9.3	0.077
RHINE	FAR 6 mg IVT Q4-16W	319	8.7	0.14
RHINE	FAR 6 mg IVT Q8W	317	9.3	0.085
VIVID-East	AFL 2 mg IVT Q4W	127	12.6	0.169
VIVID-East	AFL 2 mg IVT Q8W	127	8.7	0.098
YOSEMITE	AFL 2 mg IVT Q8W	311	9.2	0.083
YOSEMITE	FAR 6 mg IVT Q4-16W	313	8.4	0.138
YOSEMITE	FAR 6 mg IVT Q8W	313	9.5	0.08

Abbreviations: AFL, aflibercept; FAR, faricimab; IVT, intravitreal; PBO, placebo; PRN, treatment as needed (pro re nata); Q4/8/16W, every 4/8/16 weeks; RAN, ranibizumab; T&E, treat and extend

Figure 4: Forest Plot of Differences and 95% credible intervals (CrI) of Faricimab 6 mg IVT Q4-16W versus Other Comparators: Mean number of injections at 12m excluding high risk of bias studies (Base case, RE model)

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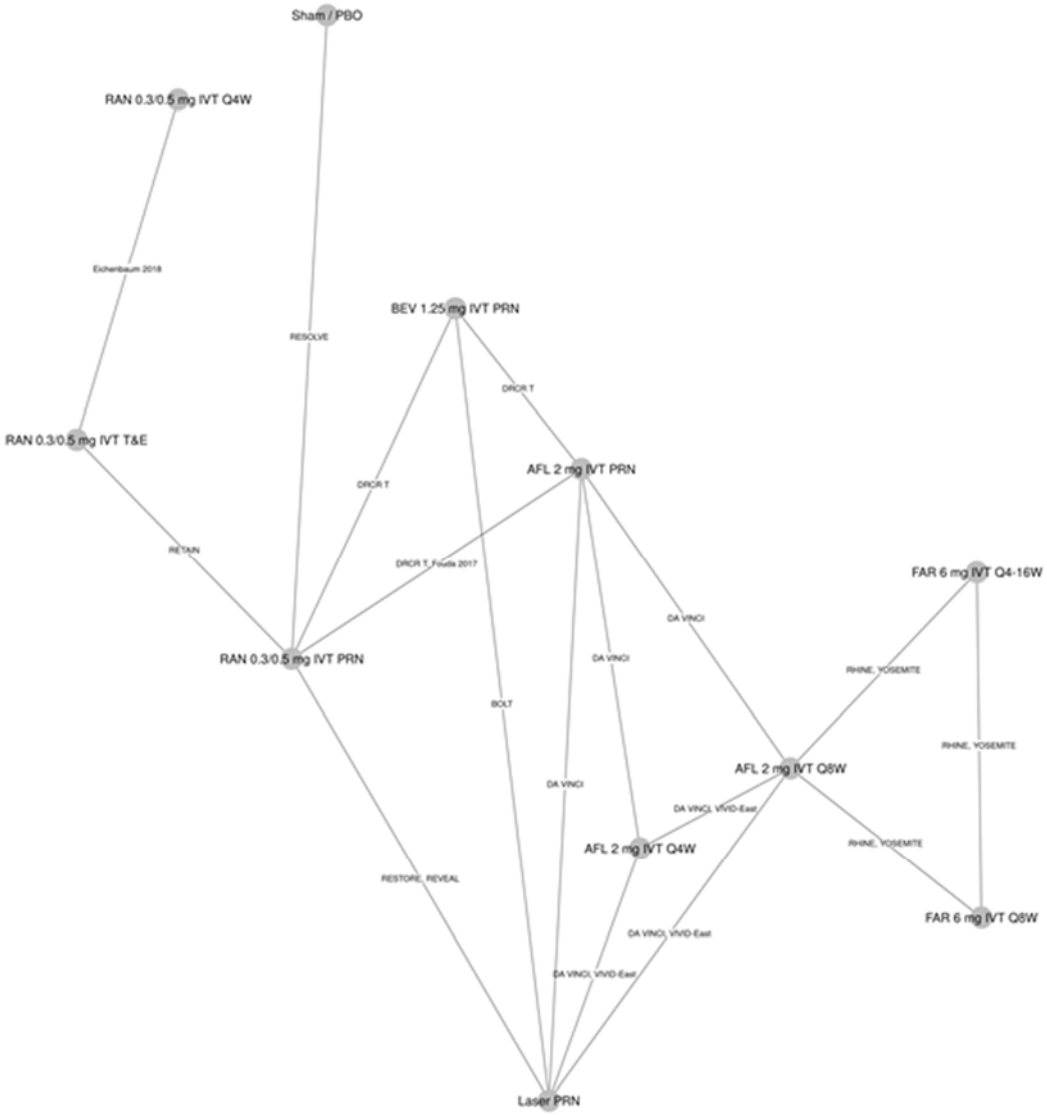
Abbreviations: AFL, aflibercept; FAR, faricimab; IVT, intravitreal; PBO, placebo; PRN, treatment as needed (pro re nata); Q4/8/16W, every 4/8/16 weeks; RAN, ranibizumab; T&E, treat and extend

Figure 5: Network Diagram: CST mean change from baseline at 12m excluding high risk of bias studies (Base case, RE model)



Abbreviations: AFL, aflibercept; BEV, bevacizumab; FAR, faricimab; IVT, intravitreal; PBO, placebo; PRN, treatment as needed (pro re nata); Q4/8/16W, every 4/8/16 weeks; RAN, ranibizumab; T&E, treat and extend

Table 7: Original extracted data: CST mean change from baseline at 12m excluding high risk of bias studies (Base case, RE model)

Study	Treatment	Patients	Mean	SE
BOLT	BEV 1.25 mg IVT PRN	42	-130	18.825
BOLT	Laser PRN	38	-68	27.74
DA VINCI	AFL 2 mg IVT PRN	45	-180.3	18.549
DA VINCI	AFL 2 mg IVT Q4W	44	-227.4	22.457
DA VINCI	AFL 2 mg IVT Q8W	42	-187.8	20.832

DA VINCI	Laser PRN	43	-58.4	27.084
DRCR T	AFL 2 mg IVT PRN	221	-167	8.812
DRCR T	BEV 1.25 mg IVT PRN	216	-99.3	7.825
DRCR T	RAN 0.3/0.5 mg IVT PRN	215	-146.6	9.03
Eichenbaum 2018	RAN 0.3/0.5 mg IVT Q4W	10	-154.6	30.959
Eichenbaum 2018	RAN 0.3/0.5 mg IVT T&E	10	-124.3	38.991
Fouda 2017	AFL 2 mg IVT PRN	35	-104.49	12.64
Fouda 2017	RAN 0.3/0.5 mg IVT PRN	35	-84.2	12.953
RESOLVE	RAN 0.3/0.5 mg IVT PRN	102	-194.2	13.377
RESOLVE	Sham / PBO	49	-48.4	21.914
RESTORE	Laser PRN	110	-61.3	12.613
RESTORE	RAN 0.3/0.5 mg IVT PRN	115	-118.7	10.73
RETAIN	RAN 0.3/0.5 mg IVT PRN	117	-100.167	2.067
RETAIN	RAN 0.3/0.5 mg IVT T&E	125	-110.1594	1.97
REVEAL	Laser PRN	128	-58.6	11.004
REVEAL	RAN 0.3/0.5 mg IVT PRN	133	-132.5	10.796
RHINE	AFL 2 mg IVT Q8W	276	-170.1	4.19
RHINE	FAR 6 mg IVT Q4-16W	291	-187.6	4.12
RHINE	FAR 6 mg IVT Q8W	265	-195.8	4.22
VIVID-East	AFL 2 mg IVT Q4W	127	-231.1	11.048
VIVID-East	AFL 2 mg IVT Q8W	127	-232	11.048
VIVID-East	Laser PRN	124	-100.6	11.181
YOSEMITE	AFL 2 mg IVT Q8W	272	-170.3	4.16
YOSEMITE	FAR 6 mg IVT Q4-16W	275	-196.5	4.13
YOSEMITE	FAR 6 mg IVT Q8W	271	-206.6	4.15

Abbreviations: AFL, aflibercept; BEV, bevacizumab; FAR, faricimab; IVT, intravitreal; PBO, placebo; PRN, treatment as needed (pro re nata); Q4/8/16W, every 4/8/16 weeks; RAN, ranibizumab; T&E, treat and extend

Figure 6: Forest Plot of Differences and 95% credible intervals (CrI) of Faricimab 6 mg IVT Q4-16W versus Other Comparators: CST mean change from baseline at 12m excluding high risk of bias studies (Base case, RE model)

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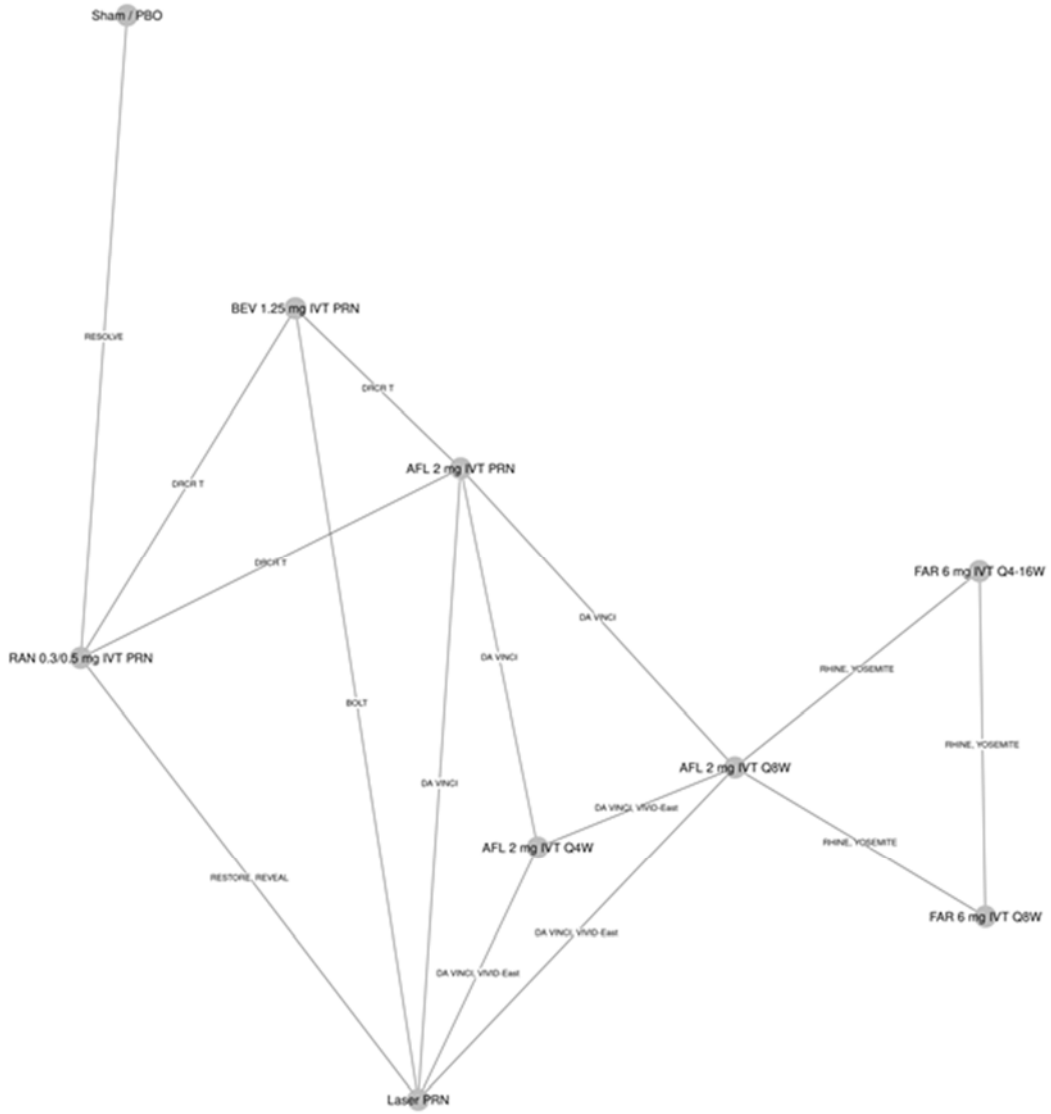
Abbreviations: AFL, aflibercept; FAR, faricimab; IVT, intravitreal; PBO, placebo; PRN, treatment as needed (pro re nata); Q4/8/16W, every 4/8/16 weeks; RAN, ranibizumab; T&E, treat and extend

Figure 7: Network Diagram: ETDRS letters categories at 12m excluding high risk of bias studies (Base case, RE model)



Abbreviations: AFL, aflibercept; BEV, bevacizumab; FAR, faricimab; IVT, intravitreal; PBO, placebo; PRN, treatment as needed (pro re nata); Q4/8/16W, every 4/8/16 weeks; RAN, ranibizumab; T&E, treat and extend

Table 8: Original extracted data: ETDRS letters categories at 12m excluding high risk of bias studies (Base case, RE model)

Study	Treatment	Patients	Gained >=15	Gained >=10	Lost >=10	Lost >=15
BOLT	BEV 1.25 mg IVT PRN	42	5	13		1
BOLT	Laser PRN	38	2	3		8
DA VINCI	AFL 2 mg IVT PRN	45	19	28		
DA VINCI	AFL 2 mg IVT Q4W	44	20	31		
DA VINCI	AFL 2 mg IVT Q8W	42	10	19		
DA VINCI	Laser PRN	44	5	13		
DRCR T	AFL 2 mg IVT PRN	208	87	132	5	3
DRCR T	BEV 1.25 mg IVT PRN	206	59	108	6	3
DRCR T	RAN 0.3/0.5 mg IVT PRN	206	66	122	3	3
RESOLVE	RAN 0.3/0.5 mg IVT PRN	102	33	62	5	3
RESOLVE	Sham / PBO	49	5	9	12	10
RESTORE	Laser PRN	110	9	17	14	9
RESTORE	RAN 0.3/0.5 mg IVT PRN	115	26	43	4	1
REVEAL	Laser PRN	128	10	17	8	5
REVEAL	RAN 0.3/0.5 mg IVT PRN	133	25	45	4	2
RHINE	AFL 2 mg IVT Q8W	279	85	151		
RHINE	FAR 6 mg IVT Q4-16W	293	83	155		
RHINE	FAR 6 mg IVT Q8W	268	90	158		
VIVID-East	AFL 2 mg IVT Q4W	127	55	90		
VIVID-East	AFL 2 mg IVT Q8W	127	46	80		
VIVID-East	Laser PRN	124	15	29		
YOSEMITE	AFL 2 mg IVT Q8W	276	88	159		
YOSEMITE	FAR 6 mg IVT Q4-16W	276	98	161		
YOSEMITE	FAR 6 mg IVT Q8W	271	79	155		

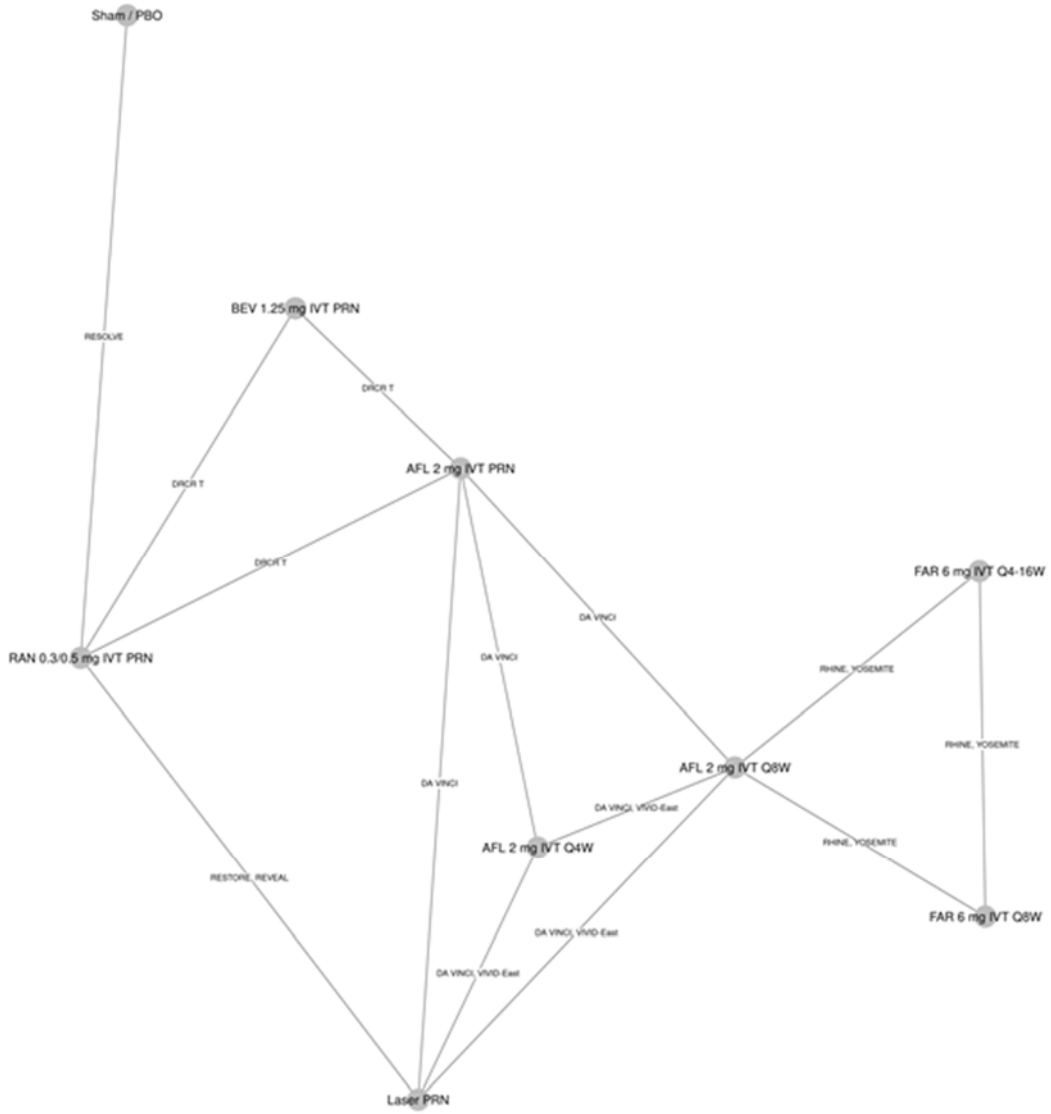
Abbreviations: AFL, aflibercept; BEV, bevacizumab; FAR, faricimab; IVT, intravitreal; PBO, placebo; PRN, treatment as needed (pro re nata); Q4/8/16W, every 4/8/16 weeks; RAN, ranibizumab; T&E, treat and extend

Figure 8: Forest Plot of Probit scale Treatment Differences and 95% credible intervals (CrI) of Faricimab 6 mg IVT Q4-16W versus Other Comparators: ETDRS letters categories at 12m excluding high risk of bias studies (Base case, RE model)

[redacted] *Figure redacted*

Abbreviations: AFL, aflibercept; FAR, faricimab; IVT, intravitreal; PBO, placebo; PRN, treatment as needed (pro re nata); Q4/8/16W, every 4/8/16 weeks; RAN, ranibizumab; T&E, treat and extend

Figure 9: Network Diagram: All cause discontinuation at 12m excluding high risk of bias studies (Base case, RE model)



Abbreviations: AFL, aflibercept; FAR, faricimab; IVT, intravitreal; PBO, placebo; PRN, treatment as needed (pro re nata); Q4/8/16W, every 4/8/16 weeks; RAN, ranibizumab; T&E, treat and extend

Table 9: Original extracted data: All cause discontinuation at 12m excluding high risk of bias studies (Base case, RE model)

Study	Treatment	Patients	Events	Percent
DA VINCI	AFL 2 mg IVT PRN	45	7	15.6
DA VINCI	AFL 2 mg IVT Q4W	44	11	25
DA VINCI	AFL 2 mg IVT Q8W	44	8	18.2
DA VINCI	Laser PRN	44	11	25
DRCR T	AFL 2 mg IVT PRN	224	16	7.1
DRCR T	BEV 1.25 mg IVT PRN	218	12	5.5
DRCR T	RAN 0.3/0.5 mg IVT PRN	218	12	5.5
RESOLVE	RAN 0.3/0.5 mg IVT PRN	102	10	9.8
RESOLVE	Sham / PBO	49	9	18.4
RESTORE	Laser PRN	111	13	11.7
RESTORE	RAN 0.3/0.5 mg IVT PRN	116	14	12.1
REVEAL	Laser PRN	131	23	17.6
REVEAL	RAN 0.3/0.5 mg IVT PRN	133	10	7.5
RHINE	AFL 2 mg IVT Q8W	315	19	6
RHINE	FAR 6 mg IVT Q4-16W	319	11	3.5
RHINE	FAR 6 mg IVT Q8W	317	24	7.6
VIVID-East	AFL 2 mg IVT Q4W	127	5	3.9
VIVID-East	AFL 2 mg IVT Q8W	127	11	8.7
VIVID-East	Laser PRN	127	10	7.9
YOSEMITE	AFL 2 mg IVT Q8W	311	26	8.4
YOSEMITE	FAR 6 mg IVT Q4-16W	313	30	9.6
YOSEMITE	FAR 6 mg IVT Q8W	313	31	9.9

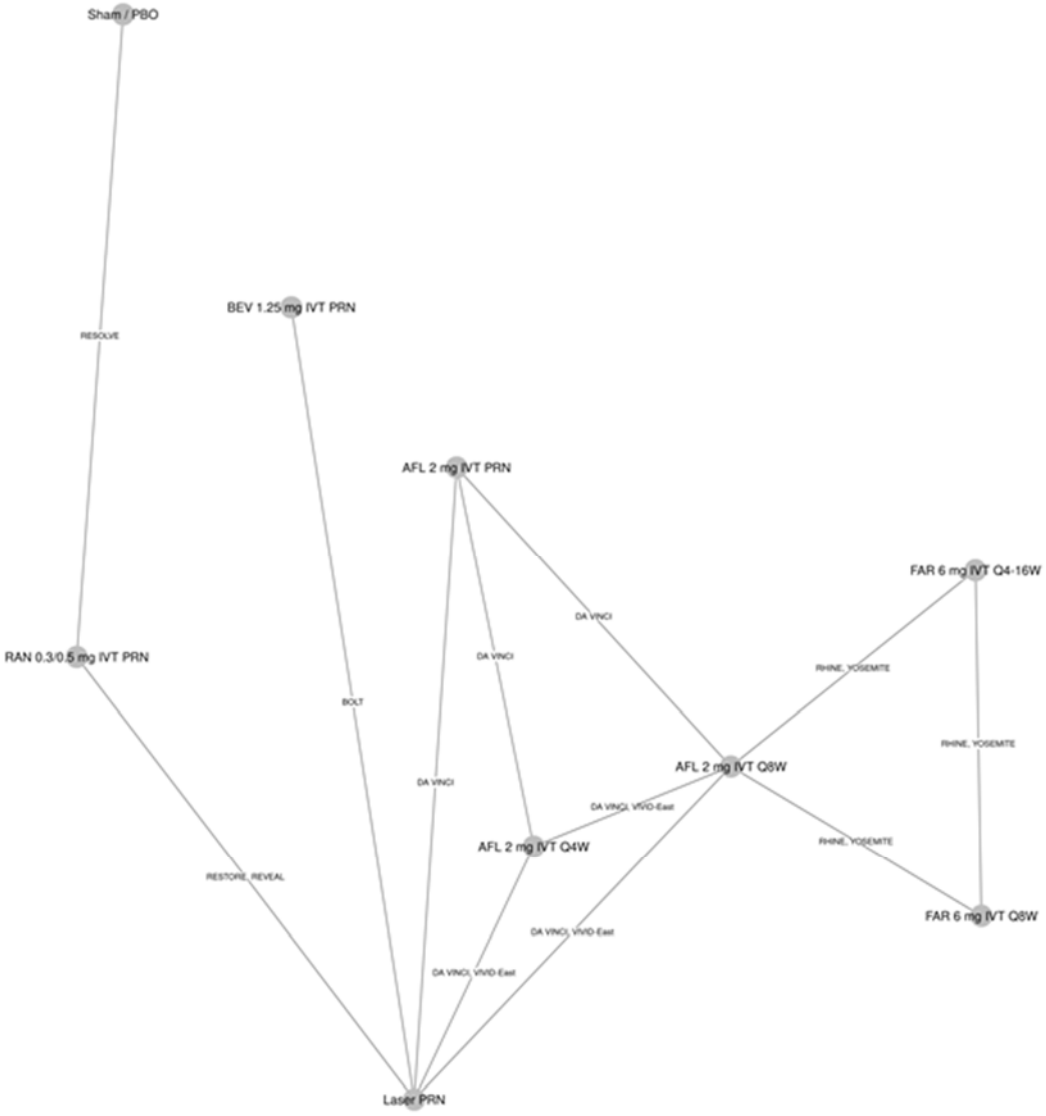
Abbreviations: AFL, aflibercept; FAR, faricimab; IVT, intravitreal; PBO, placebo; PRN, treatment as needed (pro re nata); Q4/8/16W, every 4/8/16 weeks; RAN, ranibizumab; T&E, treat and extend

Figure 10: Forest Plot of Odds Ratios and 95% credible intervals (CrI) of Faricimab 6 mg IVT Q4-16W versus Other Comparators: All cause discontinuation at 12m excluding high risk of bias studies (Base case, RE model)

[redacted] *Figure redacted*

Abbreviations: AFL, aflibercept; FAR, faricimab; IVT, intravitreal; PBO, placebo; PRN, treatment as needed (pro re nata); Q4/8/16W, every 4/8/16 weeks; RAN, ranibizumab; T&E, treat and extend

Figure 11: Network Diagram: Ocular AEs at 12m excluding high risk of bias studies (Base case, RE model)



Abbreviations: AFL, aflibercept; BEV, bevacizumab; FAR, faricimab; IVT, intravitreal; PBO, placebo; PRN, treatment as needed (pro re nata); Q4/8/16W, every 4/8/16 weeks; RAN, ranibizumab; T&E, treat and extend

Table 10: Original extracted data: Ocular AEs at 12m excluding high risk of bias studies (Base case, RE model)

Study	Treatment	Patients	Events	Percent

BOLT	BEV 1.25 mg IVT PRN	42	20	47.6
BOLT	Laser PRN	38	8	21.1
DA VINCI	AFL 2 mg IVT PRN	45	29	64.4
DA VINCI	AFL 2 mg IVT Q4W	44	26	59.1
DA VINCI	AFL 2 mg IVT Q8W	42	28	66.7
DA VINCI	Laser PRN	44	27	61.4
RESOLVE	RAN 0.3/0.5 mg IVT PRN	102	80	78.4
RESOLVE	Sham / PBO	49	28	57.1
RESTORE	Laser PRN	110	43	39.1
RESTORE	RAN 0.3/0.5 mg IVT PRN	115	49	42.6
REVEAL	Laser PRN	128	28	21.9
REVEAL	RAN 0.3/0.5 mg IVT PRN	133	43	32.3
RHINE	AFL 2 mg IVT Q8W	314	113	36
RHINE	FAR 6 mg IVT Q4-16W	319	119	37.3
RHINE	FAR 6 mg IVT Q8W	317	137	43.2
VIVID-East	AFL 2 mg IVT Q4W	127	65	51.2
VIVID-East	AFL 2 mg IVT Q8W	127	60	47.2
VIVID-East	Laser PRN	124	72	58.1
YOSEMITE	AFL 2 mg IVT Q8W	311	102	32.8
YOSEMITE	FAR 6 mg IVT Q4-16W	313	106	33.9
YOSEMITE	FAR 6 mg IVT Q8W	313	98	31.3

Abbreviations: AFL, aflibercept; BEV, bevacizumab; FAR, faricimab; IVT, intravitreal; PBO, placebo; PRN, treatment as needed (pro re nata); Q4/8/16W, every 4/8/16 weeks; RAN, ranibizumab; T&E, treat and extend

Figure 12: Forest Plot of Odds Ratios and 95% credible intervals (CrI) of Faricimab 6 mg IVT Q4-16W versus Other Comparators: Ocular AEs at 12m excluding high risk of bias studies (Base case, RE model)

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Abbreviations: AFL, aflibercept; FAR, faricimab; IVT, intravitreal; PRN, treatment as needed (pro re nata); Q4/8/16W, every 4/8/16 weeks; RAN, ranibizumab; T&E, treat and extend

Although excluding studies with a high-risk of bias substantially reduced the size of the network, it was possible to maintain connected networks for all outcomes analysed in the sensitivity analyses. That said, with fewer studies in each network compared with the base-case credible intervals are wider, suggesting a greater degree of uncertainty in the results. This is an expected finding when reducing the

size of the network. Overall, the results of the sensitivity analysis remained consistent with the base-case NMA results. This suggests the base-case network was unlikely influenced by within-study bias, therefore highlighting the robustness of original analysis and results. That said, given the small sample size in this sensitivity analysis, the results must be interpreted with caution.

A16. PRIORITY QUESTION. The CS does not mention potential effect modifiers or prognostic factors when interpreting the clinical efficacy evidence.

(a) Please explain, with a clear rationale, what the potential prognostic factors are for DMO.

Prognostic factors for DMO include baseline visual acuity and intraretinal fluid (IRF) morphology (78)). An analysis of OCT images using computational measures from treatment initiation indicated that intraretinal cystoid fluid is the most relevant predictive factor in the determination of BCVA gains (79).

The risk of vision loss is highest if the oedema is at the centre of the macula (80).

The risk of developing DMO increases with high alcohol use, cataracts, HbA1c ≥7%, systolic blood pressure ≥160 mmHg, total cholesterol ≥5 mmol/L, LDL ≥3 mmol/L, and microalbuminuria, as reported by a study in the UK in patients with Type 2 diabetes in a primary care setting (81).

Genetic factors are associated with the development of DMO. Patients of African-American and Latino descent are more likely to develop DMO compared with Caucasians, according to one US study (82). This study also reported that individuals with diabetic neuropathy or diabetic nephropathy had a higher probability of developing DMO compared with those without these conditions. Individuals with uncomplicated hypertension or end-organ damage caused by hypertension had a 25% or 45% increased chance of developing DMO, respectively. Each unit increase in the baseline value of the HbA1c lab test was also a significant predictor and was associated with a 16% increase in the probability of developing DME (82).

(b) Please explain, with a clear rationale, what the potential effect modifiers are for each of the outcomes assessed in this appraisal.

Potential effect modifiers and covariates for including in exploratory meta-regression analyses were identified from previous NMAs, the key variables being reported as baseline BCVA and baseline CRT. However, it should be noted that one published study found a strong correlation between baseline CRT and baseline BCVA (83), so including both of these variables should be done with caution.

(c) Please tabulate the baseline characteristics for all studies included in the NMAs in such a way that the characteristics can be readily compared both between arms within studies and between studies. Please include all potential prognostic factors and effect modifiers identified in (a) and (b) above.

Baseline characteristics for each study identified in the SLR feasibility assessment can be found in the "Baseline characteristics" sheet! of the data extraction table spreadsheet. This sheet can be filtered by study in column C. Prognostic factors and potential effect modifiers are reported on this sheet.

(d) Please comment on any heterogeneity in the studies' baseline characteristics and whether this would warrant further investigation, e.g., through sensitivity analyses.

Meta-regressions were conducted to investigate whether heterogeneity in patient characteristics would affect NMA results.

The following patient characteristics were investigated using standard network meta-regression methods to determine if the treatment effect varies according to levels of the covariate: BCVA at baseline, CST (or if not reported, CRT/CFT/CMT) at baseline. As these covariates may be highly correlated, they were investigated in separate models.

Analyses were performed where (1) the interaction between the characteristic and the treatment effect will be assumed to be the same across all treatments relative to aflibercept (fixed interactions), and (2) the interaction terms for each treatment are drawn from a distribution with an overall mean and between-treatment variability (exchangeable interactions).

Study-level patient characteristics were reduced to dichotomous variables to avoid issues with ecological fallacy. The median value of the covariate was calculated across all trials included in the analysis and used to define trials less than or greater than or equal to the median. To keep the same studies in the meta-regression as in the primary analysis, and thus enable easy comparison of model fits, any studies with missing covariates were assumed to be equal to the median. For the meta-regressions using exchangeable interaction effects, a U(0,10) prior was used for the between treatment standard deviation.

The results found that there was no evidence that the treatment effect differed by patient characteristics or that model fit was improved in the patient characteristics meta-regressions. Therefore, analyses of other outcomes are conducted using a standard NMA framework where random effects models are preferred.

The results of the meta-regressions can be seen in response to question A25 (Table 17 and Table 18).

A17. PRIORITY QUESTION. There are several uncertainties around the Central Retinal Thickness (CRT) data, as also noted in the previous appraisals of aflibercept and ranibizumab. The ERG are concerned that there may be potential for heterogeneity or bias in the NMAs due to variation in CRT between and/or within studies which would render the NMA results uncertain. To address these uncertainties please:

(a) Clarify the proportions of participants in each arm of each study included in the NMAs, including the YOSEMITE and RHINE studies, who had baseline CRT <400 µm and baseline CRT ≥400 µm.

Table 11: Number of study participants with CRT ≥\< 400 µm

	YOSEMITE			RHINE			Pooled YOSEMITE and RHINE		
Population	**Fari 6.0 mg Q8W**	**Fari 6.0 mg PTI**	**Afli 2.0 mg Q8W**	**Fari 6.0 mg Q8W**	**Fari 6.0 mg PTI**	**Afli 2.0 mg Q8W**	**Fari 6.0 mg Q8W**	**Fari 6.0 mg PTI**	**Afli 2.0 mg Q8W**
Total (n)	315	313	312	317	319	315	632	632	627

CST≥ 400 µm (n)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CST < 400 µm (n)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Afli, aflibercept; CST, central subfield thickness; Fari, faricimab; qXw, treatment every X weeks

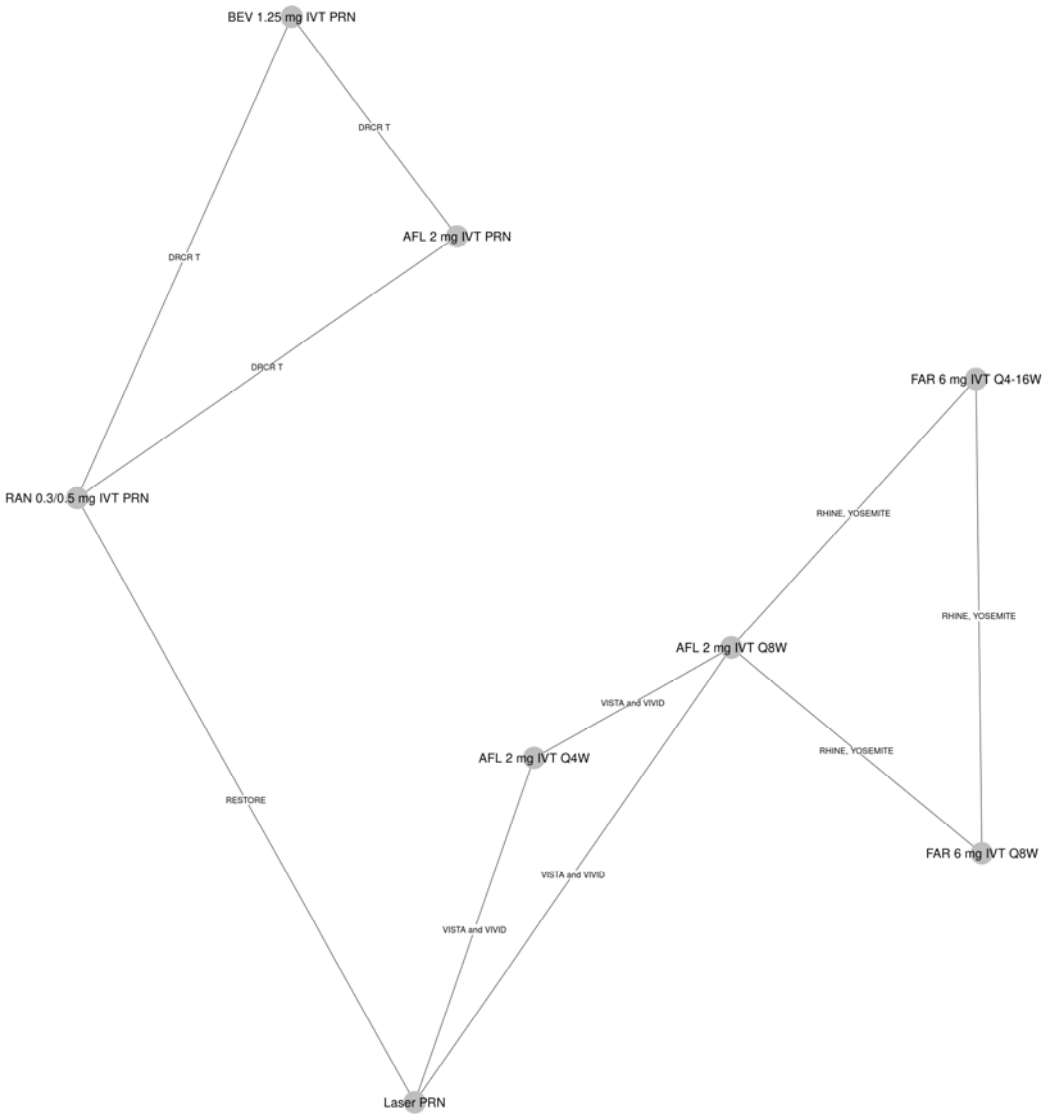
(b) Where possible, present subgroup analyses for baseline CRT <400 µm and baseline CRT ≥400 µm to explore the impact of CRT subgroup on each efficacy outcome. NB, we note that, as stated in CS section B.4.2.3 this would involve breaking randomisation; however, we are requesting this as an illustrative analysis to clarify the external validity of the NMAs (i.e., how well the randomised trial populations match the intended indication population) (for an example see Table 21 in the ERG report for the ranibizumab appraisal TA274).

Following a screening of publications, 6 studies were identified which report subgroup data by baseline CRT above and below 400 µm:

- DRCR Network Protocol B (21)
- DRCR Network Protocol I (84)
- DRCR Network Protocol T (65)
- RESTORE (7) and RESTORE open label extension (85)
- BOLT (59)
- VIVID and VISTA (58)

As the primary outcome of the faricimab studies, and given its incorporation in the cost-comparison model structure, change in BCVA was deemed the most relevant efficacy outcome in which to conduct the subgroup analysis. Of the studies identified, Protocol T (65), RESTORE (7), and VIVID and VISTA (58), reported change in BCVA from baseline to 12 months in the subgroup of interest. A network of these studies was formed with the addition of YOSEMITE and RHINE, to conduct the subgroup analysis (see Figure 13). The data extracted from these studies can be seen in Table 12.

Figure 13: Network Diagram: BCVA score mean change from baseline at 12m (Base case, RE model)



Abbreviations: AFL, aflibercept; BEV, bevacizumab; FAR, faricimab; IVT, intravitreal; PRN, treatment as needed (pro re nata); Q4/8/16W, every 4/8/16 weeks; RAN, ranibizumab; T&E, treat and extend

Table 12: Original extracted data: BCVA score mean change from baseline at 12m subgroup CRT ≥400 µm (Base case, RE model)

Study	Treatment	Patients	Mean	SE
DRCR T	AFL 2 mg IVT PRN	93	16.2	1.213
DRCR T	BEV 1.25 mg IVT PRN	91	9.6	1.226

DRCR T	RAN 0.3/0.5 mg IVT PRN	93	12.4	0.933
RESTORE	Laser PRN	53	-0.9	1.324
RESTORE	RAN 0.3/0.5 mg IVT PRN	62	7.3	1.224
RHINE	AFL 2 mg IVT Q8W	[redacted]	[redacted]	[redacted]
RHINE	FAR 6 mg IVT Q4-16W	[redacted]	[redacted]	[redacted]
RHINE	FAR 6 mg IVT Q8W	[redacted]	[redacted]	[redacted]
VISTA and VIVID	AFL 2 mg IVT Q4W	200	11.9	0.7
VISTA and VIVID	AFL 2 mg IVT Q8W	208	10.7	0.7
VISTA and VIVID	Laser PRN	208	-0.2	0.7
YOSEMITE	AFL 2 mg IVT Q8W	[redacted]	[redacted]	[redacted]
YOSEMITE	FAR 6 mg IVT Q4-16W	[redacted]	[redacted]	[redacted]
YOSEMITE	FAR 6 mg IVT Q8W	[redacted]	[redacted]	[redacted]

Abbreviations: AFL, aflibercept; BEV, bevacizumab; FAR, faricimab; IVT, intravitreal; PRN, treatment as needed (pro re nata); Q4/8/16W, every 4/8/16 weeks; RAN, ranibizumab; T&E, treat and extend

The results of a network meta-analysis for change in BCVA score from baseline to 12 months in the subgroup of people with CST/CRT ≥400 µm are presented in the forest plot below (see Figure 14).

[redacted] *Given the scarcity of data available to conduct this analysis, and that several of the trials included in the network had not pre-specified CRT subgroups meaning the breaking of randomisation was required, the results of the subgroup analysis must be interpreted with caution.*

Figure 14: Forest Plot of Differences and 95% credible intervals (CrI) of Faricimab 6 mg IVT Q4-16W versus Other Comparators: BCVA score mean change from baseline at 12m subgroup CRT ≥400 µm (Base case, RE model)

[redacted]- Figure redacted

Abbreviations: AFL, aflibercept; BEV, bevacizumab; FAR, faricimab; IVT, intravitreal; PRN, treatment as needed (pro re nata); Q4/8/16W, every 4/8/16 weeks; RAN, ranibizumab; T&E, treat and extend

No subgroup analyses were conducted for the subgroup of CRT < 400 µm. This population falls outside of the recommendations for the comparator technologies, and therefore is not relevant to the population being appraisal.

(c) If not already included in your response to Question 16, please tabulate the baseline CRT values for all arms of all studies included in the NMAs. Please assess whether the variation in CRT values between arms within studies and between studies would be a source of sufficient heterogeneity in the NMAs to warrant sensitivity analyses. If so, please conduct these sensitivity analyses.

As described in the responses to question A16d and A17b, meta-regression and subgroup NMA results demonstrate that there was no evidence that the treatment effect differed by patient characteristics.

The results of the meta-regressions can be seen in response to question A25 (Table 17 and Table 18).

A18. PRIORITY QUESTION. For the BCVA outcome please clarify whether the same method for scoring BCVA was used in all studies included in the NMAs. If not, how this was adjusted or corrected for (given potential comparability issues for different BCVA scales [1])?

Details of how BCVA was measured in each study included in the NMA can be seen in the "Study design" sheet of the data extraction table.
To ensure comparability, only studies which measured change in BCVA by EDTRS letters were included in the change in BCVA network. Four studies were excluded from the network because they measured change in BCVA using logMAR or Snellen scales.

A19. PRIORITY QUESTION. Please clarify which eye(s) were included for each study in the NMAs. Was there a single eye per study in all cases? If not, how were any within-subject correlations between eyes accounted for?

Details of the number of eyes assessed in each study and whether efficacy outcomes were reported for the fellow eye can be seen in columns AK and AL in the in the "Study design" sheet of the data extraction table. The main outcomes of interest for the NMA (BCVA, CST, Injections, AEs) are measured separately by eye. Therefore, the number of eyes assessed in each study was not believed to be an influential factor of results, so was not accounted for in the network meta-analysis.

A20. PRIORITY QUESTION. CS section B.3.9.1 states that the search update identified four studies but "None of these studies were deemed large enough, if incorporated in the ITC, to influence results in a meaningful way".

(a) Please identify which studies these were and explain the criteria that were used to exclude them.

After screening and full text review, a total of 4 publications (1 full publication and 3 conference abstracts) and 3 trial registry records, have been included in the SLR from October 2020 to August 2021, reporting data for 5 studies. Of these 5 studies, 3 new studies have been identified in the updated literature searches (ALBA (86), KITE and KESTREL (87)). None of these new studies were deemed relevant to the NMA given their small sample size. Additionally, ALBA (86) included a comparison of laser and brolucizumab, neither of which are relevant comparators in this cost-comparison. The remaining 2 studies, YOSEMITE and RHINE (1), were already included in the original SLR, as data were available via in-house clinical study reports. No new data are reported for these studies in the new publications.

(b) Please conduct sensitivity analyses to explore the impact of excluding these four studies.

Please see response to A20a. None of the newly identified studies were deemed relevant for inclusion in the NMA.

A21. The NMAs pool the 0.3mg and 0.5mg doses of ranibizumab. The CS (section B.3.9.2) argues that these doses have similar clinical efficacy, citing reference 95 (Heier et al). The Heier et al reference does not directly compare the two doses but

cites a further reference to the RIDE and RISE trials. Neither of these trials are included in any of the NMAs so their generalisability is uncertain. Please provide more comprehensive evidence that the two ranibizumab doses have comparable efficacy or incorporate these doses separately in the NMAs.

Heier et al (2016) (88) comments on the results from RIDE and RISE (76) which compare change in BCVA from baseline to 2 years for patients on either dose of ranibizumab. The trial results show that the mean visual acuity change from baseline to year 2 differed between the 2 doses by 0.6 and 1.1 letters in the 2 studies (Table 13). These results demonstrate that any differences in visual acuity outcomes from different ranibizumab doses are not clinically significant. These findings are supportive of the decision to pool 0.3 mg and 0.5 mg doses of ranibizumab in the NMA. RIDE and RISE (76) were not included in the 12-month network, as the studies did not repor0t any relevant data for the outcomes of interest at 12 months.

Table 13: Comparison of change in BCVA in different ranibizumab doses

Study	Time point	Ranibizumab dose and regimen	BCVA change, mean (SD)
RIDE	24 months	0.3 mg Q4W	10.9 (10.4)
		0.5 mg Q4W	12 (14.9)
RIDE	24 months	0.3 mg Q4W	12.5 (14.1)
		0.5 mg Q4W	11.9 (12.1)

Abbreviations: BCVA, best-corrected visual acuity PRN, treatment as needed (pro re nata); Q4W, every 4 weeks;

A22. PRIORITY QUESTION. The networks include closed loops but there is no discussion of the consistency assumption of NMA. Please perform the analysis using node splitting and provide the results for each of the outcomes.

Node splitting analysis was not undertaken when assessing the consistency of the NMA model. However, the inconsistency of direct and indirect evidence in the Bayesian framework was assessed using inconsistency models, as described in NICE DSU TSD 4 (89). These models are the same as the standard Bayesian NMA models, but they fit a separate treatment effect for every pairwise comparison without making the consistency assumption. The fit of the standard (consistency)

and inconsistency models was compared using DIC and residual deviance. If the DIC is lower or similar for the standard model, this indicates a better fit to the data and no evidence of substantial inconsistency. The inconsistency assessment was performed for the change from baseline in BCVA score outcome in the over-all population initially.

The results in

*Table **14** and Table 15 demonstrate that there was no evidence of inconsistency from the comparison of the consistency and in-consistency model fits for BCVA score change models. Further inconsistency assessments were not undertaken for other outcomes and populations if there was evidence of inconsistency for this first outcome.*

Table 14: Comparison of consistency and inconsistency models, BCVA score mean change from baseline, random effects

	Consistency model	Inconsistency model
DIC	203.427555259614	204.174184127642
Mean residual deviance	53.309325821972	52.4211872469137
Effective parameters	39.8661014178604	41.2976836313505

Abbreviations: DIC, deviance information criterion

Table 15: Comparison of consistency and inconsistency models, BCVA score mean change from baseline, fixed effects

	Consistency model	Inconsistency model
DIC	204.952726423838	203.961826301555
Mean residual deviance	61.8615460735679	56.7671880460079
Effective parameters	32.9106567158706	37.0182600020005

Abbreviations: DIC, deviance information criterion

A23. PRIORITY QUESTION. Please provide a tabulation of the input data used for the NMAs so that these can be traced to the data in the study publications and checked. Please provide any calculations required.

Tabulations of the data included in each NMA can be seen in "NMA data tables" file. Methods for calculating certain data values are described below.

Where multiple methods are presented for deriving missing observations, the first one listed with available data for the study was used.

Continuous variables, Change from baseline (BCVA, CST)

The key values for analysis are mean change from baseline and standard error (SE) of change from baseline, which was calculated as standard deviation (SD) of change from baseline / √ number of patients(n).

Missing mean change from baseline was derived using

1. *Baseline mean – Follow-up mean*
2. *Median change from baseline*

Missing SD for change from baseline was derived using

1. *SE x √ n*
    a. *Missing SE for change from baseline was derived using (Upper (1- α)% CI limit – Lower (1-α)% CI limit) / 2z $_{α/2}$*

2. *SDs at baseline and follow-up: √ (SD baseline 2 + SD follow-up 2 - SD baseline SD follow-up)*

3. *Pooled SD for change from baseline using study arms with values (reported or derived via methods 1 or 2):*

If a study only reported mean % change from baseline but a baseline value was available (RETAIN study for CST), the mean absolute change from baseline was set to be baseline value x % change from baseline/100. The SD was derived using SD method (3).

Other continuous variables (injection frequency)

The key values are mean and standard error, calculated as SD/√ n. Missing means were derived using median. Missing SDs were derived using pooled SD from studies reporting values.

Binary and ordered categorical data (discontinuations, AEs, letter categories)

If the number of events was missing, it was calculated as % events x n, rounded to the nearest integer.

Pooling RAN 0.3 mg and 0.5 mg arms

If a study had multiple arms for RAN 0.3 mg and 0.5 mg, these were pooled into a single RAN 0.3/0.5 mg arm. Means were pooled across arms using and SDs were pooled using - number of events/patients was summed across arms.

Meta-regressions (on baseline BCVA and baseline CST)

The meta-regression covariate was coded to 1 if the study level mean baseline value was greater than or equal to the median of the study level mean baseline values across studies, and 0 if it were less. The small number of studies with missing covariate values were set to be equal to the median for analysis.

The study level mean baseline value was calculated from the individual arm mean baseline values using the same pooling techniques as described above for RAN 0.3 mg and 0.5 mg arms.

A24. PRIORITY QUESTION. Please provide the model code and input data used in the NMAs.

The model code and input data used for the NMAs can be viewed in the "Data and model codes" folder.

A25. PRIORITY QUESTION. CS section B.3.9.3 states that "To assess whether treatment effects were influenced by patient characteristics, meta-regressions were conducted to determine the best fit for each NMA model" but no further details are given. Please provide the methods and results of the meta-regression analyses.

Please see the response to question A16d for a description of the meta-regression methods.

The study level data used in the meta-regression is presented in Table 16.

Table 16: Study level data for meta-regression on patient characteristics, BCVA score mean change from baseline

Study	Treatment	Patients	Mean	SE	Baseline BCVA score	Baseline retinal thickness
BEVORDEX	BEV 1.25 mg IVT PRN	42	8.9	1.36	0	1
BEVORDEX	DEX 0.7 mg PRN	46	5.6	2.4	0	1
BOLT	BEV 1.25 mg IVT PRN	42	5.599	1.55	0	1
BOLT	Laser PRN	38	-4.6	2.33	0	1
Chatzirallis 2020	AFL 2 mg IVT PRN	58	5.8	1.31	0	0
Chatzirallis 2020	RAN 0.3/0.5 mg IVT PRN	54	6.2	1.36	0	0
DA VINCI	AFL 2 mg IVT PRN	45	12	1.65	0	0
DA VINCI	AFL 2 mg IVT Q4W	44	13.1	1.59	0	0
DA VINCI	AFL 2 mg IVT Q8W	42	9.7	1.38	0	0
DA VINCI	Laser PRN	44	-1.3	3.12	0	0
DRCR T	AFL 2 mg IVT PRN	208	13.3	0.77	1	0
DRCR T	BEV 1.25 mg IVT PRN	206	9.7	0.7	1	0
DRCR T	RAN 0.3/0.5 mg IVT PRN	206	11.2	0.65	1	0
Eichenbaum 2018	RAN 0.3/0.5 mg IVT Q4W	10	8.2	1.99	0	1

Eichenbaum 2018	RAN 0.3/0.5 mg IVT T&E	10	7	2.72	0	1
LUCIDATE	Laser PRN	11	-0.9	2.77	1	1
LUCIDATE	RAN 0.3/0.5 mg IVT PRN	22	6	1.58	1	1
Ozsaygili 2020	AFL 2 mg IVT PRN	33	9.3	1.74		
Ozsaygili 2020	DEX 0.7 mg PRN	29	6.4	1.86		
REACT	RAN 0.3/0.5 mg IVT Q4W	15	2.1	2.14	1	0
REACT	RAN 0.3/0.5 mg IVT T&E	12	7.4	3	1	0
REFINE	Laser PRN	77	2.5	1	0	1
REFINE	RAN 0.3/0.5 mg IVT PRN	307	7.8	0.5	0	1
RESOLVE	RAN 0.3/0.5 mg IVT PRN	204	10.3	0.64	1	0
RESOLVE	Sham / PBO	49	-1.4	2.03	1	0
RESPOND	Laser PRN	72	0.3	1.47	1	0
RESPOND	RAN 0.3/0.5 mg IVT PRN	75	8.9	0.9	1	0
RESTORE	Laser PRN	110	0.9	1.09	1	0
RESTORE	RAN 0.3/0.5 mg IVT PRN	115	6.8	0.77	1	0
RETAIN	RAN 0.3/0.5 mg IVT PRN	117	7.44	0.78	1	0
RETAIN	RAN 0.3/0.5 mg IVT T&E	125	6.8	0.78	1	0
REVEAL	Laser PRN	128	1.8	0.73	0	0
REVEAL	RAN 0.3/0.5 mg IVT PRN	133	6.6	0.67	0	0
RHINE	AFL 2 mg IVT Q8W	315	10.3	0.52		
RHINE	FAR 6 mg IVT Q4-16W	319	10.8	0.51		
RHINE	FAR 6 mg IVT Q8W	317	11.8	0.52		
ROTATE	RAN 0.3/0.5 mg IVT PRN	20	6.35	2.17	1	0
ROTATE	RAN 0.3/0.5 mg IVT Q4W	10	6.7	3.67	1	0
TREX-DME	RAN 0.3/0.5 mg IVT Q4W	30	8.6	1.82	1	1
TREX-DME	RAN 0.3/0.5 mg IVT T&E	60	9.6	1.29	1	1
VISTA	AFL 2 mg IVT Q4W	154	12.5	0.77	0	1

VISTA	AFL 2 mg IVT Q8W	151	10.7	0.67	0	1
VISTA	Laser PRN	154	0.2	1.01	0	1
VIVID	AFL 2 mg IVT Q4W	136	10.5	0.81	0	1
VIVID	AFL 2 mg IVT Q8W	135	10.7	0.8	0	1
VIVID	Laser PRN	132	1.2	0.92	0	1
VIVID-East	AFL 2 mg IVT Q4W	127	13.6	0.9	0	1
VIVID-East	AFL 2 mg IVT Q8W	127	13.1	1	0	1
VIVID-East	Laser PRN	124	-0.5	1.4	0	1
YOSEMITE	AFL 2 mg IVT Q8W	276	10.9	0.56	1	1
YOSEMITE	FAR 6 mg IVT Q4-16W	276	11.6	0.56	1	1
YOSEMITE	FAR 6 mg IVT Q8W	271	10.7	0.56	1	1

Abbreviations: AFL, aflibercept; BEV, bevacizumab; DEX, dexamethasone; FAR, faricimab; IVT, intravitreal; PBO, placebo; PRN, treatment as needed (pro re nata); Q4/8/16W, every 4/8/16 weeks; RAN, ranibizumab; T&E, treat and extend. Note: 1: >= median, 0: < median. Missing data were set to be equal to the median for analysis. Medians: Baseline BCVA score=60.3 Baseline retinal thickness=457.7

The results of the meta-regression analyses are presented in Table 17 and Table 18. The results found that there was no evidence that the treatment effect differed by patient characteristics or that model fit was improved in the patient characteristics meta-regressions.

Table 17: Comparison of meta-regression models using patient characteristics, BCVA score mean change from baseline, random effects

	DIC	Mean residual deviance	Effective parameters	Covariate estimate (95% CrI)	Between trt SD (95% CrI)
No meta-regression	203.43	53.31	39.87		
Baseline BCVA score, fixed interaction	204.76	53.31	41.08	0.15 (-4.53, 4.66)	
Baseline BCVA score, exchangeable interaction	205.69	53.19	41.98	-0.55 (-6.19, 4.89)	1.87 (0.09, 7.48)
Baseline retinal thickness, fixed interaction	204.51	53.7	40.59	3.54 (-4.96, 11.86)	
Baseline retinal thickness, exchangeable interaction	205.17	53.18	41.81	2.6 (-6.34, 11.48)	1.43 (0.07, 5.98)

Abbreviations: BCVA, best-corrected visual acuity; CrI, credible interval; DIC, deviance information criterion. Note: Covariate parameter estimates <0 indicate a poorer outcome in studies with higher covariate levels (>= median)

Table 18: Individual treatment-by-covariate estimates from exchangeable interaction meta-regression models using patient characteristics, BCVA score mean change from baseline, random effects

Treatment	Baseline BCVA score	Baseline retinal thickness
AFL 2 mg IVT PRN	0 (0, 0)	0 (0, 0)
AFL 2 mg IVT Q4W	-0.49 (-9.47, 7.2)	2.39 (-7.09, 11.35)
AFL 2 mg IVT Q8W	-0.45 (-9.09, 7.61)	3.38 (-5.93, 12.37)
BEV 1.25 mg IVT PRN	-1.85 (-8.7, 4)	3.51 (-4.93, 12.02)
DEX 0.7 mg PRN	-0.21 (-6.82, 5.99)	2.63 (-7.91, 12.41)
FAR 6 mg IVT Q4-16W	-0.55 (-9.61, 7.09)	2.65 (-8.13, 12.58)
FAR 6 mg IVT Q8W	-0.46 (-9.44, 7.13)	2.63 (-7.84, 12.51)
Laser PRN	-0.41 (-5.22, 4.47)	1.95 (-7.26, 11.1)
RAN 0.3/0.5 mg IVT PRN	0.36 (-4.21, 4.92)	1.8 (-7.73, 10.99)
RAN 0.3/0.5 mg IVT Q4W	-0.86 (-9.47, 5.79)	2.92 (-6.77, 12.66)
RAN 0.3/0.5 mg IVT T&E	-0.12 (-7.64, 7.51)	2.29 (-8.06, 11.78)
Sham / PBO	-0.46 (-9.32, 7.61)	2.7 (-7.91, 12.64)

Abbreviations: AFL, aflibercept; BEV, bevacizumab; DEX, dexamethasone; FAR, faricimab; IVT, intravitreal; PBO, placebo; PRN, treatment as needed (pro re nata); Q4/8/16W, every 4/8/16 weeks; RAN, ranibizumab; T&E, treat and extend

A26. PRIORITY QUESTION. CS summary document section A.8 states that NMA model fit was assessed. Please explain how this was done and present the results.

DIC was used to compare the relative fit of competing models. Models with lower DIC are preferred. Differences in DIC of less than 5 points are not considered meaningful.

To judge the absolute fit, the total residual deviance was calculated and compared against the total number of independent data points. For random effects models, the estimate and 95% CI for the between-study standard deviation is also presented (see response to question A27). See Table 19 for model fit statistics.

Table 19: Model fit statistics for NMA models (random and fixed effects)

		Random effects models		Fixed effect models	
NMA model	**Data points**	**DIC**	**Total residual deviance**	**DIC**	**Total residual deviance**
BCVA change	52	203.428	53.309	204.953	61.862
Injection frequency	26	9.240	28.297	12.545	35.864
CRT/CST	54	463.696	53.449	461.722	54.609
Letter categories	132	737.593	195.888	738.764	212.044
Discontinuation	36	212.100	36.350	211.205	40.740
Adverse events	26	179.069	24.049	177.319	24.693

Abbreviations: BCVA, best-corrected visual acuity; CrI, credible interval; CRT, central retinal thickness; CST, central subfield thickness; NMA, network meta-analysis

Model fit was good in most cases. The following exceptions are noted:

For the models for BCVA letter categories, the posterior for tau is truncated at the upper limit of the uniform prior (5), suggesting it is not well estimated. Increasing the upper limit of the prior even as high as 500 did not resolve this, suggesting that there may be insufficient data to estimate the between study heterogeneity well in this model. Therefore, this result should be interpreted with caution.

A27. PRIORITY QUESTION. For each of the NMA models please provide the standard deviation for random effects.

Assuming that the standard deviation for random effects is referring to between study standard deviation for the random effect models, tau posterior median and 95% credible intervals are presented in Table 20.

Table 20: Between study standard deviation (tau posterior deviation)

NMA model	Tau posterior median (95% CrI):
BCVA change	1.043 (0.089, 2.366)
Injection frequency	0.292 (0.046, 0.922)
CRT/CST	4.838 (0.260, 17.684)
Letter categories	4.529 (2.970, 4.983)
Discontinuation	0.247 (0.015, 0.688)
Adverse events	0.111 (0.007, 0.405)

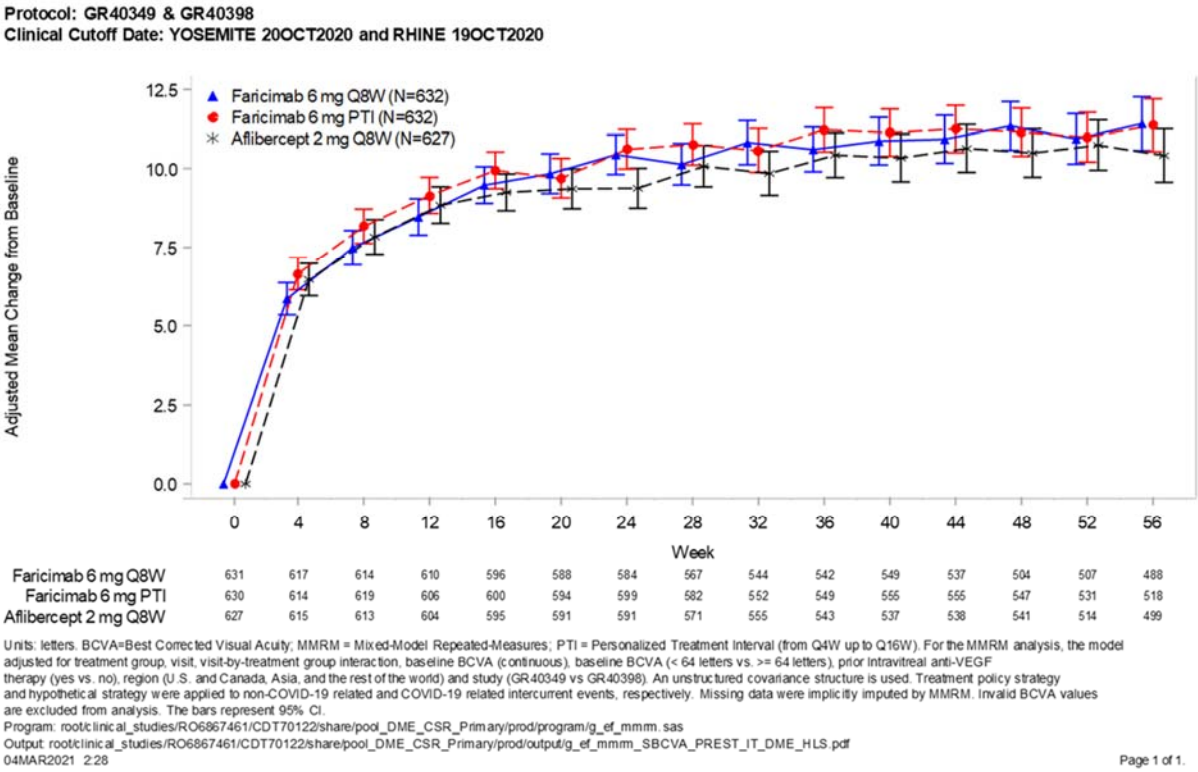
Abbreviations: BCVA, best-corrected visual acuity; CrI, credible interval; CRT, central retinal thickness; CST, central subfield thickness; NMA, network meta-analysis

A28. Please provide evidence for assuming equivalence across timepoints (CS section B.3.9.5). A multivariate longitudinal analysis (e.g., see Multivariate meta-analysis TSD20) could presumably have included all the data, avoiding the need for assuming time equivalence. Please explain why such an analysis was not conducted.

Visual acuity gains usually occur in the first months following anti-VEGF therapy (90). Treatment beyond that point usually preserves initial gains, without further improving visual acuity (90). The change in BCVA from baseline to week 56 observed in YOSEMITE and RHINE (1) demonstrates this, while also showing limited/no difference in change in BCVA between weeks 48 and 56 in all study arms

(see Figure 15). These findings suggest that the assumption of time equivalence would be very unlikely to affect results, because of this multivariate longitudinal analysis was not conducted.

Figure 15: Pooled Phase III DME Studies: Plot of Change from Baseline in BCVA in the Study Eye through Week 56: MMRM Method (Primary Estimand) (ITT Population)



A29. For change in BCVA and injection frequency please clarify which studies and outcomes in the NMAs have 24-month data available. Where studies have both 12-month, and 24-month data please comment on how well the 12-month outcomes predict those at 24 months.

In the absence of 24-month data for faricimab, a network of 24 month outcomes for BCVA change and injection frequency could not be created. 12-month and 24-month data for change in BCVA and injection frequency are available for the studies included in Table 21 and Table 22.

BCVA change

As highlighted in A28, DMO treatment with IVT agents is characterised by visual acuity gains occurring during the first couple of months after treatment initiation. Following that period, visual acuity is typically maintained or slightly decreasing over

time. This can also be seen in Table 21, highlighting that BCVA changes after 12 months are mostly preserved after 24 months.

Injection frequency

DMO treatment with IVT agents is characterized by an intensive loading phase (4-6 months) typically followed by a maintenance phase requiring less frequent treatment. This can be seen in Table 22, highlighting a lower frequency of injections during the second year of treatment.

Table 21: Study reported outcomes for change from baseline in BCVA at 12 and 24 months

12 months					24 months				
Study	**Treatment**	**Patients**	**Mean**	**SE**	**Study**	**Treatment**	**Patients**	**Mean**	**SE**
BEVORDEX	BEV 1.25 mg IVT PRN	42	8.9	1.358	BEVORDEX	BEV 1.25 mg IVT PRN	42	9.6	1.378
BEVORDEX	DEX 0.7 mg PRN	46	5.6	2.403	BEVORDEX	DEX 0.7 mg PRN	46	6.9	2.143
BOLT	BEV 1.25 mg IVT PRN	42	5.6	1.554	BOLT	BEV 1.25 mg IVT PRN	37	8.6	1.496
BOLT	Laser PRN	38	-4.6	2.333	BOLT	Laser PRN	28	-0.5	2.003
DRCR T	AFL 2 mg IVT PRN	208	13.3	0.77	DRCR T	AFL 2 mg IVT PRN	201	12.8	0.875
DRCR T	BEV 1.25 mg IVT PRN	206	9.7	0.704	DRCR T	BEV 1.25 mg IVT PRN	185	10	0.868
DRCR T	RAN 0.3/0.5 mg IVT PRN	206	11.2	0.655	DRCR T	RAN 0.3/0.5 mg IVT PRN	191	12.3	0.76
Eichenbaum 2018	RAN 0.3/0.5 mg IVT Q4W	10	8.2	1.992	Eichenbaum 2018	RAN 0.3/0.5 mg IVT Q4W	10	8.3	2.277
Eichenbaum 2018	RAN 0.3/0.5 mg IVT T&E	10	7	2.72	Eichenbaum 2018	RAN 0.3/0.5 mg IVT T&E	10	8.5	2.814
RETAIN	RAN 0.3/0.5 mg IVT PRN	117	7.44	0.782	RETAIN	RAN 0.3/0.5 mg IVT PRN	117	8.06	0.782
RETAIN	RAN 0.3/0.5 mg IVT T&E	125	6.8	0.78	RETAIN	RAN 0.3/0.5 mg IVT T&E	125	6.49	0.971
TREX-DME	RAN 0.3/0.5 mg IVT Q4W	30	8.6	1.825	TREX-DME	RAN 0.3/0.5 mg IVT Q4W	30	7.5	2.213
TREX-DME	RAN 0.3/0.5 mg IVT T&E	60	9.6	1.29	TREX-DME	RAN 0.3/0.5 mg IVT T&E	60	9.6	1.565
VISTA	AFL 2 mg IVT Q4W	154	12.5	0.766	VISTA	AFL 2 mg IVT Q4W	154	11.5	1.112
VISTA	AFL 2 mg IVT Q8W	151	10.7	0.667	VISTA	AFL 2 mg IVT Q8W	151	11.1	0.871
VISTA	Laser PRN	154	0.2	1.007	VISTA	Laser PRN	154	0.9	1.12

VIVID	AFL 2 mg IVT Q4W	136	10.5	0.815	VIVID	AFL 2 mg IVT Q4W	136	11.4	0.96
VIVID	AFL 2 mg IVT Q8W	135	10.7	0.8	VIVID	AFL 2 mg IVT Q8W	135	9.4	0.904
VIVID	Laser PRN	132	1.2	0.923	VIVID	Laser PRN	132	0.7	1.027

Abbreviations: AFL, aflibercept; BEV, bevacizumab; DEX, dexamethasone; FAR, faricimab; IVT, intravitreal; PBO, placebo; PRN, treatment as needed (pro re nata); Q4/8/16W, every 4/8/16 weeks; RAN, ranibizumab; T&E, treat and extend

Table 22: Study reported injection frequencies at 12 and 24 months

12 months					24 months				
Study	**Treatment**	**Patients**	**Mean**	**SE**	**Study**	**Treatment**	**Patients**	**Mean**	**SE**
DRCR T	AFL 2 mg IVT PRN	208	9.2	0.139	DRCR T	AFL 2 mg IVT PRN	201	14.2	0.324
DRCR T	BEV 1.25 mg IVT PRN	206	9.7	0.16	DRCR T	BEV 1.25 mg IVT PRN	185	15.3	0.39
DRCR T	RAN 0.3/0.5 mg IVT PRN	206	9.4	0.146	DRCR T	RAN 0.3/0.5 mg IVT PRN	192	14.8	0.361
Eichenbaum 2018	RAN 0.3/0.5 mg IVT Q4W	10	10.9	0.601	Eichenbaum 2018	RAN 0.3/0.5 mg IVT Q4W	10	19.4	1.866
Eichenbaum 2018	RAN 0.3/0.5 mg IVT T&E	10	10.7	0.506	Eichenbaum 2018	RAN 0.3/0.5 mg IVT T&E	10	18.8	0.917
RETAIN	RAN 0.3/0.5 mg IVT PRN	118	7	0.179	RETAIN	RAN 0.3/0.5 mg IVT PRN	118	10.7	0.516
RETAIN	RAN 0.3/0.5 mg IVT T&E	126	7	0.174	RETAIN	RAN 0.3/0.5 mg IVT T&E	126	12.8	0.33
TREX-DME	RAN 0.3/0.5 mg IVT Q4W	30	13.1	0.356	TREX-DME	RAN 0.3/0.5 mg IVT Q4W	30	24.7	0.871
TREX-DME	RAN 0.3/0.5 mg IVT T&E	60	10.7	0.251	TREX-DME	RAN 0.3/0.5 mg IVT T&E	60	18.9	0.616
VISTA	AFL 2 mg IVT Q4W	154	11.8	0.21	VISTA	AFL 2 mg IVT Q4W	154	21.3	0.467
VISTA	AFL 2 mg IVT Q8W	151	8.4	0.106	VISTA	AFL 2 mg IVT Q8W	151	13.5	0.236
VIVID	AFL 2 mg IVT Q4W	136	12.2	0.223	VIVID	AFL 2 mg IVT Q4W	136	22.6	0.497
VIVID	AFL 2 mg IVT Q8W	135	8.7	0.103	VIVID	AFL 2 mg IVT Q8W	135	13.6	0.25

Abbreviations: AFL, aflibercept; BEV, bevacizumab; DEX, dexamethasone; FAR, faricimab; IVT, intravitreal; PBO, placebo; PRN, treatment as needed (pro re nata); Q4/8/16W, every 4/8/16 weeks; RAN, ranibizumab; T&E, treat and extend

Section B: Clarification on cost-effectiveness data

B1. Patients in the economic model transition between visual acuity health states ranging from >85 to ≤ 25. No explanation of this numeric scale is given. Is this the number of readable letters? If so, please clarify which scoring system is used or assumed (e.g., see discussion in [1]).

The model structure is designed to describe the natural course of the disease and the development of DMO, and includes 6 visual acuity health states. The numerical scale of these health states is based on the measure of best corrected visual acuity.

For the purpose of the cost-comparison analysis, disease progression through these health states and associated changes in efficacy and safety outcomes are assumed equivalent across all modelled treatments.

B2. PRIORITY QUESTION. Please provide instructions on how the ERG can run the following scenarios listed in CS Table 40:

i. Aflibercept dosing regimen

Alternative dosing regimens can be selected in the cost input sheet of the cost-minimisation model. To select non-base-case dosing regimens, the aflibercept data source (cell E41) and treatment regimen (cell E35) cells may both need to be changed.

ii. Ranibizumab dosing regimen

Alternative dosing regimens can be selected in the cost input sheet of the cost-minimisation model. To select non-base-case dosing regimens, the ranibizumab data source (cell E42) and treatment regimen (cell E36) cells may both need to be changed.

iii. Absence of DME/ positive discontinuation proportions at year 1.

In YOSEMITE and RHINE, [redacted] of patients on faricimab and [redacted] of patients on aflibercept had absence of DME at 12 months defined as having a CST < 325 micrometres. The scenario where patients discontinue once they have reached that definition can be implemented by doing the following:

1. *Go to sheet "Model Inputs", section "Treatment duration", part "Annual treatment discontinuation probability based on VA state".*
2. *Enter [redacted] in the user override for the 1st year for all visual acuity states.*
3. *Copy the results for faricimab from sheet "Result Table" to the absence of DMO table in the "Results Table" sheet*
4. *Go back to sheet "Model Inputs" and implement [redacted] and copy the results for aflibercept and ranibumab from sheet "Result Table" in to the absence of DMO table*

B3. PRIORITY QUESTION. CS Table 39 states an alternate dosing regimen for faricimab for scenario analysis (6LP→ T&E, equivalent visits in year 3+). Please provide the results for this scenario, as it is missing from CS Table 40.

This scenario is reflected in the base-case assumptions where total visits are assumed to be equivalent across all modelled treatments. Table 39 has been updated to remove the row including this scenario.

B4. PRIORITY QUESTION. In the CS Table 29, the cost of Outpatient Procedure for Retinal Tomography is reported as £117.11. However, the NHS reference cost for the code BZ88A is reported as £125 for outpatient procedures. Please explain this discrepancy.

The cost for retinal tomography originally included in the model represented the cost code BZ88A from the non-elective short stay sheet of the NHS reference costs 19/20 (91). This cost has been updated to £125.88 to reflect the cost of retinal tomography in an outpatient setting (cost code BZ88A, outpatient procedures sheet).

The cost of retinal tomography has been updated in table 29 of the company submission, and reflected in the base-case and scenario analyses.

B5. PRIORITY QUESTION. Please provide the data source for the administration cost of injection in the model Sheet!Administration Costs cell E25.

In the absence of a robust estimate for the cost of an injection administration, the cost of an injection administration was sourced from the ERG report in the appraisal of aflibercept for DMO (TA346) (92). The cost was estimated as the difference between the cost of an administration injection visit and a monitoring visit.

Section C: Textual clarification and additional points

C1. Should footnote b in CS Table 9 apply to both of the pooled faricimab groups?

Footnote b should apply to both arms in the pooled analysis. Table 9 in the company submission has updated with this correction.

C2. For CS Figure 6 we presume the y-axis refers to the number of letters. Is this correct?

That is correct. The unit on the y-axis of Figure 6 is change in letters.

C3. Please clarify why the calculable data reported in CS Table 15 are marked academic in confidence.

The calculable data in Table 15 has been unmarked.

C4. In the text in CS section B.3.6.3 some NEI VFQ-25 results are marked as academic confidence whereas others are not. Is this correct?

The confidential marking in section B.3.6.3 has been amended to correct for an inconsistency in the original marking approach.

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NICE additional information request response [ID3899]

Additional information request

In December 2021, NICE's FTA scrutiny panel agreed faricimab was a suitable candidate for the abbreviated fast track appraisal process. Following the communication of this decision, NICE shared a request for additional information with Roche.

In this request, NICE asked Roche to provide an analysis with the following assumptions incorporated:

- 50% treatment discontinuation at 5 years
- Non-consultant led appointments for treatment and monitoring
- No OCT procedure for injection administration
- Injections in year 1 are based on the loading phases for each treatment as specified in the summary of product characteristics (SPC), followed by a treat and extend regimen for all treatments
- Number of injections should be the same for all treatments in subsequent years based on treat and extend
- Monitoring visits should be the same across arms.

These assumptions deviate from those incorporated in Roche's base-case. Therefore, the results of the analysis do not represent Roche's preferred assumptions, and are provided for illustrative purposes only.

Methodology

A description of the approach taken for amending each model parameter or assumption specified in the request can be seen below:

- 50% treatment discontinuation at 5 years
    - Change parameter value in cell F140 in model inputs sheet from 15% (base-case value) to 50%
- Non-consultant led appointments for treatment and monitoring
    - Change parameter value from £101.80 (base-case value) to £89.13 in cells: E23 in administration costs sheet; E77 in supportive care costs sheet
- No OCT procedure for injection administration
    - Change OCT cost from £125.88 (base-case value) to £0 in cell E24 in administration cost sheet
- Injections in year 1 are based on the loading phases for each treatment as specified in the SPC, followed by a treat and extend regimen for all treatments.
    - See Table 1 for assumed injection numbers.
    - The wording of the aflibercept SPC states treatment is initiated with one injection per month for five consecutive doses, followed by one

injection every two months. There is no requirement for monitoring between injections.
        - 5 monthly loading dosing
        - 1 dose month 7 (q8w)
        - 1 dose month 9 (q8w)
        - 1 dose month 11 (q8w)
        - 1 dose month 13 (q8w) = 0.5 doses from month 11 to 12
        - **8 completed doses at month 12**
        - Alternative results, where the next planned dose is taken into consideration, are also presented. These results incorporate a proportion of the next planned dose, calculated as the amount of time expired in the treatment interval at month 12 as a proportion of the overall treatment interval. For example, for aflibercept, at month 12, patients will be 1 month in to a 2-month treatment interval, which represents an additional 0.5 doses (1 divided by 2).
            - **8.5 including planned doses after month 12**
    - The draft SPC for faricimab states that it should be administered by intravitreal injection every 4 weeks (monthly) for the first 4 doses. Then dosing interval may be extended up to every 16 weeks (4 months), in increments of up to 4 weeks.
        - 4 monthly loading doses
        - 1 dose month 6 (q8w)
        - 1 dose month 9 (q12w)
        - 1 dose month 13 (q16w) = 0.75 doses from month 9 to 12
        - Total at month 12
            - **6 completed doses**
            - **6.75 including planned doses after month 12**
    - Ranibizumab SPC is unclear on year 1 dosing under a treat and extend regimen. To reflect the views of clinical experts consulted by Roche and the analyses provided in the ERG report, **the number of ranibizumab injections in year 1 is assumed to align with aflibercept.**
- Number of injections should be the same for all treatments in subsequent years based on treat and extend.
    - See Table 1 for assumed injection numbers.
    - Year 2 - aligning to the assumptions adopted in TA346[1] and the ERG preferred analysis, 4 injections are assumed for all treatments in year 2.
    - Year 3+ - capturing a mid-point between the projected injection administrations for faricimab and the comparators, 2 injections are assumed for all treatments in year 3 and beyond.
- Monitoring visits should be the same across arms.
    - See Table 1 for assumed monitoring visit numbers.
    - In line with the views of the clinical experts consulted by Roche, no additional monitoring visits are applied in years 1 and 2 for people on treat and extend regimens.
    - In year 3 and beyond, 2 additional monitoring visits are modelled respectively. This reflects the views of clinical experts who suggested

that they would see patients at least 4 times a year, for either injections or monitoring.

Table 1: SPC and treat and extend injection and monitoring frequencies [NICE requested]

Dosing regimen	Injections			Separate Monitoring visits		
	Year 1	Year 2	Year 3+	Year 1	Year 2	Year 3+
SPC dosing in year 1 (completed doses only); Treat and Extend in subsequent years						
Faricimab (6 LP → T&E)	6	4	2	0	0	2
Aflibercept (2 LP → T&E)	8	4	2	0	0	2
Ranibizumab (0.5 LP → T&E)	8	4	2	0	0	2
SPC dosing in year 1 (including proportions of planned doses beyond month 12); Treat and Extend in subsequent years						
Faricimab (6 LP → T&E)	6.75	4	2	0	0	2
Aflibercept (2 LP → T&E)	8.5	4	2	0	0	2
Ranibizumab (0.5 LP → T&E)	8.5	4	2	0	0	2

LP: loading phase; PRN: pro re nata; SPC: summary of product characteristics; T&E: treat and extend

Results

The results of the requested analysis, following the approaches described in the methodology section, are presented in Table 2 and Table 3.

Table 2: SPC and T&E injection and monitoring scenario (including completed doses only); faricimab PAS price, aflibercept and ranibizumab list price

Cost	Faricimab 6 mg LP → T&E	Aflibercept 2 LP → T&E	Ranibizumab 0.5 LP → T&E
Drug cost	[redacted]	£29,670	£20,034
Administration cost	[redacted]	£5,028	£5,028
Monitoring cost	[redacted]	£3,696	£3,696
Diagnostic cost	£195	£195	£195
Mean total cost	[redacted]	[redacted]	£28,953

Incremental cost vs faricimab	N/A	[redacted]	[redacted]

LP: loading phase; SPC: summary of product characteristics; T&E: treat and extend

Table 3: SPC and T&E injection and monitoring scenario (including planned doses); faricimab PAS price, aflibercept and ranibizumab list price

Cost	Faricimab 6 mg LP → T&E	Aflibercept 2 LP → T&E	Ranibizumab 0.5 LP → T&E
Drug cost	[redacted]	£30,381	£20,514
Administration cost	[redacted]	£5,147	£5,147
Monitoring cost	[redacted]	£3,696	£3,696
Diagnostic cost	£195	£195	£195
Mean total cost	[redacted]	£39,419	£29,553
Incremental cost vs faricimab	N/A	[redacted]	[redacted]

LP: loading phase; SPC: summary of product characteristics; T&E: treat and extend

The results of the requested analysis find faricimab to be a cost saving treatment option, when comparing faricimab at its discounted net price to aflibercept and ranibizumab at list price. Of the alternative approaches presented, Roche acknowledges the results of the scenarios are similar, but prefers the results presented in Table 2, where injection frequencies are calculated using the completed doses method. Comparator injection frequency estimates in this scenario are more closely aligned to the ERG's preferred analysis than those presented in Table 3. Therefore, the results presented in Table 2 can be considered more externally valid and robust than those in Table 3.

Acknowledging that aflibercept and ranibizumab are available to the NHS at a discounted price, the impact of varying the level of discount to list price for aflibercept and ranibizumab was explored in a threshold analysis presented in Table 4. When adopting the base case cost-comparison assumption, this analysis demonstrated that at its net price faricimab remains [redacted] compared with aflibercept and ranibizumab up to a discount level of [redacted] and [redacted] respectively. However, the assumptions included in the analysis do not reflect assumptions considered to be clinically plausible by Roche, so the results provided are for illustrative purposes only.

Table 4: threshold analysis: incremental cost of faricimab compared with aflibercept and ranibizumab at varying list price discount levels (NICE requested assumptions)

Discount	Aflibercept		Ranibizumab	
	Discounted aflibercept price	Incremental cost vs faricimab	Discounted ranibizumab price	Incremental cost vs faricimab
0%	£816.00	[redacted]	£551.00	[redacted]
5%	£775.20	[redacted]	£523.50	[redacted]
10%	£734.40	[redacted]	£495.90	[redacted]
15%	£693.60	[redacted]	£468.40	[redacted]
20%	£652.80	[redacted]	£440.80	[redacted]
25%	£612.00	[redacted]	£413.30	[redacted]
30%	£571.20	[redacted]	£385.70	[redacted]
35%	£530.40	[redacted]	£358.20	[redacted]
40%	£489.60	[redacted]	£330.60	[redacted]
45%	£448.80	[redacted]	£303.10	[redacted]
50%	£408.00	[redacted]	£275.50	[redacted]
55%	£367.20	[redacted]	£248.00	[redacted]
60%	£326.40	[redacted]	£220.40	[redacted]
65%	£285.60	[redacted]	£192.90	[redacted]

Discussion

The results of the analyses provided above incorporate specific assumptions included in NICE's additional analysis request. A number of these assumptions are inconsistent with the assumptions presented in the company's base-case and with opinions of UK clinical experts consulted by Roche in the development of the company submission.

A summary of the key discrepancies in opinion for each of assumption is presented in the discussion points below:

- Roche acknowledges that the proportion of people remaining on treatment beyond 5 years is uncertain. There was no consensus among experts consulted by Roche on this assumption. Estimates of the proportion of people remaining on treatment beyond year 5 ranged from 10 to 40%. With that in

mind, Roche believes a midpoint of the opinions elicited by Roche and the ERG of 30% would be a more appropriate estimate to apply.

- Further to the above, experts consulted by Roche noted that discontinuation due to positive efficacy is expected to be greater for faricimab compared to currently available anti-VEGF therapies. Differential discounting was not modelled in the base-case analysis to retain consistency with the other assumptions around equal efficacy. However, this suggests a conservative approach was adopted in the base-case discontinuation assumptions.
- Assuming non-consultant led appointments for treatment and monitoring has a negligible impact on the cost-comparison results. Although, clinical experts validated cost and resource use assumptions applied in the company base-case, Roche has no major concerns about this alternative assumption.
- Roche acknowledges that OCT procedures will not be undertaken in the treatment-loading phase when monitoring is not required. However, in the maintenance phase of treat and extend regimens, patients will be assessed using OCT and other measures to determine whether treatment intervals should be extended, maintained or reduced. Therefore, it is inconsistent to assume no OCT procedures take place at injection visits when following a treat and extend strategy. Further to this, the majority of injection visits take place after the initial loading phase, where OCT procedures are conducted. To maintain consistency in the assumptions, Roche recommends retaining the cost of OCT procedures during injection visits. This is also consistent with the feedback of clinical experts consulted by Roche who noted that OCT procedures are performed at injection and monitoring visits.
- Roche recognises that assumptions around injection and monitoring visits are a key driver of the cost-comparison analysis. However, the assumptions incorporated in this request fail to recognise much of the evidence and expert opinion presented in the company submission. Roche believes the injection and monitoring visits included in the submission base-case are a more accurate reflection of how these treatments are, or will be, used in clinical practice. The base-case assumptions represent a fair and consistent trial-to-trial comparison of all treatments relevant to the decision problem. Further discussion points relating to injection and monitoring assumptions are provided below.
- Experts consulted by Roche, expect patients treated with faricimab to follow a treat and extend regimen in line with the personalised treatment interval arms from YOSEMITE and RHINE[2]. They noted that they expected to be able to extend treatment intervals further and with more confidence on faricimab than is currently achievable with aflibercept and ranibizumab. This sentiment applied across all years of treatment. They also agreed that currently available anti-VEGF therapies are most commonly administered using a PRN regimen, and that additional monitoring would be required for PRN treatment strategies, but not treat and extend.
- The analysis request put forward by NICE fails to recognise that treatment intervals could be further extended on faricimab than aflibercept or ranibizumab after the first year of treatment. This oversight could be explained

by absence of any commentary on the proportions of people extending faricimab treatment intervals to q12w or q16w in the ERG report.

- Injection assumptions in for year 2 in the requested analysis aligns to what was accepted by committee in the appraisal of aflibercept (TA346)[1]. These assumptions are based on the views of ophthalmologists who were consulted in 2014. UK clinical experts, who either treat, or have a special interest in DMO, validated the company base-case assumptions around injection and monitoring visits in 2021. Therefore, the assumptions applied in the base-case analysis are more representative of current clinical practice.
- Optimal visual outcomes can be achieved with fewer injections when treating with the most durable treatments. At week 52 in YOSEMITE and RHINE[2], efficacy and safety results were comparable for patients in the faricimab personalised treatment interval study arms, where over 70% had extended to q12w or beyond, to those treated with aflibercept on a q8w regimen.
- Extended treatment intervals could alleviate health service capacity at a time where health care services are stretched and planned doses can be missed.

In conclusion, Roche welcomes the opportunity to engage with NICE and the appraisal committee to support the decision-making process, but has concerns with the analyses presented in this response. Despite this, when adopting the requested assumptions, this analysis demonstrated that at its net price faricimab remains cost-saving compared with aflibercept and ranibizumab up to a discount level of [redacted] and [redacted] respectively.

References

1. National Institute for Health and Care Excellence. TA346: Aflibercept for treating diabetic macular oedema. 2015.
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NICE National Institute for Health and Care Excellence

Patient organisation submission

Faricimab for treating diabetic macular oedema [ID3899]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Diabetes UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Diabetes UK is the country's leading diabetes charity, representing the over 4.9 million people living with diabetes in the UK, people affected by diabetes and those at risk of developing the condition. We help people effectively self-manage their diabetes by providing information, advice and support. We campaign and work with people with diabetes and healthcare professionals to improve the quality of diabetes care across the UK's health services. We also fund pioneering research into all types of diabetes that will one day allow us to cure or prevent the condition. We are fighting for a world where diabetes can do no harm. We are a growing community with more than 300,000 supporters nationwide – including people with diabetes, their friends and families – and more than 100,000 lay and healthcare professional members.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]	**Roche**: Jun 2020 - £20,000 for Learning Zone as part of our urgent COVID response funding appeal Dec 2020 - £25,000 for Engaging Communities & addressing health inequalities for ethnically diverse populations (project scoping) Aug 2021 - £100,000 for Engaging Communities & addressing health inequalities for ethnically diverse populations (project delivery) **Sanofi**: 2020 - £72,000 for improving Inpatient Care programme 2020 – £48,000 for sponsorship of Diabetes UK Professional Conference online series 2021 - £72,000 for Improving Inpatient Care Programme **Novartis**: 2021 – £10,000 for sponsorship of Diabetes UK Professional Conference

If so, please state the name of manufacturer, amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	Conversations, interviews and surveys of people living with diabetes Insights from other relevant patient organisations with whom we work closely The Diabetes UK online forum The Diabetes UK helpline
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Diabetes is one of the leading causes of preventable sight loss in the UK and more than 1,700 people have their sight seriously affected by their diabetes every year in the UK - more than 30 people every week. Diabetic macular oedema (DMO) is a serious eye condition which can lead to sight loss as a result of fluid leaking from the small blood vessels in the eye and there are an estimated 300,000 people living with the condition in the UK. 7% of people with diabetes, or 1 in 14, develop DMO which results in a noticeable loss of vision. Onset and escalation of DMO can be very sudden and shocking

	The onset of symptoms of DMO can be very sudden and shocking for patients. Many people living with diabetes are aware of the potential eye complications that can develop as a result of consistently higher blood glucose levels but are **unaware or unclear about how these can escalate and cause sight loss**. One man in his 50s who had diabetes for over 10 years told us he found it difficult to adjust to managing the condition for many years following diagnosis. He became aware of "floaters" in his eyes and after speaking to an optician was told that this was related to his diabetes control but **not told** about retinopathy. He was referred for laser treatment for DMO but sadly lost his sight during treatment and is now registered blind. Similarly, a woman in her 40s who had diabetes since an infant told us she was referred for laser treatment after signs of DMO were picked up in a regular screening. Whilst waiting for treatment, however, she noticed her eyesight become cloudy in a shop one day and woke up without any sight the next morning. <u>Uncertainty and worry about further deterioration of eyesight</u> There is a high level of anxiety amongst people with DMO about further deterioration of their eyesight and potential blindness because of the condition. This is exacerbated by the lack of clear information many patients are offered at the point of diagnosis and the limited treatment options. A person with diabetes we spoke to who had symptoms of DMO identified early, managed to have much of their eyesight stabilised with regular laser treatment for over a decade. However, they told us they are still "terrified" their sight will degenerate further. This person also developed cataracts during their laser treatment and, though treated early and successfully, was unaware this was a common side-effect of their treatment – highlighting the part that unclear explanations and discussions with healthcare professionals can play in creating and heightening uncertainty for people with DMO. People with diabetes are twice as likely to suffer from depression and are more likely to be depressed for longer and more frequently. Furthermore, people with macular disease are seven times more likely to feel distressed or depressed. The psychological effects of losing sight are acute and uncertainty and worry caused by DMO can have a major impact on emotional and psychological wellbeing.

	Employment issues due to DMO DMO can be life-changing and have a devastating effect on people with diabetes and their livelihoods – forcing them to make adjustments to their employment or in some cases stop altogether. We have spoken to people with DMO who have had to stop working entirely due to the condition and this can place an enormous financial pressure on people and their loved ones. For example, we spoke to a man whose profession was as a full-time driver. This individual had to relinquish their licence because of sight loss and stop work – which left them feeling "literally suicidal". Although their partner was able to start work full-time, this individual "finds this hard to come to terms with and also finds the lack of routine challenging". His partner also had to adjust to begin working full-time and become the main breadwinner for the household – which included two young children and an elderly dependent parent – and the knock-on effects of DMO on carers and the wider family dynamic are important to note. In cases where people can continue in their current employment there is often additional attention that needs to be paid to manage the effects of DMO like limiting work that requires close focus like reading or typing as this can cause headaches. Other issues impacting day-to-day life and wellbeing Aside from employment DMO affects many other aspects of day-to-day life. One man we spoke to who has DMO said that "his loss of sight affects every area of his life" but he says "it is the small things that are most difficult. If [he] cook[s] for [himself] and [he] take[s] the lid off a jar and puts it down, it takes ages to find it again." DMO also makes it much harder for people with diabetes to manage blood glucose levels through regular tasks like taking blood glucose readings, injecting insulin and using devices such as continuous glucose monitors and insulin pumps. Whilst there are innovations that can help, like a talking meter, people with diabetes and DMO still need to code their readings and often require additional assistance from someone else to complete these tasks.

	Good management of diabetes is also essential to stopping complications like DMO worsening and this has the potential to create a very difficult situation for people with DMO: dependent on good management to help prevent further sight loss but faced with practical challenges as a result of their complication that hinders their ability to do so.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	There are two drugs in routine use for treating DMO currently: Lucentis (ranibizumab) and Eylea (aflibercept). These are both anti-VEGF drugs used as a first line response and the frequency and number of injections depends on how a patient responds to the drug. Some people are also given steroid injections if they do not respond well to anti-VEGF drugs but use of these are often limited as they can cause cataracts as a side-effect. The nature of the treatments currently available to stabilise vision and halt the progression of DMO makes many people worried in the first instance as they are often already highly sensitive to their developing sight loss. Injections directly into or behind the eye are unusual for most and very unappealing even when people are keen to undergo treatment and address the issue. <u>Confusing and worrying</u> Some of the people with DMO we have spoken to also relate a confusing series of appointments with different health professionals offering varying advice when they start treatment. One man we spoke to – who was already uneasy about injections – recounted being referred from his optician to a doctor at a local hospital who discussed injections and laser with him but decided against starting these treatments before eventually seeking help at Moorfields Eye Hospital and beginning laser treatment. Unfortunately, this treatment did not stop their vision deteriorating, gave them a phobia of laser treatment and resulted in a loss of confidence in the potential for other treatments to help.

	The healthcare professionals who were treating this person were no doubt offering the best advice they could at the time but the inconsistency of the care ultimately left him "terrified that any further treatment on his eyes will result in further sight loss and confused by the treatment options available." As laser treatment only stops vision from deteriorating further and eye injections cannot restore sight if there is already significant damage to the macula, there is a worrying element of resignation or even fatalism from and towards some people with DMO. For example, in one case we heard from a taxi driver who had signs of DMO who was asked what he did for a living by their doctor. After telling them the doctor replied "not anymore, you're not". We know from our insight and campaigning work that 7 of 10 people with diabetes feel overwhelmed by the demands of living with it and emotional support is a key aspect of their care three quarters say is lacking. The experience of the taxi driver above highlights the lack of consideration for psychological effects sometimes felt by people with DMO. <u>Further disruption and uncertainty due to lockdown and backlog</u> The disruption to eye screening and other healthcare services during the COVID-19 pandemic has had a damaging impact on treatment, with eye screening for potential issues much reduced and people being forced to miss their usual face-to-face treatment. These missed appointments have huge real-world effects. In a response to our survey of over 4000 people with diabetes about their care during the pandemic one respondent reported that their eye appointment was cancelled during lockdown and whilst waiting for another, lost sight in one eye. Though services are working hard to recover and public data is not currently available showing the proportion of people who have not had their eyes screened it is likely that many thousands will not have had their eye screening check in the last 18 months and may therefore now be at higher risk of DMO and in urgent need of treatment.

8. Is there an unmet need for patients with this condition?	Yes. While there is currently no cure for DMO, stabilisation of the condition is crucial and can prevent devastating sight loss in people living with the condition. There is significant concern that HbA1c levels in people with type 2 diabetes have risen during the COVID-19 pandemic. This, combined with the high number of missed or cancelled eye screenings during this time, mean the need for fewer injections with this treatment may help ensure DMO is treated more efficiently.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Any additional guidance and new technologies being considered to treat this sensitive and potentially life-changing condition are welcome. As discussed above, injections to treat DMO can be very alarming and deeply unpleasant for those receiving the treatment. The need for fewer injections with this technology compared to the anti-VEGF drugs available at the moment is particularly welcome. Reducing the number of appointments a patient has to attend will have a positive impact for many who are worried about the treatment, find the practicalities of attending appointments difficult, or both.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	This technology is still an injection and one that does not restore lost central vision. For those with an acute aversion to injections this technology remains a significant barrier to accessing treatment. This technology still requires a relatively high number of appointments and will require regular check-ups for the individual with DMO.

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	People who struggle to attend appointments due to child care responsibilities, mobility issues or employment obligations may benefit from this technology in comparison to others because it requires fewer appointments.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	

Other issues	
13. Are there any other issues that you would like the committee to consider?	

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission:

- DMO creates high levels of anxiety and fear in people living with diabetes
- Sight loss can turn people's lives upside down. Any additional treatments that can delay or mitigate this are hugely welcome and should be made available to the widest possible group.
- Current routine treatments for DMO require regular face-to-face appointments. A treatment that is effective but requires fewer appointments and longer intervals between injections is welcome and will prove beneficial for many.
- This is particularly important given the disruptions to health care services during the lockdown with an increased risk of complications in people who haven't had routine care and the backlog of appointments increasing pressure on services as they recover
-

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Patient organisation submission

Faricimab for treating diabetic macular oedema [ID3899]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

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- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Macular Society
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	The Macular Society is the leading national charity fighting to end sight loss caused by macular disease. Every day over 300 people in the UK face the shock of a diagnosis of macular disease. This sight loss can rob people of their independence, leaving them unable to drive, read or recognise their family. Our members tell us what a profoundly isolating condition it is. People with macular disease are seven times more likely to feel distressed or depressed. We help people adapt to life with sight loss, regain their confidence and independence and take back control of their lives. We are one of the few sight loss charities that actively fund and support medical research into macular disease. With the exception of the details in the answer to 4b, all our income is fundraised from legacies, grants, donations from individuals and fundraising activities such as our lottery, raffle, appeals and community and challenge events. We have 28,000 members who we communicate with on a regular basis, 370,000 website visitors a year and our Advice & Information (A&I) Service responds to over 16,000 queries a year.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant	• ADVANZ Pharma (dexamethasone) – NA • Alimera Sciences (fluocinolone acetonide) - NA • Allergan (dexamethasone) - £56,000 (contribution to support activities around information, support and education) • Aspen (dexamethasone) - NA • Aspire Pharma (dexamethasone) - NA • Bausch & Lomb (dexamethasone) - NA • Bayer (aflibercept) - £8,100 (contribution to support activities around information, support and education)

manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	• Glenmark Pharmaceuticals (dexamethasone) - NA • Hameln pharma (dexamethasone) - NA • Hospira (dexamethasone) - NA • Martindale Pharma (dexamethasone) - NA • Novartis Pharmaceuticals (dexamethasone, ranibizumab) - NA • Organon Pharma (bevacizumab) - NA • Panpharma (dexamethasone) - NA • Pfizer (bevacizumab) - • Rayner Pharmaceuticals (dexamethasone) - NA • Roche (bevacizumab) - £30,000 (contribution to support activities around information, support and education) • Rosemont Pharmaceuticals (dexamethasone) - NA • Sanofi (dexamethasone) - NA • Synchrony Pharma (dexamethasone) - NA • Teva (dexamethasone) - NA • Thame Laboratories (dexamethasone) - NA • Thea Pharmaceuticals (dexamethasone) - NA • Wockhardt (dexamethasone) - NA
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

5. How did you gather information about the experiences of patients and carers to include in your submission?	**DMO patient survey** We carried out a survey and published a report highlighting patient experience of DMO in June 2021. A total of 41 patients with DMO were surveyed about their experiences and their perceptions of the management and support they have received for their diabetes and DMO. This work aimed to understand how the information and support for diabetes compares to that for DMO. **Wet AMD survey** A survey was conducted by the Macular Society in early 2020 to understand the burden that frequent anti-VEGF injections and ophthalmology appointments has on wet AMD patients and their carers or family. A total of 449 responses were received from across the UK. A full report was published August 2020. **Service users** Users of the charities services, such as our Befriending service and Advice and Information service are surveyed every other year. The last survey was completed in April 2020 and had 300 respondents. We also survey our volunteers every other year, most of our volunteers are also affected by macular disease. **Local peer support groups** Our Regional Managers who manage our network of over 400 local groups across the UK feedback regularly. They are our 'frontline', having face to face (or phone to phone) interaction every day with people affected by macular disease. We gather case studies which record the experiences of individuals living with macular disease and the impact on their families and carers. We use our social media channels to interact with people with macular disease and provide information and advice. It is also an important way for people to find others with the same condition where they have a rare form of macular disease and to share experiences.

Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Diabetic macular oedema (DMO) is a complication of diabetes that can lead to irreversible sight loss. It is a build-up of fluid in the macula due to leaky blood vessels damaged by high blood sugar due to diabetes. It is one of the most common causes of sight loss in the working age group. There are currently around 300,000 people living with the condition in the UK. However, the effects of DMO are still not well known, with recent research from Australia showing only a quarter (26 per cent) of people aged 50-70 are aware of DMO. Less is known about the levels of understanding in the UK. Several treatments are available for DMO. Earlier treatment usually means better outcomes for the patient, including maintaining better sight or stable sight for longer. To address early diagnosis and referral for timely treatment, the UK has set up the Diabetic Eye Screening Programme, where those who have been diagnosed with diabetes aged 12 and over are invited to get an eye screen every year. This programme has been very successful in getting patients diagnosed earlier and referring patients to treatment if needed. The lack of information for those newly diagnosed with DMO can lead to higher levels of anxiety, as patients aren't sure of what their diagnosis means for their future. This anxiety can be worsened when patients aren't aware of the support available to help them. Diabetes management is vital for maintaining a healthy life and reducing the risk of developing or accelerating complications such as DMO. However, tasks needed to help manage diabetes, such as reading blood glucose levels and injecting insulin, can become much more difficult after losing central vision. Nearly three-quarters of responders to our survey said they felt anxious about their DMO and the sight loss it might cause, compared to only one person who said they rarely felt anxious. No responders said they never felt anxious about their DMO and possible sight loss

	“It makes me worry what my future may look like. I also would love children and I worry about the impact this would have on my eyes loss.” **“Straight lines look wavy and blurry. It feels very scary and I’m frightened of losing more of my vision in both eyes.”** Loss of central vision through DMO can be very frustrating and can greatly affect everyday life as well as financial impact due to changes in employment and able to drive. Vision loss can make daily tasks more difficult, including tasks needed to monitor and manage diabetes. This can risk further vision loss as poor management of diabetes is a risk factor for DMO progression. This highlights the need for more support and guidance for those newly diagnosed with DMO. Some people with DMO experience visual hallucinations called Charles Bonnet syndrome which adds another level of impact on health and mental well being. In addition to living with and managing sight loss patients still need to manage their diabetes and the other morbidities and complications related to this. **Family and carers** There is a significant burden on family and carers supporting a patient with DMO. A patient with DMO needs to adapt and change to the emotional and practical impacts of the condition and will often rely on family and carers to provide additional support. **“Very difficult to carry out my office work for the small business that I run and also driving issues.”** **“Travel to clinic is difficult my daughter has to take time off work for me.”** **“Unable to get anyone to take me. I live alone and I am 82 years old.”**

	It can be hard attending appointments, as people with diabetes have to attend multiple check-ups for their condition and other complications. Difficulties might include taking time off work or arranging friends or family to take them to these clinics.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	**Treatments** Two-thirds of responders (65 per cent) were receiving anti-VEGF injections to treat their DMO. Another 7.5 per cent (those who responded "other") had stable DMO and were under observation, receiving injections when needed. One in ten (10 per cent) were receiving steroid injection as treatment and one in eight (12.5 per cent) had laser treatment. One responder was not receiving any treatment due to their sight loss being 'too bad to treat'. Anti-vascular endothelial growth factor (anti-VEGF) injections are the first line of treatment for DMO, and involve injecting these drugs into the eye at repeated intervals. These drugs work to stop the growth and leaking of blood vessels which leads to the damage and vision loss seen in DMO. Some patients do not respond well to these anti-VEGF drugs, or respond better to steroid injections. However, currently there are more restrictions on the use of steroids for DMO due to the increased risk of developing cataracts after steroid use in the eye. Almost four in five participants (78 per cent) feel anxious at least sometimes about their DMO treatment. Often this anxiety is due to having injections, which can be painful. Planning their life around injections can also be stressful, including taking time off work or finding someone to take them to the clinic. **"Regular trips to the hospital for check-ups, having to arrange holidays etc around treatment. Painful treatment."**

	The remaining 22 per cent do not feel anxious about their treatment, and see injections as a positive step to maintaining their vision. **"Only positively. It has given me reassurance that my sight is being preserved as well as it can be for as long as possible."** **Care** There is significant pressure on NHS eye care services. Patients regularly feedback personal experiences of cancelled appointments, frustration over communication with clinics, and many hours spent waiting around in clinic. Injections are not available in local health care settings, meaning many patients travel a good distance to attend injection clinics and need a driver to accompany them. There is also a challenge between the management of diabetes and eye condition. Around one in five (22 per cent) responded that they feel like they weren't managing their eye health well, compared to only one in 20 (5 per cent) who felt they weren't managing their diabetes well. Overall responders felt less able to manage their eye health and DMO compared to their diabetes. This lack of control may be a reason why responders felt anxious about their eye condition and the sight loss it can cause. It is important that patients feel that they are able to manage their condition and have all the necessary information and support. **"I think it's hard to manage how unpredictable sugar levels can be. Also to calculate the amount of insulin and correction doses are required takes a lot of hard work and concentration."** **"[It can be hard] keeping it [blood sugar] under control some difficulty reading syringes."**

	"Fear of the unknown is difficult with my eye condition. I have been given great care once it was discovered DMO but there did not appear to be anybody on hand to explain things properly or talk from experience." **"Just struggling with understanding it all re HBA1C time in target blood pressure exercise etc."** More than two in five responders (42.5 per cent) were not given any information about managing their DMO, while only a quarter (24 per cent) were not given any information about managing their diabetes. The importance of managing diabetes is well established, with poor blood sugar management being a major risk factor for developing complications such as diabetic macular oedema. Better management of diabetes through lifestyle changes and monitoring blood sugar levels help maintain good vision. **"I was told blood sugar too high and to bring it down quickly. I did bring it down within three months from 116 to 58. Shortly after this I started a range of treatments for retinopathy and DMO."** Only one in four (25 per cent) of those who took the survey felt they were given all the information about DMO that they needed when they were diagnosed. On the other hand, a similar proportion (28 per cent) were given no information at all. It can be difficult for patients to receive a diagnosis of DMO and learn that they could lose their vision. Understanding more about the condition and what treatments are available can be reassuring, and help patients feel more in control of the situation.
8. Is there an unmet need for patients with this condition?	There is no current cure for the condition and treatments can only manage and stabilise the sight loss. There is a need for longer acting treatments to reduce the time between treatment and injections

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Patients will welcome the need for fewer injections compared to the current anti-VEGF drugs, due to the potential for longer intervals between injections with faricimab. Each appointment where there may be an injection can cause anxiety. In our survey of patients with wet AMD, 31% of patients reported always feeling anxious about injection appointments and 24% reported that they were sometimes anxious. When asked to say which of 4 statements on appointments was most important to them, 39% said that 'Keeping the same level of vision with fewer injections' was most important. Some people also experience pain and discomfort following eye injections and a very small minority can suffer serious complications, such as an infection. Fewer eye clinic appointments will mean less disruption to day to day life, particularly where patients need to be accompanied to appointments by family or friends, who may need to take time off work. There will also be less cost to the patient of attending the eye clinic, such as taxi or bus fares and parking fees. In our survey 62% of patients said that they are driven to hospital by family or friends and 28% take public transport. Patients will also welcome that faricimab is a new innovation in treatment as it is dual action targeting both angiopoietin (Ang-2) and vascular endothelial growth factor (VEGF). This offers additional hope to currently available treatments.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	The main disadvantage is that it will be an intravitreal injection which will need to be given regularly, sometimes for years. Appointments at an eye clinic, with all the attendant difficulties of travelling, needing someone to accompany them, costs of transport and hours at the hospital, will still be required, if at a reduced rate.

	Intravitreal injections carry a very small but serious risk of sight loss due to complications, such as endophthalmitis. Some patients can also experience significant pain for a short time afterwards due to corneal abrasion or drying of the cornea, which can be alleviated with lubricating gel.
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Those who already struggle to attend all their eye clinic appointments, for the reasons given above, will benefit if they have to attend less often. Many patients also suffer from other health conditions associated with diabetes and advancing age, which can leave them unable to maintain their treatment regime. For some just leaving home can be extremely difficult. Only patients who are well enough, have the right transport means and the ability to make arrangements to attend can benefit.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Yes, age and disability are issues that need to be considered. As the drugs currently available are not a cure and do not work effectively in everyone, a proportion of patients will still experience significant sight loss such that they will be registered as sight impaired or severely sight impaired. As with diabetes there are particular ethnic groups that have a higher risk of DMO.

Other issues	
13. Are there any other issues that you would like the committee to consider?	The technology appraisal guidance (TAG) for the drugs currently licenced to treat DMO and wet AMD, Lucentis and Eylea, have parameters for when they can be used which include the level of vision i.e. the best-corrected visual acuity is between 6/12 and 6/96. This means that we have the phenomenon of eyes being 'too good to treat' and people having to wait for their vision to deteriorate before they can be treated with these drugs. However, the NICE Clinical Guidelines for AMD states that anti-VEGF treatment for eyes with wet AMD is clinically effective even before visual acuity drops below 6/12. We would strongly ask that the committee do not follow the TAG for Lucentis and Eylea and do not include a stipulation that vision must be lost before treatment can be administered. Faricimab should be available for ophthalmologists to prescribe if they consider there is a clinical need and the patient will benefit through it preserving their vision.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission:

- The numbers of people with DMO is increasing and over burdening hospital eye clinics
- The treatment burden on patients and carers is significant and longer acting drugs can alleviate the problem.
- Any measures that reduce the need or frequency of travelling to eye clinics for an invasive, distressing and sometimes painful treatment is a step in the right direction.
- Patients should not have to wait for their vision to deteriorate before they can be treated - the 'too good to treat' situation.
- The COVID-19 pandemic has significantly reduced eye clinic capacity due to the infection control measures now required. Any measures that might help to alleviate the pressure on eye clinics, such as longer acting drugs, are therefore even more important.

Thank you for your time.

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Patient organisation submission

Faricimab for treating diabetic macular oedema [ID3899]

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- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Royal National Institute of Blind People (RNIB)
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	The Royal National Institute of Blind People (RNIB) is one of the UK's leading sight loss charities and the largest community of blind and partially sighted people. We provide a wealth of services including practical and emotional support through our RNIB Connect community and our Sight Loss Advice Service, guide business and public services on accessibility, campaign for change, and have a library of over 60,000 accessible reading materials, including daily newspapers.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	Bayer - 2020: £18,086 (including VAT) towards Sight Loss Advice Service National pharmacies bags campaign. Novartis - 2021: £25,000 towards our sight loss pathway optom project Roche - 2021: £50,000 towards Greater Manchester pilot - multi agency pathways work 2020: £25,000 towards emergency outbound wellbeing calls

4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	From discussion with our Expert Patient Group, using their personal experiences of current treatment. We have also discussed the issue with Stephen Scowcroft, Director of Services at Macular Society, whose submission we also support as part of the VI Charity Sector Partnership, and can be regarded as the partnership's opinion.
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Diabetic maculopathy occurs when the macular is affected by retinopathy, resulting in loss of fine detail and colour vision. Diabetic macular oedema occurs when blood vessels near the macular leak and fluid builds up neat the macular causing swelling, causing further distortion or loss of vision. RNIB estimates that there are 1,110,000 people at risk of or living with sight loss due to diabetic retinopathy, of whom 102,000 have severe diabetic retinopathy. It is anticipated that these figures will increase to 1,170,000 and 108,000 respectively by 2030. People with diabetes over 12 are offered annual screening, which is essential to identifying issues early and maximising the chances of successful treatment. RNIB's last available figures, from 2015/2016 indicate that 83% of those offered a screening appointment, attended. Losing central vision can have a major impact on an individual's ability to remain independent, without timely vision rehabilitation training and support, and a significant increase in risk from accidents and falls. As a group, older blind and partially sighted people are at more than twice the risk of a fall as sighted

	older people [National Academies of Sciences, Engineering, and Medicine. “Making eye health a population health imperative: Vision for tomorrow.” National Academies Press, (2017).]. Loss of vision is traumatic, and has well-documented impacts on an individual’s mental health [Nollett, Ryan et al. “Depressive symptoms in people with vision impairment: a cross-sectional study to identify who is most at risk.” BMJ Open (2019)]. This will have impacts on families and carers, who will need to support the individual in their day-to-day lives, and with any eye clinic appointments for monitoring and treatment.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	While current first and second-line anti-VEGF and steroid capsule treatments are effective in stabilising the condition for most patients, injections into the eye are an understandable source of anxiety. [Senra, Ali et al. “Psychological impact of anti-VEGF treatments for wet macular degeneration—a review.” Graefe's Archive for Clinical and Experimental Ophthalmology (2016).], particularly for initial treatment appointments. Monthly treatments can be intrusive, and difficult to organise around personal and family life, and for those of working age.
8. Is there an unmet need for patients with this condition?	

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Patients and carers would welcome any treatment which increases the time between treatment appointments.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	None were identified that were unique to this appraisal – it's based on a known form of treatment (injections)
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	It was suggested that those who are less tolerant of injections would welcome an increase in the time between treatments, but the idea of an increased interval was well received by all that were asked.

Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Diabetes is more likely to affect older people, particular ethnicities (primarily South Asian and African-Caribbean communities) and pregnant women.
Other issues	
13. Are there any other issues that you would like the committee to consider?	NICE Clinical Guidelines for wet AMD state that treatment is clinically effective even before visual acuity drops below 6/12. However, current treatments are not recommended for us until acuity is between 6/12 and 6/96. RNIB would argue that the guidance should be made consistent for the treatment of wet AMD and DMO, so that clinicians are not limited by a patient's acuity if they feel treatment is clinically warranted. Eye clinics were facing demand pressures prior to COVID, which the pandemic has exacerbated. An increased interval between appointments would have the additional effect of improving capacity.
Key messages	
14. In up to 5 bullet points, please summarise the key messages of your submission: • The number of people with DMO is increasing and over burdening hospital eye clinics	

- The treatment burden on patients and carers is significant and longer acting drugs can alleviate the problem.
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NICE National Institute for Health and Care Excellence

Professional organisation submission

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- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**The College of Optometrists**

3. Job title or position	[redacted]
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	**The College is the professional body for optometrists. It qualifies the profession and delivers the guidance, development and training to ensure optometrists provide the best possible care. We recognise excellence through the College's affixes, by building the evidence base for optometry, and by raising awareness of the profession with the public, commissioners, and health care professionals.** **It is mainly funded by its members' fees.**
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]	**Yes.** **Aspire Pharma paid £1,950 for advertisements in our journal Acuity. The fee is paid directly to our publishing agency.**

If so, please state the name of manufacturer, amount, and purpose of funding.	
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To treat and stop the progression of diabetic macula oedema in order to stabilise vision.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by	This is considered an improvement in visual acuity by more than 2 lines on EDTRS chart. Secondary outcomes include a reduction in central retinal thickness.

x cm, or a reduction in disease activity by a certain amount.)	
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	No, as there are already several ways of treating and managing this condition.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	With the use of intravitreal injections such as Aflibercept or Ranibizumab or Bevacizumab but this is used outside its marketing authorisation in some NHS trusts. Laser photocoagulation can also be considered in appropriate patients. Fluocinolone acetonide intravitreal implant and Dexamethosone intravitreal implants can also be considered.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Yes, there are NICE clinical guidelines for the treatment of the condition with the following treatments: • Ranibizumab TA274 • Aflibercept TA346 • Fluocinolone acetonide TA301 • Dexamethosone TA349
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals	

across the NHS? (Please state if your experience is from outside England.)	
• What impact would the technology have on the current pathway of care?	The introduction of this treatment would mean clinicians have access to another treatment option in addition to those currently in place. Existing pathways can be utilised for people to access treatment. Individual services may need to review their service provision to account for a potential change in volume.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes
• How does healthcare resource use differ between the technology and current care?	There is a potential reduction in the frequency of people needing treatment.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care within NHS Trusts as well as independent ophthalmology providers.
• What investment is needed to introduce the technology? (For	Existing infrastructure and models of care currently in place can be utilised.

example, for facilities, equipment, or training.)	
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	
• Do you expect the technology to increase length of life more than current care?	
• Do you expect the technology to increase health-related quality of life more than current care?	People undergoing treatment may have indirect improvements in their quality of life with a reduction in frequency of treatments.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	

The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Yes. Based on initial trials, the treatment may last longer than the current treatment options. This could translate into a reduction of the overall number of treatments given and help to reduce the overall burden of treatment on the eye health system. This would be beneficial to both patients and clinical services. No new safety signals have been identified with this treatment compared to the existing treatment options already available based on current trials.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Yes. Further investigation will be needed to provide recommendations on the appropriate intervals between treatment. For example, Aflibercept and Ranibizumab are both recommended to be more effective on a Treat and Extend regime rather than PRN. Stopping rules should be considered as part of the technology appraisal, although may be better considered by a clinical guideline.

15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes Further investigation will be needed to provide recommendations on the appropriate intervals between treatment. For example, Aflibercept and Ranibizumab are both recommended to be more effective on a Treat and Extend regime rather than PRN. Stopping rules should be considered as part of the technology appraisal, although may be better considered by a clinical guideline. However, the impact is likely to be on the service provision organisation rather than a novel way of treating people with DMO.
• Is the technology a 'step-change' in the	

management of the condition?	
• Does the use of the technology address any particular unmet need of the patient population?	
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Recent studies of this treatment have shown no new or unexpected side effects. However, one would expect any side effects to be similar or identical to those present for other treatment options that are delivered using the same method, intravitreal injection. These side effects include raised intraocular pressure, retinal detachment, vitreous haemorrhage, damage to intraocular lens, heart attack, stroke and artery occlusion. Although they are extremely rare they have the potential of affecting a patient's quality of life.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
• If not, how could the results be extrapolated to the UK setting?	

• What, in your view, are the most important outcomes, and were they measured in the trials?	• Is the drug as effective than current treatment options in treating diabetic macula oedema? – This has been measured in trials. • Are there any new or unwanted side effects? - This has been measured in trials. • Is the drug more cost effective than current treatment options - This has been measured in trials.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	
20. Are you aware of any new evidence for the comparator treatments since the publication of NICE technology	

appraisal guidance (aflibercept: TA346, dexamethasone intravitreal implant: TA349, fluocinolone acetonide intravitreal implant: TA301 and TA613, ranibizumab: TA274)?	
21. How do data on real-world experience compare with the trial data?	
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	The prevalence of diabetes varies across several protected characteristics and socioeconomic groups. There might be inequalities inherent in the trial data the evidence review is based on.
22b. Consider whether these issues are different from issues with current care and why.	

Key messages
23. In up to 5 bullet points, please summarise the key messages of your submission. • Based on initial trials, the treatment effect may last longer than the current treatment options. This could help to reduce the overall number of treatments given and help to reduce the overall burden of treatment for people undergoing treatment and the eye health system. This would be beneficial to both patients and clinical services. • No new safety signals have been identified with this treatment compared to the existing treatment options already available based on current trials • The introduction of this treatment would mean clinicians have access to another treatment option in addition to those currently in place.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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NICE National Institute for Health and Care Excellence

Professional organisation submission

Faricimab for treating diabetic macular oedema [ID3899]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**The Royal College of Ophthalmologists**

3. Job title or position	[redacted]
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☒ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	The Royal College of Ophthalmologists (RCOphth) is the only professional body for medically qualified eye doctors, who specialise in the prevention, treatment and management of eye disease, including surgery to optimise care for all patients. RCOphth acts as the voice of the profession and champions excellence in the practice of ophthalmology. We set the curriculum and examinations for trainee ophthalmologists, provide continued education and training, maintain professional standards and promote research and science in the specialty. As an independent charity, we pride ourselves on providing impartial and clinically based evidence, putting patient care and safety at the heart of everything we do. We are not a regulatory body, but we work collaboratively with government, health departments, charities and eye health organisations to develop recommendations and support improvements in the co-ordination and management of hospital eye care services both nationally and regionally. RCOphth has over 3,500 members in the UK and overseas. Our strategy and areas of work are developed by our Trustees, Council and committees, who are supported by a staff of 30 employees based in our prestigious office space in Euston, London.

5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	Yes: The new RCOphth National Ophthalmology Database Age-Related Macular Degeneration (AMD) Audit is currently funded by the Macular Society, Novartis, Roche and Bayer. AMD Audit Roche £65,000 AMD Audit Bayer £65,000 and ST1 web-based animated education resource £4,000 AMD Audit Novartis £130,000 https://www.nodaudit.org.uk/news The RCOphth National Cataract Audit is currently has received funding from Alcon and Bausch + Lomb. Bausch + Lomb. £10,000 Alcon £90,520
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve	Diabetic macular oedema (DMO) is the most common cause of visual impairment in diabetes mellitus causing significant adverse effects on their ability for daily task such as reading, driving and working. The

mobility, to cure the condition, or prevent progression or disability.)	primary aim of the treatment is to improve a patient's visual acuity and prevent further irreversible established visual loss.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	A gain of 5-10 letters of best corrected visual acuity (ETDRS letter score of visual acuity) would be considered clinically significant and would impact favourable on a patients daily activity. Available therapies can achieve these results but with the need for frequent intravitreal injections. Faricimab has the potential for achieving these clinically relevant gains but with a significant reduction in the frequency of injections. The reduction in the frequency of injections whilst maintaining the gains in vision would have a significant impact on the burden of injection visits for patients and health service alike.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Although existing treatment with anti-VEGF intravitreal injections and /or steroid implants has had a major impact in improving the care of patients with DMO and preventing blindness the need for frequent injections or monitoring for side effects such as raised intra-ocular pressure in the case of steroids is a significant challenge for both patients and health care providers. There is a significant unmet need for treatments with a reduced frequency of delivery and monitoring.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	DMO is routinely screened for in the UK annual Diabetic Retinopathy Screening Service. In addition, patients are identified through a range of different routes including community optometric examination and opportunistic dilated examination in ophthalmic clinics. Once identified pts are either observed at 3-4 monthly intervals in the hospital eye service if the have mild DMO with no or minimal visual disturbance. However, if the DMO is affecting the central macula (foveal involving) and central acuity is affected then treatment options include focal thermal laser, antivegf intravitreal injections (Licensed Ranibizumab or

	Aflibercept as per NICE TAs 274 and 346 respectively if the central retinal thickness is > 400um – this is approximately 50% of patients with DMO), intravitreal steroid implants if pseudophakic and non responsive/not suitable for anti-VEGF (as per NICE TAs 349 and 613) and occasional off label treatment with bevacizumab if central retinal thickness is < 400um.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	The Royal College of Ophthalmologists Guidelines are used as a benchmark reference for management of DMO (https://www.rcophth.ac.uk/wp-content/uploads/2014/12/2013-SCI-301-FINAL-DR-GUIDELINES-DEC-2012-updated-July-2013.pdf) More recently the Guidelines for the Management of Diabetic Macular Edema by the European Society of Retinal Specialists (EURETINA) have given a more contemporaneous update on this condition and specific recommendations that are considered a useful resource. (https://www.euretina.org/resource/guidelines-for-the-management-of-diabetic-macular-edema-by-the-european-society-of-retina-specialists-euretina/)
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The general pathway as outlined above in section 9 with regards laser, antivegf and steroid implant use is reasonably well established. In general, aflibercept is used first line more often than ranibizumab. However there are variations in the particular regimes used for intravitreal antiVEGf injections. Some units use fixed dosing regimes (eg bimonthly Aflibercept), some a closely monitored fixed PRN monitoring regime after maximal visual function and/or anatomical benefit has been reached and some a pro-active “Treat and Extend” regime where by intravitreal injection interval is individualised to patients whilst maintain an absence of DMO.
• What impact would the technology have on the current pathway of care?	The Faricimab technology under consideration would fit well into the current pathways of management as the monitoring and delivery is familiar to units treating DMO. The potential for extending the intervals between either fixed dosing or treat and extend interval regimes is promising and if real world experience mirrors similar pivotal trial data then it certainly has the potential to rapidly become the first line treatment option for DMO

10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	As stated above, The Faricimab technology under consideration would fit well into the current pathways of management as the monitoring and delivery is familiar to units treating DMO. The potential for extending the treatment intervals, whichever regime is used, would be greatly welcomed by patients and health care providers alike. The pivotal trials of Farcimab in DMO use a "Personalised Treatment Interval" which is akin to the commonly used "treat and extend" regime used in the management of many medical retinal disorders including Age related macular degeneration (AMD), retinal vein occlusion and DMO
• How does healthcare resource use differ between the technology and current care?	Most intravitreal injections in the UK are delivered by allied health care providers (majority nurses) under supervision by a Consultant Ophthalmologists. The technology under appraisal is very similar to the currently used intravitreal injections in terms of how it is delivered and should not pose a barrier to delivery. No specific change would be needed in existing units to monitor/deliver the proposed Faricimab technology.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Most intravitreal injections are provided under supervision of secondary care Consultant Ophthalmologists. The model of delivery varies from region to region in terms of venue – most are secondary care Ophthalmic departments, some are community outreach clinics and some mobile delivery units in easily accessible sites (eg supermarket carparks)
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	There will need to be some educational launch resources in terms of learning about the technology and its potential benefits. However, the use of intravitreal injections and the assessment/management decision pathway are all familiar with the new technology and thus no significant barriers are envisaged to its appropriate use in existing facilities with the standard equipment.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	It is likely that the Faricimab will provide an incremental improvement in terms of durability of reducing the macular oedema and improving visual acuity beyond existing NICE approved technologies for DMO. The opportunity to extend the treatment intervals between intravitreal injections would be greatly welcomed by both patients and healthcare providers

• Do you expect the technology to increase length of life more than current care?	No
• Do you expect the technology to increase health-related quality of life more than current care?	Yes – “burden of treatment” in terms of returning for repeated intravitreal injections is often mentioned by patients and thus if we can reduce the frequency of these injection/monitoring visits whilst maintain improvements in visual acuity this will have a positive effect on quality of life.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Patients affected with Diabetes and DMO have many numerous healthcare visits and touch points and thus any technology which reduces the frequency of visits will have a significant benefit to the them
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for	The technology will be very similar in the use to current standard of care. The delivery of intravitreal injections and the assessment/management decision pathway are all familiar with the new technology and thus no significant barriers are envisaged to its appropriate use in existing facilities with the standard equipment. No extra specific tests are required for assessment or delivery of the proposed new technology

example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Current NICE Guidance for antiVEGF treatment restricts use to patients with DMO and a central thickness of >400um. This is approximately 50% of the DMO cohort and thus the group of patients with <400um thickness (the other 50%) have suboptimal options in terms of destructive focal laser therapy or off label bevacizumab (used only in a few units). It would be helpful if patients with DMO but <400um could also be considered for treatment, assuming pivotal trials demonstrate a positive result. Often this cohort of patients effectively stay in limbo until there DMO progresses to >400um when licensed NICE approved Ranibziumab or Aflibercept can then be given. This cause concern and worry for patients and increased monitoring by health care providers watching for this threshold to be reached. In general terms if no or minimal improvement in vison and/or anatomical parameters are seen after 3 initial injections of the existing agents or this new technology then an alternative treatment would be sought (eg steroid implant, vitrectomy surgery). Different regimes have different stopping rules and it is likely that the new technology would be having similar informal rules. For instance, in fixed dosing regimes if anatomical and functional parameters are

	stable for >12mths then a trial of no treatment is considered. In “Treat and Extend” regimes once the maximal interval has been reached for >12mths then a trial of no treatment is considered. These are very informal rules and are variably adhered to based on individual patient or ophthalmic unit factors.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	The QALY calculation based on utility scores has been driven by high contract visual acuity changes. Although this method is robust and has it clear merits the derived utility scores may not fully reflect the improved quality of life changes experienced by patients in terms of contrast sensitivity, visual function in low light, reading speed ability etc.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	The innovative nature of this technology in terms of using Ang-2 blockade in partnership with the well established anti VEGF effect in DMO has the potential to have a significant and substantial impact on patients in terms of reduced injection intervals. This will have benefits for patients and healthcare providers freeing up resources and time to see the growing number of DMO patients.

• Is the technology a 'step-change' in the management of the condition?	The technology has potential for an incremental step change in improving care of patients with DMO in terms of increased durability in particular.
• Does the use of the technology address any particular unmet need of the patient population?	The repeated injection burden for patients is directly positively influenced by the introduction of the new technology
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The side effect profile of the novel Faricimab technology is equivalent to the side effect profiles of commonly used anti VEGFF used in current practice. No novel side effects have been identified. The most feared complication of antiVEGF injections is infective endophthalmtis whch can severely educe visual acuity. The rate for antiVEGF injections is thankfully low in the region of 1 every 2000 injections. Any technology that reduces the frequency of these injections is likely to positively influence he over all life time risk for the patient of this complication.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	The RHINE and YOSEMITE clinical trials compare Faricimab to the most commonly used antiVEGF for DMO in the UK namely Aflibercept. The Aflibercept bimonthly comparator arm of these trials reflect current UK use of licensed and NICE approved Aflibercept.

• If not, how could the results be extrapolated to the UK setting?	In the UK Aflibercept is reserved for DMO >400um thickness whilst the trail did include patients with <400um DMO – however the mean central retinal thickness in the trials was approximately 480um and thus is reflective of current UK standard of care.
• What, in your view, are the most important outcomes, and were they measured in the trials?	The ability to extend the treatment intervals with intravitreal Faricimab upto 12 weeks in >70% in trial participants and 16 weeks in >50% in trial participants without compromising visual acuity gains compared to routine standard of care is impressive and reassuring as a potential incremental step forward in care for the patients.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Anatomical gains and stability in OCT thickness of central retina thickness are commonly used in cliinacl practice as signs of effective treatment response.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	The side effect profile of the novel Faricimab technology is equivalent to the side effect profiles of commonly used anti VEGFF used in current practice. No novel side effects have been identified.
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No

20. Are you aware of any new evidence for the comparator treatments since the publication of NICE technology appraisal guidance (aflibercept: TA346, dexamethasone intravitreal implant: TA349, fluocinolone acetonide intravitreal implant: TA301 and TA613, ranibizumab: TA274)?	DRCR.net Protocol T is a key paper in comparing Aflibercept to Bevacizumab to Ranibizumab (0.3mg dsoe – used in US varies to 0.5mg dose in UK). Aflibercept and Ranibizumab showed anatomical superiority to Bevacizumab for DMO patients and Aflibercept showed visual function benefits over Ranibzimumab (1yr) and Bevacizumab (2yrs). Excellent contemporaneous review in EURETINA DMO Guidelines (https://www.euretina.org/resource/guidelines-for-the-management-of-diabetic-macular-edema-by-the-european-society-of-retina-specialists-euretina/)
21. How do data on real-world experience compare with the trial data?	No real world data available for Faricimab
Equality	
22a. Are there any potential equality issues that should be	No

taken into account when considering this treatment?	
22b. Consider whether these issues are different from issues with current care and why.	No

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.

- DMO has a significant impact on patients quality of life and activities of daily living
- Over past decade the availability of licensed and NICE approved technologies, in particular, antiVEGf have revolutionized the care of DMO patients by improving vision and maintaining this sustained improvement.
- The burden of repeated intravitreal injections for DMO affects patients and healthcare providers
- Robust 1 year data from RHINE/YOSEMITE DMO trials of Faricimab versus the most commonly used comparator treatment in UK DMO care (Aflibercept) has shown encouraging results
- The ability to extend the treatment intervals with intravitreal Faricimab upto 12 weeks in >70% of trial participants and upto16 weeks in >50% of trial participants without compromising visual acuity gains compared to routine standard of care is impressive and reassuring as a potential incremental step forward in care for the patients.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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NICE National Institute for Health and Care Excellence

Clinical expert statement

Faricimab for treating diabetic macular oedema [ID3899]

Thank you for agreeing to comment on the ERG report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form:

- In **part 1** we are asking you to complete questions where we ask for your views on this technology. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.
- In **part 2** we are asking you to provide 5 summary sentences on the main points contained in this document.

Please return this form by **5pm** on **Friday 26 November 2021**

Completing this form

Important information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Do not include medical information about yourself or another person that could identify you or the other person.

- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow.If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

PART 1 – Treating a patient with this condition and current treatment options	
About you	
1. Your name	**Jagdeep Singh**
2. Name of organisation	**College of Optometrists**
3. Job title or position	**Specialist Optometrist**
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it

encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☒ yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	
The aim of treatment for this condition	
8. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	

9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	
10. In your view, is there an unmet need for patients and healthcare professionals in this condition?	
What is the expected place of the technology in current practice?	
11. How is the condition currently treated in the NHS?	
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please	

state if your experience is from outside England.)	
• What impact would the technology have on the current pathway of care?	
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	
13. Do you expect the technology to provide clinically meaningful	

benefits compared with current care?	
• Do you expect the technology to increase length of life more than current care?	
• Do you expect the technology to increase health-related quality of life more than current care?	
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	
The use of the technology	
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant	

treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it	

improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	
• Does the use of the technology address any particular unmet need of the patient population?	
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	
Sources of evidence	
20. Do the clinical trials on the technology reflect current UK clinical practice?	
• If not, how could the results be extrapolated to the UK setting?	

• What, in your view, are the most important outcomes, and were they measured in the trials?	
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA346 and TA274?	

23. How do data on real-world experience compare with the trial data?	
Equality	
24a. Are there any potential equality issues that should be taken into account when considering this treatment?	
24b. Consider whether these issues are different from issues with current care and why.	
Topic-specific questions	
25. What proportion of patients in this population are treated with aflibercept and ranibizumab respectively?	Approximately 65 per cent
26. Are aflibercept and ranibizumab considered	No. Some studies have shown a greater efficacy with aflibercept compared to ranibizumab

clinically equivalent for treating this population?	
27. Is the dosing of aflibercept and ranibizumab equivalent and are the assumptions around dosing in the company submission plausible? • *(Please look at document B, section B.1.3.1 Table 3 for the dosing regimens and section B.4.2.4 Table 28 for the dosing assumptions)*	No the dosing regimens for aflibercept and ranibizumab are different.
28. Are the assumptions around dosing in the company submission reflective of updates made since the previous appraisals (aflibercept (TA346) and ranibizumab (TA274))? • *(A key assumption and driver of cost effectiveness in the*	Yes

aflibercept appraisal (TA346) was the number of ranibizumab injections at year 1: 7.93 injections and 12 monitoring visits. It was noted in the guidance that the summary of product characteristics for ranibizumab had recently changed to reduce the number of monitoring visits needed in the first year).	
29. Have there been substantial changes to the treatment pathway since the appraisals of aflibercept and ranibizumab?	No, they have remained relatively the same
30. Have there been any changes to clinical practice that might increase or decrease healthcare resource costs since the appraisals of aflibercept and ranibizumab?	Outbreak of COVID-19 and the issues this has had on healthcare provision and availability. Virtual reviews being considered and implemented amongst many NHS Trusts.

31. Would you expect the relative efficacy and safety of faricimab and the comparators (aflibercept and ranibizumab) to be the same in people with diabetic macular oedema regardless of their central retina thickness?	Yes

PART 2 -Key messages
32. In up to 5 sentences, please summarise the key messages of your statement: • • • • •

Thank you for your time.

Please log in to your NICE Docs account to upload your completed document, declaration of interest form and consent form.

……

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

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NICE National Institute for Health and Care Excellence

Clinical expert statement

Faricimab for treating diabetic macular oedema [ID3899]

Thank you for agreeing to comment on the ERG report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form:

- In **part 1** we are asking you to complete questions where we ask for your views on this technology. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.
- In **part 2** we are asking you to provide 5 summary sentences on the main points contained in this document.

Please return this form by **5pm** on **Friday 26 November 2021**

Completing this form

Important information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Do not include medical information about yourself or another person that could identify you or the other person.

- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow.If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

PART 1 – Treating a patient with this condition and current treatment options	
About you	
1. Your name	**Richard P. Gale**
2. Name of organisation	**York Teaching Hospital NHS Foundation Trust**
3. Job title or position	**Consultant Medical Ophthalmologist, Honorary Professor, University of York**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? **x**☐ a specialist in the treatment of people with this condition? ☐ **x** a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would	☐**x** yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it

encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**Nil**
The aim of treatment for this condition	
8. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To maintain, if not improve vision of people affected by diabetic macular oedema.

9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Prevention of vision loss (>/= 15 ETDRS letters) in 95% Mean gain in vision of 5 >/= ETDRS letters
10. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes Treatments to provide, better efficacy with reduced burden (number of treatments of visits).
What is the expected place of the technology in current practice?	
11. How is the condition currently treated in the NHS?	**For vision affecting centre involving DMO:** If central retinal thickness is >/= 400um licensed anti-VEGF (Lucentis or Eylea) given by intravitreal injection. In those that are not suitable for anti -VEGF, had previous cataract surgery, Dexamethasone or fluocinolone implants are an option. These are largely considered second line. For those <400um macular laser (if 'clinically significant macular oedema'), unlicensed treatments or non-NHS funded treatments. **For non centre involving 'clinical significant macular oedema'** Macular laser. Used much less now intravitreal treatments are available

• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Royal College of Ophthalmologist's guidelines (Dec 2012) NICE guidelines TA272, TA346, TA349, TA 613 Published clinical guidelines e.g. Amoaku et EYE, 34 1-51 (2020)
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	A number of different treatments exist and a number of different posologies have been studied. This has lead to inconsistency in how clinicians interpret the optimal manage their patients in their setting. An example is that after the initiation (loading) phase some clinicians will use a treat and extend approach and other will use a modified prn (as required) approach. Definition of adequate response is poorly understood and hence the time of any potential treatment switch is variable amongst clinicians
• What impact would the technology have on the current pathway of care?	Reduction in the number or treatments, although a clinically useable posology need to be established. This will help with service capacity. Possible increased efficacy (better drying effect on the macular, but this is not certain) Another treatment option will be available
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	It will be given in the same way as established licences anti-VEGF treatments, via intravitreal injection. Clinical services are already established to deliver this, although under strain due to lack of capacity. A clinically useable posology needs to be established.
• How does healthcare resource use differ between the technology and current care?	Very similar- see above.
• In what clinical setting should the technology be	Specialist clinics with established intravitreal services.

used? (For example, primary or secondary care, specialist clinics.)	
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Education about the posology and monitoring. This would replace rather than add to existing treatments, unless access to treatment is made easier with central retain thickness less than 400um being approved as a treatment criteria.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes.
• Do you expect the technology to increase length of life more than current care?	No
• Do you expect the technology to increase health-related quality of life more than current care?	Less treatment burden with the posology, yes.
14. Are there any groups of people for whom the technology would be more or less effective	Appropriate for all. There may be some sub population where effectiveness is better. Sub group analyses with pervious similar intravitreal technologies used in DMO demonstrated that those with worse starting visual acuity has a greater response (DRCR.net Protocol T)

(or appropriate) than the general population?	
The use of the technology	
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	If fewer treatments are required then burden will be reduced on patients and services. The actual treatment method will be very similar. Patient and clinics education will be important.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	To start: Centre involving vision affecting diabetic macular oedema. Ideally no central retinal thickness threshold for treatment but precedent already setting for other intravitreal technologies used in DMO.

	Not advised in pregnancy or breast feeding. The phase 3 clinical trials have not recommended a stopping point however some clinical guidelines such as those used by the DRCR.net study group (in particular Protocol T) have suggested success criteria. The same technologies that are used now (visual acuity measurement and OCT to determine retinal thickness) can be used for such criteria.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes. Its dual mode of action via the anti-VEGF and Ang-2 pathways makes the technology innovative. The reduction in number of treatments, should impact on current unmet needs.

• Is the technology a 'step-change' in the management of the condition?	Yes.
• Does the use of the technology address any particular unmet need of the patient population?	Yes. The potential reduction in number of treatments should impact on current unmet needs.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The principle side effects of the treatment are similar to ones experienced for existing intravitreal technologies. These are generally well tolerated. Similar emergent technologies have demonstrated a small percentage of individuals being affected by ocular inflammation side effects. These are particularly important if they lead to occlusive vasculitis. This technology, so far, does not appear to have this occlusive side effect.
Sources of evidence	
20. Do the clinical trials on the technology reflect current UK clinical practice?	Largely yes in term of the treatment, but the posology needs addressing. The PTI as used in the study is complex and would need simplifying to enable cohesion of clinical practice. There may be concern about implementing a whole new posology for a different technology due to necessary changes in clinical pathways of assessment. I suspect many clinicians may use either a simpler Treat and Extend approach or less commonly a form of as required posology extrapolated from experience with Lucentis or Eylea.
• If not, how could the results be extrapolated to the UK setting?	See above. Treat and extend regimens often use 2 or 4 weekly increments in UK practice.

• What, in your view, are the most important outcomes, and were they measured in the trials?	Visual acuity mean gain, central retinal thickness mean change, number of treatments in time frame. Safety signals appropriate. Yes all measured.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Central retinal thickness is a surrogate for efficacy and a reasonable one. Central retinal thickness has a relationship with visual acuity, although not always a good correlate, certainly in the short term. Visual acuity measurement is not a perfect marker of overall visual function but is used as a marker of Quality of life. The measures used in the phase three studies are appropriate.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No but brolicizumab (Novartis) has reminded the ophthalmic community about the importance of clinical vigilance and a phase 4 programme to help identify and unsuspected adverse events. The formation of Anti Drug Antibodies and their subsequent effects is an important consideration. The safety of monthly treatment needs to be evaluated (this is theoretically possible with the proposed posology and indeed was with the phase 3 studies)
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. Are you aware of any new evidence for the comparator treatment(s) since the publication	TA349 and TA 613 but these are often second line.

of NICE technology appraisal guidance TA346 and TA274?	
23. How do data on real-world experience compare with the trial data?	Generally the visual acuity outcomes are not as good (Egan, BJOphthalmol, 2016;0;1-6, Cuilla et al, Br J Ophthalmol April 2020, Korobelnik et al, Graefes Arch Cli Exp Ophthlamol 2020;258:521-528). This is due to under treatment (lack of access or a broader inclusion criteria). Some series are comparable when intense initial year treatment is used. (Lukic et al, Eur J Ophthalmology 2020;30:557-562)
Equality	
24a. Are there any potential equality issues that should be taken into account when considering this treatment?	None known
24b. Consider whether these issues are different from issues with current care and why.	
Topic-specific questions	
25. What proportion of patients in this population are treated with aflibercept and ranibizumab respectively?	This is an estimate but I suspect more are being treated with aflibercept (60%) than ranibizumab (30%). Around 5% with dexamethasone or fluocinalone, 5% off label bevacizumab

26. Are aflibercept and ranibizumab considered clinically equivalent for treating this population?	The perception is that aflibercept has marginal greater efficacy / clinical effectiveness particularly for those with worse starting visual acuity.
27. Is the dosing of aflibercept and ranibizumab equivalent and are the assumptions around dosing in the company submission plausible? • *(Please look at document B, section B.1.3.1 Table 3 for the dosing regimens and section B.4.2.4 Table 28 for the dosing assumptions)*	Many centres will use predominantly one treatment over the other. Although some clinicians use different treatment regimens for different drugs- similar to that suggested in table 3, many will use the same posology for either treatment, especially if both treatments are used in one centre. This is to try to reduce the chance of posology error particularly when much of the service is being delivered by non-doctor grade staff following protocols in very busy clinical settings.
28. Are the assumptions around dosing in the company submission reflective of updates made since the previous appraisals (aflibercept (TA346) and ranibizumab (TA274))?	Yes the SmPC for Lucentis allows a Treat and Extend approach with monthly extensions.

• *(A key assumption and driver of cost effectiveness in the aflibercept appraisal (TA346) was the number of ranibizumab injections at year 1: 7.93 injections and 12 monitoring visits. It was noted in the guidance that the summary of product characteristics for ranibizumab had recently changed to reduce the number of monitoring visits needed in the first year).*	
29. Have there been substantial changes to the treatment pathway since the appraisals of aflibercept and ranibizumab?	Change's to the SmPC for Lucentis as above may mean more clinicians will use a Treat and extend approach and reduced the number of monitoring visits. Eylea SpMC advised Loading then fixed for the first year before No monitoring required between injections. Treat and Extend with interval change by 2 weeks. It is likely that many clinician are using Treat and extend from after the loading phase. I am unsure how many clinics are using a prn now this data would be useful however the number of monitoring visits in table 28 needs revising down for the first 2 years to reflect this i.e. zero if not close to zero.

	It is reasonable to assume that at year three there will be more as required visits (i.e. monitoring).
30. Have there been any changes to clinical practice that might increase or decrease healthcare resource costs since the appraisals of aflibercept and ranibizumab?	The majority of injections are now given by non physicians. Many centres are also using non physician assessors. The main driver of this is to meet demand.
31. Would you expect the relative efficacy and safety of faricimab and the comparators (aflibercept and ranibizumab) to be the same in people with diabetic macular oedema regardless of their central retina thickness?	Difficult to be certain re efficacy. There is some signal towards better drying of the retina in the loading phases of the Yosemite trial in particular with faricimab. However this did not translate to a difference in visual acuity. Protocol T (DRCR.net) found a difference in efficacy between higher and lower starting visual acuity between ranibizumab, and aflibercept. No differences in safety expected.

PART 2 -Key messages
32. In up to 5 sentences, please summarise the key messages of your statement: • Diabetic Macular Oedema is a very important disease process and its burden will increase. New treatments and technologies are welcomed. Faricimab should be supported as it provides a step wise increment forward in the management of Diabetic Macular Oedema • Faricimab provides equivalent visual acuity efficacy with the potential for less treatments and hence help with burden to patients, carers and health care systems. This may help capacity current issues. • Faricimab may dry the retina better than its comparator but the significance of this is unknown and requires further investigation. • No clinically meaningful new safety signals have been identified but a robust motoring strategy needs to be established • Clarity on treatment posology recommendations that are easily implemented, are required. Patient and clinician education will be required.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed document, declaration of interest form and consent form.

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Your privacy

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Patient expert statement

Faricimab for treating diabetic macular oedema [ID3899]

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

About this Form

In **part 1** we are asking you to complete questions about living with or caring for a patient with the condition.

In **part 2** we are asking you to provide 5 summary sentences on the main points contained in this document.

If you have any questions or need help with completing this form please email the public involvement team via pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please return this form by **5pm** on **Friday 26 November 2021**

Completing this form

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide.

You do not have to answer every question – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee. The text boxes will expand as you type.

Important information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 15 pages.

PART 1 – Living with or caring for a patient with this condition and current treatment options	
About you	
1.Your name	Bernadette Warren
2. Are you (please tick all that apply):	☒ a patient with this condition? ☐ a patient with experience of the treatment being evaluated? ☐ a carer of a patient with this condition? ☐ a patient organisation employee or volunteer? ☐ other (please specify):
3. Name of your nominating organisation.	Macular Society
4. Has your nominating organisation provided a submission? Please tick all options that apply.	☐ No, (please review all the questions below and provide answers where possible)

	☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing a statement
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience. ☒ I have other relevant knowledge/experience (e.g. I am drawing on others' experiences). Please specify what other experience: My other experience come from conversations that have been had on a one to one basis or with groups of others with DMO through the facebook group 'Diabetic retinopathy uk support group' as well as the Macular Society DMO support group

	which met on line in September, October and November 2021. these people reside all across the UK ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☒ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
Living with the condition	
6. What is your experience of living with this condition? If you are a carer (for someone with this condition) please share your experience of caring for them.	I was diagnosed with DMO (CSMO) in 2011 at the time I was in my early 40's working as a teacher in a primary school I am married and at the time of diagnosis my children were aged 12 and 14. Little did I know the severe impact that this condition would have not only on myself but on my family and friends too. Below I describe the treatment I have had for DMO and the

	impact the condition has had on myself and my family. **Treatment** Once I had been diagnosed treatment started promptly with injections in both eyes, but it soon became apparent that my left eye which was my best seeing eye then was not responding. A Fluorescein Angiogram was performed in 2015 and it was found I had ischemia in that eye and so all treatment for that eye stopped. My vision in that eye at the start of treatment was 6/9 it is now 1/60 (snellen). We were able to carry on treatment with my right eye and to date I have had over 90 injections in that eye. My vision at the start of treatment was 6/12 and it is now 6/24-30 Unfortunately with the injections I developed cataracts that then caused ocular hypertension for which I had bilateral iridotomies in 2016. My injections have generally caused no short term issues however in September 2021 and November of the same

	year I developed corneal abrasions after my injections these were extremely painful and far worse than the injection itself. On examination I was found to have very dry eyes and now take Clinitas 4 times a day as well as Carbomer eye gel at night. At a recent appointment I was told the dry eye syndrome could well be a complication of diabetes as well as having the injections. Not many clinicians I have seen know of many (if any) patients that have had so many injections. We have tried all 3 drugs available, unfortunately I could not try any steroid implants as I have been found to be a steroid responder (someone who experiences raised intraocular pressure while taking steroid medication). This means the only drug available to me are VEG-F drugs. **Impact** The impact of DMO has been huge not only on my physical life but at times my mental health too. As already stated when diagnosed I was

	starting middle age and was working as well as driving and very much enjoying life. Within 14 months of diagnosis I lost my beloved job and the following year my driving license. The loss was so quick and sudden it took me 6 months to regain any feeling of self worth. Feelings of guilt and shame overwhelmed me and I honestly did not know what I would do with my life whilst trying to set a good example to my children and supporting my husband financially as well as with all the practical issues bringing up children bring. My eldest daughter started to blame herself because at that time it was thought my diabetes had been gestational. It has been a really hard few years. I have attended appointments every month for DMO since 2011. I have great difficulty with my sight and was registered sight impaired in 2016. Difficulties include recognising peoples faces, colours, reading of text and contrast. As someone with poor sight I have missed out on clearly seeing

	some of the things I would normally see without issue such as the recent graduation of both my daughters, and last year the funerals of my father and father-in-law. Everyday life is a challenge with many forgetting or not realising I have a sight issue, though more often than not I do use a long cane now which helps. On a day-to-day basis life with DMO has been a struggle, not being able to drive has left me dependent on public transport or family or friends giving me a lift. My husband has recently been away for six weeks and so the onus has been on my daughter to take me and collect me from places I want to go and to be honest the embarrassment of asking for a lift or the effort to go by public transport is sometimes too much to bear and I stay at home. When going out socially with my husband he can never enjoy a drink because he will always be the driver and that has made me feel guilty.

	Recently my hospital appointments for diabetes have changed to a hospital I cannot get to by public transport and it has made me feel annoyed that my needs have not been met especially as my appointments used to be at a hospital just down the road from me. it was only when I pointed this out and said I might need to change hospitals that they gave me an appointment more easily accessible. Things I used to enjoy doing are now difficult and my hobbies and interests have had to adapt. I have however tried to remain positive and concentrate on things I can do not things I can't but I miss the things I so enjoyed doing such as driving to garden centres and walking around on my own for a couple of hours having some 'me' time or being able to nip down to supermarket to get the items I have run out of. I now struggle to recognise friends as I go about my business I just don't see them and unless they say 'Hello' I just don't know who they are.

	As mentioned earlier people often forget I have sight loss and because they can see well they forget I cannot. I often end up confused and left out of conversations because I can't see what others are referring too, this is particularly the case when watching television.
Current treatment of the condition in the NHS	
7a. What do you think of the current treatments and care available for this condition on the NHS?	At the moment the main treatment option is injection therapy. Those with diabetes not just myself are told many a time that diabetes can sometimes complicate the way we respond to treatments whether that be for the eyes or any other part of the body. Many for example are given 5 loading injections for DMO instead of the usual 3 as “Diabetics sometimes take longer to respond to treatment”. I am an active Facebook user and often see posts on ‘Diabetic retinopathy UK support group’ page and it does seem to be a difference in care and treatment for DMO around the country which can lead to confusion and misunderstanding. I also found this when taking part and helping to

	lead the Macular Society DMO support group. One example of this involves after care. Once an injection has been administrated some are given chloramphenicol antibiotic eye drops to be taken for 4 days after an injection some are not. When I questioned why these were not given at a hospital I was told that they did not want someone to build up an immunity to it incase it was really needed for an actual infection yet my hospital give them to me each month and it leads me to wonder should I take them or not. Another example is that some hospitals have a 'One stop shop' appointment system but some do not. A friend of mine has to attend one appointment for the assessment and another for the injection this not only takes up a lot of time but also costs twice as much to attend by public transport.

7b. How do your views on these current treatments compare to those of other people that you may be aware of?	Lastly I have felt myself that at times we with DMO are being left behind as far as drugs and research go and that those with AMD are given priority over us. It is only in the last two months that I have heard of any research for DMO. Through conversations I found I am not the only one who has felt this way. The role out of ranibizumab helped to fuel this thought as it was offered for AMD many months before it was offered to myself. I had to sit next to patients receiving the very drug I and my ophthalmologist were desperate for me to try. 7b. The views that I have are very similar to those of the others that I have responded with for example when I asked about research not one person with DMO knew that any research primarily for DMO takes place, only that of AMD. In the DMO support group patients described their treatments and it was surprising to find how different their experiences were which led to some confusion and some feelings of insecurity

	over the way their treatment was manged. This was particularly in the case of the antibacterial eye drops which were given to some patients and not others.
8. If there are disadvantages for patients of **current NHS treatments** for this condition (for example how the treatment is given or taken, side effects of treatment etc) please describe these	There are some disadvantages of the current treatments for DMO some of these are relevant to me some to others I have communicated with over the years. he disadvantages are listed below **Time** - some even take the day off work not just themselves but a career too so that they can attend an appointment without using public transport. One employer insisted that a patient took time off for treatment as part of her annual leave. **Complications** Like me the injections can lead to other complications such as *cataracts* then *ocular hypertension*. I have cataracts (posterior subcapsular as well as nuclear) in my right eye

	which is the one having injection therapy. It is my best seeing eye and causes many issues with contrast and glare. Short term complications such as *corneal abrasions* are very painful and *dry eyes* need careful and time-consuming management. Many I have heard directly from have a *reaction to the iodine* administrated this can be very painful leading to anxiety for following appointments. Many have eyes washed out afterwards which can help but takes extra time and can be stressful. *Infection* is also a risk though I have never had this happen to me **Aftercare** The taking of antibiotics for some can be an issue these need to be kept in the fridge but if taking them 4 times a day if away from home this can be problematic.

	After an injection vision can remain blurred for many hours for me I have to get 2 buses home and my sight is very blurred this is even more difficult if appointments are in the afternoon when it can get dark quickly in the winter.
Advantages of this treatment	
9a. If there are advantages of this treatment over current treatments on the NHS please describe these. For example, the impact on your Quality of Life your ability to continue work, education, self-care, and care for others? 9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?	I have read the Final Scope. It has as I can see two main advantages. Firstly, it targets two growth factors instead of just the one. This is a real change from the other treatments available which for those with DMO seemed only to have an advantage of the length between injections which for me turned out to be no advantage at all. The fact that it targets another growth factor could be exactly what some patients need. I myself have not really responded to the drug I am currently on but this one maybe the very drug I need to see real improvements in both my sight and quality of life. Managing my diabetes has become more challenging and this drug may make that far

9c. Does this treatment help to overcome/address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these.	easier for me. Secondly, timing (I have heard) the interval between injections maybe far longer than the current 'up to 8 weeks' if it can be lengthened further than the present timings it will have a huge positive impact on the quality of life for both patients and their families. The advantages could be far reaching.
Disadvantages of this treatment	
10. If there are disadvantages of this treatment over current treatments on the NHS please describe these? For example, are there any risks with this treatment? If you are concerned about any potential side affects you have heard about, please describe them and explain why.	Not known.

Patient population	
11. Are there any groups of patients who might benefit more from this treatment or any who may benefit less? If so, please describe them and explain why. Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	As a patient it seems as if each new drug that has been brought to market has improvements over the last and the same is here. The fact that this is being targeted for those with DMO will mean that this group on the whole will benefit. This may well benefit those who have not trialled any other treatment those like me who have had treatment for a while may not see a great change though they and I live in hope. For those who are steroid responders it will be welcome news that this is not a steroid drug. Those that will not benefit will be those like me who have DMO with ischemia in one or both eyes and I see this drug as a disappointment for them that this will not address this issue.

Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme	I am not aware of any equality issues apart from a language barrier that might present itself for those who do not have English as their primary language.

More general information about the Equality Act can and equalities issues can be found at https://www.gov.uk/government/publications/easy-read-the-equality-act-making-equality-real and https://www.gov.uk/discrimination-your-rights.	
Other issues	
13. Are there any other issues that you would like the committee to consider?	DMO in its very nature combines 2 chronic conditions. I have found during the last ten years that my diabetes team know very little about DMO and what causes it. I believe that better communication is needed between diabetes experts/consultants and opthalmologists so that each can learn from each other about the challenges of both diabetes and DMO and in particular what causes DMO.

PART 3 -Key messages

14. In up to 5 sentences, please summarise the key messages of your statement:

- DMO can have a huge negative impact on a person's life leading to job loss and the ability to drive
- DMO can lead to further eye complications such as dry eye syndrome and cataracts which can cause further sight loss
- DMO treatment and after care is not the same across the UK
- Those with DMO do not realise that research takes place for them as well as AMD
- Faricimab offers real hope for those who are yet to respond positively to treatment.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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NICE National Institute for Health and Care Excellence

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NICE National Institute for Health and Care Excellence

Patient expert statement

Faricimab for treating diabetic macular oedema [ID3899]

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

About this Form
In **part 1** we are asking you to complete questions about living with or caring for a patient with the condition.
In **part 2** we are asking you to provide 5 summary sentences on the main points contained in this document.

If you have any questions or need help with completing this form please email the public involvement team via pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please return this form by **5pm** on **Friday 26 November 2021**

Completing this form
Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee. The text boxes will expand as you type.

Important information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable

- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 15 pages.

PART 1 – Living with or caring for a patient with this condition and current treatment options	
About you	
1.Your name	**Stephen Scowcroft**
2. Are you (please tick all that apply):	☐ a patient with this condition? ☐ a patient with experience of the treatment being evaluated? ☐ a carer of a patient with this condition? ☒ a patient organisation employee or volunteer? ☐ other (please specify):
3. Name of your nominating organisation.	Macular Society
4. Has your nominating organisation provided a submission? Please tick all options that apply.	☐ No, (please review all the questions below and provide answers where possible) ☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☒ Yes, I authored / was a contributor to my nominating organisations submission

	☒ I agree with it and **do not wish to** complete this statement ☐ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☐ I am drawing from personal experience. ☐ I have other relevant knowledge/experience (e.g. I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
Living with the condition	
6. What is your experience of living with this condition? If you are a carer (for someone with this condition) please share your experience of caring for them.	
Current treatment of the condition in the NHS	
7a. What do you think of the current treatments and care available for this condition on the NHS?	

7b. How do your views on these current treatments compare to those of other people that you may be aware of?	
8. If there are disadvantages for patients of **current NHS treatments** for this condition (for example how the treatment is given or taken, side effects of treatment etc) please describe these	
Advantages of this treatment	
9a. If there are advantages of this treatment over current treatments on the NHS please describe these. For example, the impact on your Quality of Life your ability to continue work, education, self-care, and care for others? 9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? 9c. Does this treatment help to overcome/address any of the listed disadvantages of current treatment	

that you have described in question 8? If so, please describe these.	
Disadvantages of this treatment	
10. If there are disadvantages of this treatment over current treatments on the NHS please describe these? For example, are there any risks with this treatment? If you are concerned about any potential side affects you have heard about, please describe them and explain why.	
Patient population	
11. Are there any groups of patients who might benefit more from this treatment or any who may benefit less? If so, please describe them and explain why. Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	

Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme More general information about the Equality Act can and equalities issues can be found at https://www.gov.uk/government/publications/easy-read-the-equality-act-making-equality-	

real and https://www.gov.uk/discrimination-your-rights.	
Other issues	
13. Are there any other issues that you would like the committee to consider?	

PART 3 -Key messages
14. In up to 5 sentences, please summarise the key messages of your statement: • • • • •

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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Faricimab for treating diabetic macular oedema

Produced by Southampton Health Technology Assessments Centre (SHTAC)

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Declared competing interests of the authors

None

Declared competing interests of the clinical experts

None from Professor Noemi Lois. Ms Romi Chhabra received fees from Novartis (manufacturer of dexamethasone and ranibizumab) for organising and speaking at educational events and for attending conferences; and fees from Bayer (manufacturer of aflibercept) for attending conferences; these were unrelated to any trials on aflibercept, dexamethasone or ranibizumab. Professor Lotery was a local investigator on the TENAYA and RHINE clinical trials (Roche) of faricimab for neovascular age-related macular degeneration and diabetic macular oedema but was masked to patient allocations and received no fees from the company. He also gave a non-promotional educational talk as part of a series of retinal education seminars ran by Allergan (manufacturer of dexamethasone); attended an advisory board for Novartis Pharmaceuticals (manufacturer of dexamethasone and ranibizumab) on gene therapy unrelated to the company's work on dexamethasone or ranibizumab; and provided consultancy to Thea Pharmaceuticals (manufacturer of dexamethasone) on novel retinal drugs unrelated to dexamethasone. Mr James Talks was a local assessor on the Roche trials of faricimab for AMD, diabetic macular oedema and retinal vein occlusions (TENAYA, RHINE, RHONE-X and COMINO) which compared faricimab to aflibercept but was masked to patient allocations and received no fees from the company. He also contributed to advisory boards for Bayer (manufacturer of aflibercept) relating to patient perceptions and adherence to

treatment with anti-VEGF treatment, including aflibercept, over time in different countries for AMD; and Novartis (manufacturer of ranibizumab) in relation to broluzicumab in AMD.

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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Contributions of authors Geoff Frampton critically appraised the clinical evidence synthesis, drafted the report, project managed the review and is the project guarantor; Neelam Kalita critically appraised the economic evaluation and drafted the report; Karen Pickett critically appraised the clinical evidence synthesis and drafted the report; Emma Maund critically appraised the clinical evidence synthesis and drafted the report; Marcia Tomie Takahashi critically appraised the economic evaluation and drafted the report; David Alexander Scott critically appraised the clinical evidence synthesis and drafted the report; Keith Cooper critically appraised the economic evaluation and drafted the report.

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

1.1 The technology is pharmacologically similar to the comparators

In the current appraisal faricimab is intended for treating the eye condition diabetic macular oedema (DMO). Faricimab is a humanised bispecific antibody that acts on two distinct pathways, angiopoietin-2 (Ang-2) and vascular endothelial growth factor A (VEGF-A). These pharmacological pathways are aimed at reducing vascular leakage, neovascularisation and inflammation (CS section 1.3.3).

The two chosen cost comparators, aflibercept and ranibizumab, target all isoforms of VEGF-A. However, aflibercept binds to VEGF-A with a higher affinity than ranibizumab, and additionally targets VEGF-B and placental growth factor.[1]

The ERG's interpretation (confirmed by all four of our clinical experts) is that all three drugs are similar in terms of targeting VEGF-A, but faricimab is distinctive in targeting Ang-2. The company suggest that faricimab's dual mechanism of action translates to extended treatment intervals up to every 16 weeks, with efficacy and safety comparable to aflibercept (CS section 1.3.3). Three of our experts considered that extended treatment intervals are desirable in clinical practice. Two experts independently expressed the opinion that that while the Ang-2 action of faricimab may reduce inflammation, this remains to be demonstrated in clinical practice.

1.2 The selected comparators are appropriate

The company have positioned faricimab as a first-line treatment for people with vision impairment due to DMO and a central retinal thickness (CRT) ≥ 400 μm (CS Figure 2). The clinical experts advising the ERG agreed with the company's positioning of faricimab in the clinical pathway as a first-line therapy (CS Table 1 and CS section B.1.3.2). As stated in CS section B.1.3.2, NICE recommend both aflibercept and ranibizumab for people with a visual impairment caused by DMO and a CRT of ≥ 400 μm.[2, 3] The ERG's clinical experts agreed that aflibercept and ranibizumab are the most appropriate comparators for faricimab for treating visual impairment due to DMO in people with a CRT of ≥ 400 μm. The other treatments specified in the NICE scope either would be used off-label in people whose treatment eye has a CRT between 200 and 400 μm (bevacizumab), or as a second-line treatment (dexamethasone intravitreal implant and flucinolone acetonide intravitreal implant). Our clinical experts also stated that laser photocoagulation is now not generally used in practice, as better alternatives are available. Two experts commented that it is mainly used now for DMO that does not involve the centre of the retina and one noted it is also used in pregnant women. Another expert disagreed that laser is mainly used where there is non-central involvement, noting that macular

laser therapy is a treatment option for people with DMO and a CRT < 400 μm. They stated that laser is a relevant comparator for faricimab for the CRT < 400 μm patient subgroup.

The CS states that market share data from January to April 2021 indicate that [redacted] (CS section B.1.3.2) but the company do not provide a reference to the source of these data or explain how these figures were obtained. The ERG's clinical advisors' estimates of the proportion of patients treated with aflibercept are higher (80% to 95%) than those stated by the company. Accordingly, the ERG's clinical experts provided lower estimates of the proportion of patients treated with ranibizumab (15% to 5%). Three of the ERG's experts agreed that treatment for DMO would be started with aflibercept or ranibizumab if a person's vision was better than 6/9 but if vision was below 6/9 aflibercept was considered more effective (based on the DRCR Protocol T trial[4]) and hence preferable. However, the fourth clinical expert questioned whether this is a standard practice.

We conclude, based on clinical expert advice, that the company's selected comparators of aflibercept and ranibizumab adequately represent NICE recommended treatments for treating visual impairment due to DMO in terms of efficacy, safety and cost for people with CRT of ≥ 400 μm.

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

2.1 Population

The NICE scope specifies the relevant population is people with visual impairment because of DMO. This is consistent with the expected marketing authorisation for faricimab, the population section of the company decision problem in CS Table 1 and the clinical effectiveness data presented in the CS. However, in the comparator section of CS Table 1 and in Figure 2 of the CS, faricimab is positioned as a first-line treatment option for patients with vision impairment due to DMO and central retinal thickness (CRT) ≥400μm. This aligns with the previous appraisals for the two chosen comparators of this cost-comparison (see section 2.2 below) and our clinical experts' opinions.

2.2 Comparators

The comparators in the company's Decision Problem are consistent with those in the NICE scope and are considered appropriate by the ERG and clinical experts (see section 1.2 above)

2.3 Outcomes

The outcomes specified in the company's decision problem are aligned with those in the NICE scope with the following two exceptions:

1. The NICE scope specifies cataract surgery as an outcome but this is not included in the company decision problem. According to the company's response to clarification question A2, ocular adverse events, including cataracts were captured in the RHINE and YOSEMITE trials, but cataract surgery was not.

2. The NICE scope specifies disease severity as an outcome but this is not included in the company decision problem. According to the company's response to clarification question A2 the severity of DMO is captured in the change in Diabetic Retinopathy Severity Score (DRSS), which is an outcome in the pivotal clinical trials included in the submission (see section 3.1.2). Two of the ERG's clinical experts independently agreed that the DRSS is a standard tool for measuring disease severity in clinical practice. However, a third expert noted that the DRSS measures severity of diabetic retinopathy, not specifically severity of DMO. The ERG understand that "disease severity" is a broad outcome that could encompass other outcomes already included such as visual acuity and CRT which each contribute different information on disease severity.

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

3.1 Clinical evidence submitted by the company

3.1.1 The company submission

The CS comprises a main evidence submission document (Document B), an evidence submission summary (Document A) and appendices to Document B. The CS includes two phase III company-sponsored trials comparing the efficacy of faricimab against aflibercept: YOSEMITE[5] and RHINE.[6] The company provided the primary clinical study report (CSR) for each trial as well as a meeting presentation reporting year one results from the trials.[7] The company state that phase III trials comparing faricimab against ranibizumab are not available (CS section B.3.9) and therefore network meta-analyses (NMAs) were conducted to assess the similarity of the efficacy and safety of faricimab versus ranibizumab (described in section 3.4 below).

3.1.2 Trial design

CS sections B.3.2 and B.3.3 provide details of the design and methodology of the YOSEMITE and RHINE trials. Participant flow is described in CS Appendix D.1.2. The trials had identical designs and included a mix of treatment-naïve patients (approximately 78%) and previously-treated patients (approximately 22%) (CS section B.3.3.3). Most analyses are based on the intention-to treat (ITT) population with results for a per protocol analysis provided to support noninferiority inferences for the primary outcome. As noted in section 2.1 above, the company's intended position of faricimab is as a

first-line treatment for people who have CRT ≥400 μm. However, this is not consistent with the trial populations which included people with any CRT and some whom had received prior therapy. Implications for the external validity of the trials are discussed in section 3.2.3 below.

The treatment groups evaluated in the trials (described in detail in CS section B.3.3.1) were faricimab Q8W (once every eight weeks), faricimab PTI (personalised treatment interval) and aflibercept Q8W. In the PTI group, faricimab dosing could be extended, reduced or maintained at 4-week increments within the range Q4W to Q16W. The dosing schedule in the faricimab PTI arm reflects that in the faricimab draft Summary of Product Characteristics (SmPC), while the dosing schedule in the faricimab Q8W arm does not. The aflibercept dosing schedule reflects that specified in the aflibercept SmPC and as such is an appropriate comparison.

Outcomes in the YOSEMITE and RHINE trials are reported during the first year of treatment. The primary outcome was mean change from baseline in best-corrected visual acuity (BCVA) (CS section B.3.6.1). The company used a noninferiority margin of > -4 letters for this outcome for assessing noninferiority of faricimab against aflibercept, which we agree is appropriate. The company defined change in the primary outcome at 1 year in the YOSEMITE and RHINE trials as the average of the week 48, 52 and 56 visit data, rather than using the week 52 results. Reasons are given in clarification response A3 (c) which we believe are appropriate. For brevity, in the present report we refer to the primary outcome being the mean change from baseline in BCVA at 1 year.

Secondary outcomes included change in Diabetic Retinopathy Severity Scale (DRSS); the proportion of patients gaining, and the proportion avoiding losing, ≥10 or ≥15 letters of vision on the ETDRS (Early Treatment Diabetic Retinopathy Study) scale; change in health-related quality of life (HRQoL) assessed using the NEI VFQ-25 instrument; mean change in central retinal thickness (CRT); the proportion of patients with absence of intraretinal fluid and with absence of DMO; and adverse events. Note that the definition of CRT varies slightly across trials of DMO therapies; in the YOSEMITE and RHINE trials CRT refers specifically to the circular area 1 mm in diameter centered around the mid point of the fovea, which the CS refers to as the central subfield thickness.

Data from the YOSEMITE and RHINE trials were pooled for the efficacy analyses, due to their identical design (CS section B.3.6) and we agree that this is appropriate.

Clinical efficacy outcomes which informed the previous NICE appraisals of aflibercept (TA346) and ranibizumab (TA274) are summarised in CS Table 4. Outcomes which inform the economic analyses for the appraisals of aflibercept, ranibizumab and faricimab are shown in Table 1 below. In the

present report we briefly summarise all the key efficacy and safety outcomes reported by the company.

Table 1. Clinical efficacy and safety outcomes which inform the economic analyses of aflibercept, ranibizumab and faricimab for treating DMO

Outcome	Included in aflibercept TA346 cost-utility model	Included in ranibizumab TA274 cost-utility model	Reported in current company evidence synthesis [a]	Included in current cost-comparison model
Mean change in BCVA based on ETDRS letters	Yes	Yes	Yes	Yes
Probabilities of gaining or avoiding loss of 10 or 15 ETDRS letters	Yes [b]	No	Yes	No
Mean change in HRQoL)	Yes (EQ-5D)	Yes (EQ-5D)	Yes (NEI VFQ-25)	No [c]
Frequency of injections	Yes [b]	No	No [d]	Yes [d]
Ocular adverse events	Yes	Yes	Yes	No [c]
Non-ocular adverse events	No	Yes	Yes	No [c]

ETDRS: Early Treatment Diabetic Retinopathy Study
[a] Source: YOSEMITE [5] and RHINE [6].
[b] This was derived from from a network meta-analysis in TA346.
[c] Assumed the same for faricimab, aflibercept and ranibizumab so excluded from the cost comparison model (CS section 4.2.1).
[d] CS section 4.2.8 states injection frequency was derived from pooled data from the YOSEMITE and RHINE trials although this outcome is not reported in the company's clinical outcomes section (CS section B.3.6).

CS section B.2.2 states that key drivers of the cost-effectiveness analysis in the aflibercept appraisal (TA346) were "the model time horizon, the relative efficacy for both aflibercept and ranibizumab, the cohort starting age and the number of ranibizumab injections at year 1". However, we note that according to the Committee papers and ERG report for TA346[3] the aflibercept cost-utility model was sensitive particularly to HRQoL and injection frequency.

3.1.3 Key clinical efficacy results from the pivotal trials

The key clinical efficacy results for the pooled ITT population across YOSEMITE and RHINE were:

- **Primary outcome: Adjusted mean change from baseline in BCVA at 1 year:** Noninferiority of faricimab was demonstrated for both faricimab Q8W and faricimab PTI when compared against aflibercept Q8W in the pooled ITT population (difference: 0.7 letters (95% CI: -0.4, 1.7) and 0.6 letters (95% CI: -0.4, 1.7), respectively) (CS section B.3.6.1). Results of the per protocol analysis (CS Table 10) [redacted].
- **Key secondary outcomes:**
  - **Change in DRSS:** Both faricimab Q8W and PTI regimens were statistically [redacted] aflibercept Q8W (CS Table 12) (consistent with per protocol analysis reported in section 5.3.1 of the clinical study reports).
  - **Proportions of participants gaining or avoiding loss of ≥15 or ≥10 letters in BVCA from baseline at 1 year:** [redacted] gained or avoided losing ≥15 or ≥10 letters (CS section B.3.6.2).
  - **Health-related quality of life:** There was [redacted] between the faricimab and aflibercept treatment arms in change from baseline in the NEI VFQ 25 composite score at 1 year. There was also [redacted] between the pooled trials arms in the proportion of participants achieving a ≥4-point improvement from baseline (the [redacted]) (CS Table 18).
  - **Change in CRT:** Both faricimab Q8W and PTI regimens were [redacted] aflibercept Q8W, with [redacted] in CRT in the faricimab groups (CS Table 16).
  - **Proportion with absence of DMO (CRT<325 µm):** This was [redacted] in both faricimab Q8W and PTI regimens than aflibercept Q8W but not tested statistically.
  - **Proportion with absence of intraretinal fluid:** This was statistically [redacted] for both faricimab Q8W and PTI regimens than aflibercept Q8W (CS Table 17).
- **Subgroup analyses:** Of the subgroups specified to be of interest in the NICE scope, the company provided results for previous treatment history (whether or not participants had received prior intravitreal anti-VEGF therapy) and baseline visual acuity (BCVA of ≥ 64 letters and ≤63 letters) (CS Appendix E) (see also discussion of the treatment-naïve subgroup in section 3.2.3). The mean change from baseline in BCVA at 1 year in these subgroups [redacted].

3.2 Critique of the clinical effectiveness evidence submitted

3.2.1 Company searches for clinical evidence

The company's searches for clinical effectiveness evidence were initially performed up to October 2020 and updated in September 2021 (CS Appendix D). Systemic therapies (non-biologic and biologic) specified in the NICE scope were included apart from fluocinolone acetonide. This omission is inconsequential, as fluocinolone acetonide was not included in the company's decision problem (see section 2). The search identified a total of 26 studies for inclusion in network meta-analyses (see section 3.4.1 below) including the two pivotal phase III randomised controlled trials (RCTs) of faricimab versus aflibercept, YOSEMITE and RHINE. The ERG consider the searches and selection criteria to be appropriate. According to the company's responses to clarification questions A10 to A14 and A20, and the ERG's scrutiny of other relevant recent systematic reviews and meta-analyses on DMO,[8-19] we believe that all relevant published trials for the company's NMAs were identified.

3.2.2 Internal validity of faricimab trials

The company assessed the RHINE[6] and YOSEMITE[5] trials as being of moderate-to-high quality, using the NICE quality appraisal checklist (CS section B.3.5 and CS Appendix D.1.3). The ERG independently assessed the quality of the trials using the NICE checklist. Based on our assessment, we considered the trials to be well conducted and of a low risk of bias. The only exception to this was footnotes to CS Tables 13 and 14 state that missing data were not imputed in the ITT analyses of the gaining or not losing ≥15 letters in the study eye BCVA in the individual. The extent of missing data and reasons for missingness are unclear for these outcomes and there is therefore an unclear risk of attrition bias for these outcomes (although they do not directly inform the economic model).

The company stated it was 'unclear' if there was adequate blinding to participant allocation in the RHINE trial[6] (CS Table 8). We note that the RHINE[6] and YOSEMITE[5] trials were both double-masked (CS section B.3.2). The trials' clinical study reports,[5,6] show that the same masking procedures were used in both trials. From the information provided in the clinical study reports, we considered that care providers, participants and outcome assessors had been adequately masked to the participants' treatment allocations. We note [redacted]. We regarded the risk of bias from this to be low.

Both trials were adequately powered, with planned sample sizes reached (CS B.3.4.3 and CS Appendix D.1.2). We consider the statistical methods used in the trials to be appropriate.

ERG conclusion: Overall, we consider the trials to have been well designed and conducted with low overall risk of bias (except for an uncertain risk of attrition bias for the change in ETDRS letters outcomes which do not directly inform the economic model).

3.2.3 External validity of faricimab trials

Relevance of the trials to people with DMO and CRT≥400 µm

NICE recommend the comparators aflibercept and ranibizumab for treatment of DMO specifically in people who have CRT ≥400 µm. As discussed in section 3.1.2 of this report, participant eligibility for the YOSEMITE and RHINE trials was not restricted to people who had a CRT ≥ 400 µm and the company have not presented subgroup analyses for this population in the CS. They also did not report the number and proportion of participants who had a CRT ≥400 µm at baseline. The company state in CS section B.4.2.3 that the trial was not stratified at randomisation by a CRT of </> 400 µm and therefore conducting post-hoc subgroup analyses would break randomisation. We agree that there would be limitations to the subgroup analyses, but we believe that provision of these analyses would have provided a useful validation of the company's assertion, based on clinical expert advice they received that the efficacy and safety of faricimab in people with a "CRT > 400 µm [sic]" (CS section B.4.2.3) would be similar to the overall trial population of people with any CRT.

In a clarification response (17 [a]) the company provided the number of participants in these subgroups which shows that 30-35% of the ITT populations in the YOSEMITE and RHINE trials had baseline CRT <400 µm. The company also provided efficacy results for the CRT ≥400 µm subgroup for the primary outcome (i.e. mean change in best-corrected visual acuity [BCVA] score at 1 year) for the YOSEMITE and RHINE trials (clarification A17 [b]). Based on these data, faricimab appears to be [redacted] in improving BCVA in the target population who have DMO and CRT ≥400 µm. However, we note that the subgroup analysis may be underpowered statistically for confirming noninferiority of faricimab. The company did not provide CRT ≥400 µm subgroup analyses for any of the other outcomes assessed. One of the ERG's four clinical experts expressed concern that relatively limited evidence has been provided for the target population with CRT ≥400 µm given that this is the population for whom NICE recommend the comparator therapies and is the population for which the company are positioning faricimab.

Relevance of the trials to treatment-naïve patients

The company's positioning of faricimab is as a first-line therapy (CS Table 1). Approximately 78% of patients in the YOSEMITE and RHINE trials were treatment-naïve whilst approximately 22% had received prior DMO therapy (CS section B.3.3.3). The company present mean change in BCVA results for the treatment-naïve subgroup in CS Table 10. Note that this was a pre-specified subgroup

and a relatively large sample size was obtained by pooling the data across the two identical pivotal trials. The mean difference in change from baseline in BCVA between both faricimab Q8W and PTI and aflibercept Q8W in the treatment-naïve subgroup was [redacted] (CS section 3.6.1). The company did not report the treatment-naïve subgroup results for other outcomes, apart from the change in DRSS, where the results were [redacted] those of the ITT analysis (CS section B.3.6.2 and CS Appendix E). Given the relatively large size of the treatment-naïve subgroup the ERG believe that the conclusion of noninferiority of faricimab against aflibercept in the treatment naïve population is appropriate for these two efficacy outcomes.

Other aspects of the trials relevant to clinical practice

The ERG's clinical experts noted that the baseline characteristics of the participants included in the RHINE and YOSEMITE trials are generally representative of the patients seen in clinical practice, except that patients in clinical practice usually have worse diabetic control than those in the trials. Baseline HbA1c across the YOSEMITE and RHINE trial arms ranged from [redacted] to [redacted] which is lower than would be seen in clinical practice (this was also noted for the pivotal trials in the aflibercept technology appraisal TA346 which had a similar HbA1c range[3]). The clinical experts also noted that there was a higher proportion of people of a Hispanic ethnicity than seen in NHS practice, but that this difference is unlikely to be clinically important and that racial diversity was generally well reflected in the trials.

Two of the ERG's clinical experts commented that the initial aflibercept dosing regimen specified in the aflibercept SmPC (as applied in the YOSEMITE and RHINE trials) may not be precisely followed in NHS practice; one of these experts suggested eye units use six initial 4-weekly aflibercept doses in line with the DRCR Protocol T trial,[4] with subsequent monitoring then guided by patient response rather than the five recommended in the aflibercept SmPC. However, the remaining two experts considered that the SmPC dosing is reflective of aflibercept use in clinical practice.

One of our experts noted that the faricimab draft SmPC states [redacted]. The expert noted that allied health care professionals mainly administer intravitreal injections in the NHS, so this aspect of the proposed label is not in line with NHS practice.

[redacted][5, 6]

ERG conclusion on external validity: Whilst the YOSEMITE and RHINE trials demonstrate noninferiority or superiority of faricimab compared to aflibercept across a range of clinical efficacy

outcomes there is uncertainty as to how well these results apply to the target subgroup of people who have CRT ≥400 μm.

3.3 Critique of the evidence on safety submitted by the company

Safety data were pooled from the YOSEMITE and RHINE trials, up to week 56 (N = 1887; CS section B.3.10). The company also provide faricimab safety summary data from the phase II BOULEVARD study (CS Appendix F). However, the ERG consider that the evidence from this study is not relevant for this appraisal because the ranibizumab treatment arm was dosed at 0.3 mg which is not used in NHS clinical practice and all the drugs were administered Q4W for a treatment period of 20 weeks, followed by an observational period of up to 16 weeks, which does not reflect the posology in the farcimab draft SmPC.

3.3.1 Comparative safety for faricimab versus cost comparators

Pooled adverse event frequencies for faricimab 6.0 mg Q8W, faricimab 6.0 mg PTI and aflibercept 2.0 mg Q8W arms of the YOSEMITE and RHINE trials up to week 56 are as follows:

- The incidence of one or more adverse events, and one or more serious adverse events (SAEs), were comparable across treatment arms (see CS Table 22 for more details).
- The incidence of participants withdrawing from the study due to adverse events (AEs) was low, but more frequent in the faricimab arms compared to aflibercept ([redacted], [redacted] and [redacted] in the faricimab Q8W, faricimab PTI, and aflibercept arms, respectively).
- The incidence of participants withdrawing from the study treatment due to adverse events was low and similar between the treatment arms ([redacted], [redacted] and [redacted] in the faricimab Q8W, faricimab PTI, and aflibercept arms, respectively).
- The incidence of at least one ocular adverse event occurring in the study eye was comparable across treatment arms (37.3%, 35.6%, and 34.4% in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arms, respectively), with the exception (≥2% difference in any treatment arms) of vitreous floaters ([redacted], [redacted], and [redacted] in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arms, respectively). These vitreous floaters were reported to be mainly mild and all non-serious (CS section B.3.10.3).
- The incidence of at least one ocular SAE, ocular AEs of special interest, intraocular inflammation events, drop in visual acuity (VA) score ≥30, endophthalmitis, and rhegmatogenous retinal detachment (all in the study eye), were overall low. However, incidence in the faricimab arms was more frequent, in some cases more than double that, of aflibercept (see Table 2 below).

Table 2 Ocular adverse events

Ocular AEs[a]	Faricimab Q8W	Faricimab PTI	Aflibercept Q8W
Serious ocular adverse event	2.4%	3.0%	1.3%

Ocular AEs of special interest[b]	2.4%	2.7%	1.0%
Intraocular inflammation	[redacted]	[redacted]	[redacted]
Drop in Visual Acuity (VA) score ≥30	[redacted]	[redacted]	[redacted]
Endophthalmitis	[redacted]	[redacted]	[redacted]
Rhegmatogenous retinal detachment	[redacted]	[redacted]	[redacted]

PTI: personalised treatment interval. Source: This table incorporates information from CS Tables 22 and 25.
[a] event occurred in study eye [b] Included: drop in VA score ≥30, associated with severe intraocular inflammation, intervention required to prevent permanent vision loss, suspected transmission of infectious agent by study drug

Two of the ERG's clinical experts commented that careful monitoring of adverse events will be important, given the experience with brolucizumab for AMD in which intraocular inflammation emerged during post-market monitoring. One expert considered that the incidence of vitreous floaters could be an early indicator of safety concerns, although within the 1-year data available so far these floaters were not classed as serious events.

ERG conclusion on safety: There are no immediate safety concerns apparent in the YOSEMITE and RHINE trials. Some specific ocular adverse events were more frequent in the faricimab arms than in the aflibercept arm but frequencies were low (≤3%).

3.4 Critique of the Network Meta-Analyses (NMAs) submitted by the company

As noted above (section 3.1.1) no RCTs have directly compared faricimab against ranibizumab. The company therefore conducted NMAs to enable this comparison.

3.4.1 Inclusion criteria for the NMAs

Inclusion criteria

The company's inclusion and exclusion criteria for their NMAs are provided in CS Appendix Table 1. The criteria are broadly consistent with the NICE scope except that the comparator broculizumab (which is not licensed for DMO) was included in the search strategy and inclusion criteria, without an explanation. However, no studies of broculizumab were included in the NMAs. The ERG consider the eligibility criteria to be broadly appropriate, except that we question whether it is appropriate to include steroid therapies in NMAs that compare effects of anti-VEGF therapies (for explanation see below in this section).

Study selection process

The company's selection process for including trials in their NMAs is outlined in CS Appendix D1.1 but contains ambiguities, including a lack of explanation of the company's NMA "feasibility assessment" and the reasons for excluding studies from the NMAs. Most of the ambiguities were resolved by the company's clarification responses.

The company's approach to developing the NMAs does not discuss other published potentially relevant evidence networks. The NMA for the NICE aflibercept appraisal TA346 contains studies which are missing from the faricimab NMAs but which the ERG for TA346 considered relevant for indirect comparison of aflibercept versus ranibizumab (e.g. [20, 21]). We could not locate specific reasons within the CS or clarification responses for excluding these studies.

Despite these limitations the ERG's clinical experts were not aware of any relevant studies that are missing from the company's NMAs, so it appears likely that all relevant evidence has been included.

Network characteristics

The NMA networks included RCTs which had arms comparing faricimab, aflibercept, ranibizumab, bevacizumab, dexamethasone, laser photocoagulation therapy and/or placebo/sham. We note that these therapies would not all be used in practice as first-line treatments (see section 1.2 above). The trials included the following anti-VEGF dosing regimens:

- dosing at fixed intervals, usually in 4-monthly increments, Q4W or Q8W;
- dosing as needed (pro re nata; PRN);
- treat and extend (T&E): in which the treatment interval is extended if the patient's response is satisfactory (as applies in the faricimab PTI regimen, within the range Q4W to Q16W).

Inclusion of steroids as comparators: In their Cochrane Review, Virgili et al.[9] considered that "steroids may be compared with anti-VEGF drugs but this needs a different approach, specifically patient subgroups and timing, and their inclusion could lead to violation of similarity in a review aiming to compare different anti-VEGF drugs". The ERG's four clinical experts concurred independently that it may be preferable to exclude steroids from the NMAs, for reasons including: steroids are a second-line therapy; steroids may be more effective in specific subgroups of people (those with chronic DMO and those who do not respond to anti-VEGF therapies); the dosing intervals and waning of steroid effects differ from those of anti-VEGF therapies; steroids have different side-effects to anti-VEGF therapies (e.g. inducing cataracts); steroids are recommended by NICE only in pseudophakic patients. The ERG therefore believe that a sensitivity analysis would be appropriate to investigate the impact of excluding the dexamethasone trial arms from the NMAs.

Inclusion of different ranibizumab doses: Six of the trials included in the NMAs (Eichenbaum 2018,[22] DRCR-T, [4] REACT,[23] RESOLVE,[24] ROTATE,[25] TREX-DME[26]) used a ranibizumab dose of 0.3 mg which is lower than that used in UK NHS clinical practice (0.5 mg) and was considered not relevant to clinical practice in the NICE appraisal of aflibercept (TA346).[3] The company pooled these two doses in their NMAs, based on an observation that at 24 months in the RIDE and RISE trials[27] the

mean change in BCVA did not differ between the doses (clarification response A21). (NB RIDE and RISE were not included in the company's NMAs as they did not report relevant 1-year outcomes). However, the company do not provide any relative efficacy or safety evidence for the 0.3 mg versus 0.5 mg doses for any of the outcomes that they evaluated in their NMAs. Three of the ERG's clinical experts agreed independently that the 0.3 mg ranibizumab dose may have the potential to introduce bias in the analyses and should have been analysed separately or excluded from the NMAs, although the fourth expert believed pooling the 0.3 mg and 0.5 mg doses would likely be inconsequential for the efficacy and safety outcomes. The ERG believe that a sensitivity analysis would be appropriate to determine the impact of pooling the 0.3 mg and 0.5 mg ranibizumab doses in the NMAs.

ERG conclusion on the NMA inclusion criteria: The inclusion of the 0.3mg dose of ranibizumab and the steroid dexamethasone in NMAs may not be appropriate. The impact of these trial arms on the NMA results should be investigated in sensitivity analyses.

3.4.2 Quality assessment of trials included in the NMAs

The company provided risk of bias assessments for each of the trials included in the NMAs (CS Appendix D1.3). In response to clarification question A15 the company provided explanations for each of their risk of bias judgements and provided a sensitivity analysis to investigate the effect of excluding high risk of bias studies.

It was not feasible for the ERG to check all the company's risk of bias judgements. For 14 of the 26 included trials we were able to compare the company's judgements against risk of bias judgements made by the authors of other recent systematic reviews[9, 10, 12, 15, 16, 28, 29] including two Cochrane Reviews[9, 29]. One ERG reviewer then checked the remaining 12 trials. We found some differences between the company, ERG and other review authors in assigning low, high and unclear risks of bias to the individual bias domains within trials (a full table of these comparisons is available from the ERG on request). However, this has little impact on the overall study-level risk of bias classification, i.e. the company, ERG and other authors were generally consistent in identifying the same trials as being at overall high risk of bias.

The company did not assess the potential risk of bias relating to between-eye correlations where more than one eye per patient was included in analyses. Five of the trials included in the NMAs included more than one eye per patient but did not report any adjustment for between-eye correlations (footnote d in Table 3 below). The company did not adjust for any correlations between eyes in their NMAs (clarification response A19) and did not record this as a source of bias or imprecision.

ERG conclusion: The company's approach for assessing the risk of bias appears appropriate, except that the potential for bias due to inter-individual correlations between eyes was not assessed and therefore the potential influence of this on the NMA results is uncertain.

3.4.3 NMA modelling approach

The company's Bayesian statistical approach to the NMA methods is explained only superficially in CS section B.3.9.3 but can be ascertained from the WinBUGS statistical code provided in clarification response A24. The company conducted six NMAs which in total included 26 studies identified during the study selection process (listed in Table 3), for the following outcomes:

- Mean change in BCVA at 1 year: 22 studies; random effects model (CS Figure 12)
- Mean number of injections in year 1: 11 studies; random effects model (CS Figure 14)
- Mean change in CRT at 1 year: 24 studies; random effects model (CS Figure 16)
- Proportion of patients gaining or not losing ≥10 or ≥15 letters at 1 year: 22 studies; random effects model (CS Figure 18). Note that for this outcome the company were unable to find an appropriate prior distribution to adequately estimate the between-study heterogeneity and therefore this outcome should be interpreted with caution (clarification response A26).
- All-cause discontinuation up to 1 year: 14 studies; fixed effects model (CS Figure 20)
- Ocular adverse events up to 1 year: 11 studies; fixed effects model (CS Figure 22).

ERG conclusion: The overall modelling approach is appropriate except that the company do not provide an explanation for using fixed-effects models for two outcomes. A random effects model would have been preferable for all outcomes, given that model fit was similar for the fixed and random effects models (clarification response A26). In addition to the NMAs the company conducted meta-regression analyses; these are discussed below in sections 3.4.4 and 3.4.5.

3.4.4 Heterogeneity assessment

The company discuss several limitations of the NMA analyses (CS section B.3.9.5) but do not mention clinical heterogeneity, i.e. the variation of baseline characteristics of participants across the trials included in the NMAs. CS section B.3.9.3 states that meta-regressions were conducted "to assess whether treatment effects were influenced by patient characteristics" but no information on the methods or results of these analyses is provided in the CS.

In response to clarification question A16 (d) the company explained that two meta-regressions were conducted, to adjust for baseline variation in BCVA and baseline variation in CRT (acknowledging that these are correlated variables). The company do not explain why these two specific moderator variables were selected and not others. The meta-regressions were run for the primary outcome only

(change in BCVA). Results of these meta-regression analyses are provided in clarification response Tables 24 and 25. However, the ERG have concerns about the statistical approach employed for these meta-regressions, discussed in section 3.4.5 below.

In clarification response 16 (a) the company suggest baseline visual acuity and intraretinal fluid morphology are prognostic factors. The ERG heard from our clinical experts that systematic factors including poor diabetic control (high HbA1c), hypertension, renal disease and dyslipidaemia can all make DMO worse. Duration of DMO, baseline visual acuity, macular thickness and macular ischaemia are also prognostic factors for DMO, although macular ischaemia is difficult to measure and define consistently.

The company provided an Excel table of trial baseline characteristics in clarification response A16 (c) which the ERG have checked against the source publications. The key participant characteristics are summarised in Table 3 below. We note that many of the prognostic factors for DMO identified by our experts were not always reported in the trials and one of our clinical experts commented that this is one of the reasons why real-world treatment results are usually inferior. Two of the ERG's clinical experts considered that (within the limitations of data available), the factors summarised in Table 3 appear adequately homogeneous for the studies to be combined in NMA. However, one expert considered that it may not be appropriate to combine treatment-experienced and treatment-naïve people in the analysis since prior treatment may reflect a worse prognosis.

The NMA networks contain several further sources of potential heterogeneity in addition to those listed in Table 3. These include differences between trials in the way PRN treatment was provided (CS Appendix Table 13), in the way sham/placebo arms were administered (CS Appendix Table 14), in aflibercept loading doses (CS Appendix Table 15) and in the permitted laser or other rescue treatment use (CS Appendix Table 16). We note that the company also identified a difference between trials regarding whether they had adjusted for the rescue treatment or not (CS Appendix Table 16) but the company do not comment on whether these studies could have been analysed separately or what their influence on outcomes would be. It is unclear whether networks could be constructed to account for any of these differences and the company do not discuss this.

ERG conclusion: There are several baseline characteristics that could introduce heterogeneity in the NMAs, most of which were not adjusted for in the meta-regression analyses, although two clinical experts felt that the trials were broadly homogeneous across those baseline characteristics that were most frequently reported. A more systematic and explicit consideration of the factors that contribute to heterogeneity and which of them can or cannot be adjusted for would be helpful. In particular,

clarification is needed on whether it is appropriate to combine treatment-naïve and treatment-experienced populations in the analysis.

3.4.5 NMA data and statistical procedures

The ERG were able to validate the statistical code by running selected analyses. Targeted checks of the NMA input data against the source publications identified only minor discrepancies which are likely inconsequential.

The company explained in clarification response A22 that there was no inconsistency between the direct and indirect evidence within their NMA for change in BCVA. The ERG agree with the company, although we note that consistency was not assessed for the other outcomes.

The ERG have two concerns relating to the meta-regressions reported by the company in clarification response A16 (d):

- Adjustment was made for only two baseline variables: BCVA and CRT. The company do not discuss whether any other factors could have been adjusted for, such as HbA1c or the duration of DMO which the ERG's clinical experts noted as prognostic factors (section 3.4.4 above).
- The company dichotomised the median values of the baseline BCVA and CRT (clarification response A16[d]). The ERG advise against dichotomising continuous data for several reasons including information loss and ignoring potential non-linearity.[54]

ERG conclusion: The company's "base case" NMA methods are appropriate. However, the ERG disagree with the statistical approach employed by the company for their meta-regression analyses to account for baseline heterogeneity in prognostic factors for DMO.

Table 3 Baseline characteristics of participants in the 26 trials included in network meta-analyses

Trial Means and medians in the table are across all arms within each trial	**Mean [median] age, years**	**DMO treatment history (laser or anti-VEGF)**	**Mean [median] duration of diabetes, years**	**Mean [median] HbA1c %**	**Mean [median] time since DMO diagnosis, years**	**Mean BCVA letters**	**Mean [median] central retinal thickness µm**	**% pseudo-phakic**	**Total eyes/ patients**
BEVORDEX [30, 31]	60.9-62.2	Prev trt	16.7-19.5	7.7-8.4	NR	55.5-59.0	451-503	30	88/61 [a]
BOLT [32]	63.5-64.9	Prev trt	13.5-14.8	7.5-7.6	NR	54.6-55.7	481-507	12-21	80/80
Chatzirallis 2020 [33]	64.4-64.8	Trt naive	11.1-12.1	NR	NR	56.3-58.9	424-430	NR	112/112
DA VINCI [34, 35]	60.7-64.0	Mixed	NR	7.9-8.1	NR	57.6-59.9	426-456	NR	221/221
DRCR Protocol T [4, 36-38]	60-62	Mixed	[15-17]	[7.6-7.8]	NR	64.6-66.3	403-460.5 [b]	21-17	313/313
Eichenbaum 2018 [22]	60.4-64.5	Mixed	NR	NR	NR	29.2-32.5	455-471	NR	20/20
ETDRS [39] [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	2998/1876 [d]
Fouda 2017 [40]	55.1-56.6	Trt naive	NR	NR	NR	Snellen decimal 0.17-0.18	465-472	NR	70/42 [d]
LUCIDATE [41]	[64.9-67.4]	Trt naive	[18-18.5]	7.25-7.93 [e]	[1.75-2.67] calculated by ERG	63.8-70.4	455-488	18-36	33/33
MEAD 1 & MEAD 2 [42-44]	62.3-62.5	Mixed	15.8-16.5	7.5-7.6	NR	MEAD 1: 55.2-57.0 [b] MEAD 2: 55.9-56.8 [b]	MEAD 1: 453.7-486 [b] MEAD 2: 436.7-468.7 [b]	24-29	1048/1048
Ozsaygili 2020 [45]	64.8-66.4	Trt naive	[10.2-10.4]	8.2-8.4	NR	[46.3-47.5]	[576.5-615.2]	54.0-60.4	98/62 [d]
REACT [23]	62.5-63.8	Prev trt	NR	NR	NR	64.2-65.1	399-444	NR	27/27
REFINE [46]	58.6-59.0	Mixed	NR [f]	7.3-7.4	1.1-1.3 [f]	58.2-59.6	473-475	NR	384/384

RESOLVE [24]	62.8-65.0	Mixed	13.9-15.1	7.3-7.6	1.1-1.4	59.2-61.2	449-460	NR	151/151
RESPOND [47]	60.8-62.8	Mixed	16.5-18.5	7.6-7.8	1.6-2.1	61.9-64.8	422-458	NR	220/220
RESTORE [48]	62.9-64.0	Mixed	12.9-15.2	NR	1.6-2.0	62.4-64.8	412-427	NR	345/345
RETAIN [49]	63.0-64.5	Mixed	NR	7.8-8.0	2.5-2.6	61.7-64.7	433-481	NR	372/372
REVEAL [50]	60.7-61.5	Trt naive	11.2-11.3	7.4-7.5	1.2-1.5	58.4-58.8	395-430	NR	396/396
ROTATE [25]	68-69	Prev trt	NR	NR	NR	63.0-63.7	401-453	NR	30/22 [d]
TREX-DME [26]	58.7-59.9	Mixed	13.6-15.8	NR	NR	64.1-65.1	434-480	20-23	150/116 [d]
VISTA [51, 52]	61.7-63.1	Mixed [c]	16.5-17.6	7.6-8.1	NR	58.9-59.7	479-485	NR	466/466
VIVID [51, 52]	62.6-64.2	Mixed	14.1-14.5	7.7-7.8	NR	58.8-60.8	502-540	NR	406/406
VIVID-East [53]	57.6-59.3	NR	11.5-12.9	7.3-7.6	NR	55.1-57.1	520-528	NR	381/381
RHINE [e]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
YOSEMITE [e]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

NR: not reported; Prev trt: previously treated; Trt naïve: treatment-naïve.
[a] More than one study eye per patient included with adjustment made for between-eye correlation.
[b] ERG unable to locate source of data as reported in the company's data extraction table provided in clarification response A16 (c).
[c] EDTRS trial baseline characteristics are not included in the company's data extraction table (clarification response A16 [c]) and several publications for this trial were not provided by the company and are not accessible to the ERG; however, this trial is only included in the NMA of change in BCVA letter categories where it is an outlier in the network and unlikely to be influential (see CS Figure 18).
[d] More than one study eye per patient included but no adjustment for between-eye correlation reported.
[e] Data provided by ERG (company's data extraction table states these data were not reported).
[f] The paper does not state whether this is duration of diabetes or duration of DMO; the company extracted this as the duration of diabetes; the ERG believe it is the duration of DMO.

3.4.6 NMA results

The company's NMA results are summarised in Table 4. The ERG regard these results illustrative only, since the company's NMAs pooled the 0.3 mg and 0.5 mg doses of ranibizumab which is not reflective of clinical practice. Note also that for the mean change in ETDRS letters outcome (i.e. the proportion of people gaining or not losing ≥10 or ≥15 letters) the company were unable to satisfactorily account for between-study statistical heterogeneity and suggest that these results should be treated with caution (clarification response A26).

Meta-regression on baseline BCVA and baseline CRT

Results of the company's meta-regression analyses that included baseline BCVA and baseline CRT as covariates are provided in clarification response A25. The model fit statistics (clarification response Table 23) and treatment-by-covariate estimates (clarification response Table 24) suggest that the models accounting for baseline variation in BCVA and CRT [redacted]. However, due to concerns about the meta-regression methodology (section 3.4.5 above) the ERG caution that the meta-regression results may not be reliable.

Sensitivity analyses excluding high risk of bias studies

The company reran their NMAs for each of the six outcomes excluding studies which had been classified as being at high risk of bias (clarification response Figures 2 to 12).

[redacted]. As with the base case NMAs, these results should be interpreted with caution, since 0.3 and 0.5 mg ranibizumab doses were pooled in the analyses.

Baseline CRT ≥400 µm subgroup analysis

The company identified six trials, including YOSEMITE and RHINE, which reported baseline CRT by subgroups <400 µm and ≥400 µm and they conducted a NMA using the CRT ≥400 µm subgroup for the mean change in BCVA to 1 year (clarification response Figure 14).

[redacted]. The company suggest that the CRT

≥400 µm subgroup results show [redacted] in terms of change in visual acuity, but they state that results must be interpreted with caution given that subgroups were not pre-specified, i.e. breaking randomisation (clarification response A17 [b]). [redacted]. Note also that one of the trials included in the subgroup analysis, DRCR-T, used the 0.3 mg ranibizumab dose which is not used in UK clinical practice.

ERG conclusion: The company's NMAs show that, across the five efficacy outcomes assessed, the PTI dosing regimen of faricimab was [redacted]. For the one safety outcome assessed, odds of an ocular AE, faricimab was [redacted]. These NMA results are subject to uncertainties in the NMA methods discussed above which are summarised in section 3.5 below.

3.4.1 Consistency of NMA results with other evidence

As would be expected, the company's NMA results for the comparison of faricimab versus aflibercept (Table 4) are generally consistent with the results of the comparison of faricimab versus aflibercept in the YOSEMITE and RHINE trials which were included in the NMAs. It is not possible to validate the results of the NMAs for the comparison of faricimab against ranibizumab since no other evaluations of the relative effectiveness of faricimab against other anti-VEGF agents have been conducted, apart from the phase II BOULEVARD study, reported in CS Appendix 7. BOULEVARD included 0.3 mg ranibizumab, a dose not used in UK NHS practice. It may be possible to partially validate the NMAs against external evidence if an alternative comparator pair is selected, such as aflibercept versus ranibizumab, for which external trial and meta-analysis evidence exists, but the company have not reported NMA results for this comparison.

Table 4 Summary of NMA results for 1-year outcomes

Faricimab PTI versus others ►	**Faricimab 6.0 mg**	**Aflibercept 2.0 mg**			**Ranibizumab 0.3 mg+ 0.5 mg pooled**			**Deferred laser**	**Data source**
Outcome	**Q8W**	**Q4W**	**Q8W**	**PRN**	**Q4W**	**T&E**	**PRN**		
Mean difference change in BCVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted][a]	[redacted][a]	[redacted][a]	[redacted]	CS Fig 13
Mean difference number of injections	[redacted][b]	[redacted][b]	[redacted][b]	[redacted]	[redacted][b]	[redacted]	[redacted]	[redacted]	CS Fig 15
Mean difference change in CRT	[redacted]	[redacted]	[redacted][a]	[redacted][a]	[redacted][a]	[redacted][a]	[redacted][a]	[redacted]	CS Fig 17
Mean change in ETDRS letters [c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	CS Fig 19
Odds all-cause discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	CS Fig 21
Odds ocular adverse events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted][d]	[redacted]	CS Fig 23

NA: comparison not available for this network; PTI: personalised treatment interval
[a] "Favoured" denotes that the mean difference is significantly higher than zero for faricimab PTI versus the specified comparator.
[b] "Favoured denotes that the mean difference is significantly lower than zero for faricimab PTI versus the specified comparator.
[c] This refers to the proportion of people gaining or not losing ≥10 or ≥15 letters.
[d] "Favoured" denotes that the odds ratio is significantly lower than 1.0 for faricimab PTI versus the specified comparator.

3.5 ERG conclusions on the clinical effectiveness evidence

Comparison of faricimab against aflibercept: YOSEMITE and RHINE trials

The clinical evidence for faricimab compared to aflibercept is from pooled data from two identical phase III trials, YOSEMITE and RHINE, which appear well designed and executed with overall low risk of bias. The trial populations were comparable for faricimab and afibercept.

- The trials demonstrate noninferiority of the proposed dosing regimen of faricimab (Q4W-Q16W) compared to aflibercept Q8W for the primary outcome of the change in visual acuity in the ITT population as well as the change in DRSS score (a key secondary outcome which assesses severity of diabetic retinopathy, but is not specific to DMO) (section 3.1.3).
- Faricimab Q4W-Q16W was statistically superior to aflibercept Q8W for the change in CRT and was statistically not different to aflibercept for other outcomes assessed (section 3.1.3).
- The results are clinically plausible and consistent with the expected pharmacological mode of action of faricimab.
- However, the applicability of the trial results to the target population with CRT ≥400 μm is uncertain (section 3.2.3).
- The efficacy data presented by the company are for one year of therapy and may not reflect longer-term outcomes.

Comparison of faricimab against ranibizumab: NMAs

The company's NMAs were informed by a comprehensive literature review. The ERG consider the review to be at low risk of bias and unlikely to have omitted any relevant studies. The NMA modelling approaches are appropriate, based on NICE DSU recommended methodology, except for meta-regressions conducted by the company (see below). The company conducted a sensitivity analysis which demonstrated that results for the primary outcome were insensitive to the exclusion of studies with a high risk of bias.

The ERG have several concerns with the company's NMAs which we believe may render these analyses potentially unreliable for decision-making, unless the following issues can be addressed:

- The company's NMAs combined ranibizumab doses of 0.3mg and 0.5 mg but the 0.3 mg dose is not recommended nor used in NHS clinical practice and has the potential to introduce bias in efficacy or safety outcomes. A sensitivity analysis would be appropriate to determine the impact on clinical and safety outcomes of pooling these doses (section 3.4.1).
- Clinical experts considered it inappropriate to include steroid therapies in the NMAs. A sensitivity analysis would be appropriate to investigate the impact of including/excluding trials with dexamethasone arms from the NMAs (section 3.4.1).

- The company's NMAs combined treatment-naïve and treatment-experienced populations. Clarification is needed on whether this is appropriate (section 3.4.4).
- The ERG do not agree that the company have used appropriate statistical methods for their meta-regressions to account for between-study baseline heterogeneity in the NMAs (section 3.4.5).
- The applicability of the NMA results to the target population of people who have CRT ≥400 μm is uncertain (section 3.4.6).

Safety of faricimab

- The YOSEMITE and RHINE trials do not currently indicate any major safety concerns, although some specific ocular adverse events were more frequent in the faricimab arm(s) compared to the aflibercept arm (section 3.3.1).
- The company's NMA of aggregate ocular adverse events did not identify any safety concerns for faricimab relative to aflibercept or ranibizumab (Table 4).

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

4.1 Decision problem for the cost comparison

4.1.1 Population

The ERG agree that the population for the cost-comparison analysis should reflect that in the NICE recommendations for the comparators. In practice, the cost analysis uses input parameters estimated from trials with a broader population:

- The modelled cohort has a mean age of 62 years, with 60% male (CS Table 27), based on the pooled ITT populations of the YOSEMITE and RHINE trials. These patient characteristics are consistent with models for the comparator appraisals (TA346 guidance for aflibercept and TA274 guidance for ranibizumab[2]). In the company model, population characteristics only affect mortality rates, which has little impact on cost estimates.

4.1.2 Comparators

The analysis compares faricimab with aflibercept and ranibizumab. As stated in section **Error! Reference source not found.** above, the ERG consider that these comparators are appropriate for the cost-comparison analysis.

4.2 Cost-comparison model

The company describe their cost-comparison model in CS section B.4.2.1. The model structure is illustrated in CS Figure 24 and described in CS section B.4.2.2, with the key assumptions given in CS Table 34. Whilst the company state that the general modelling approach and inputs were cross referenced with previous technology appraisals, they do not provide any comparison in the CS.

ERG conclusion: We view the company's modelling approach is reasonable. It shares general modelling features with previous technology appraisals (e.g. TA346).

4.3 Model parameters

4.3.1 Treatment effect

The treatment effect is modelled through treatment discontinuation. The annual probability of discontinuation for faricimab is obtained from the YOSEMITE and RHINE trials. For year 1, the annual probability is based on discontinuation probabilities observed in pooled year 1 data from the YOSEMITE and RHINE trials. In years 2 to 5, the company assumed the same probability of discontinuation, based on the annualised probability of discontinuation derived from patients' part way through the second year of the YOSEMITE and RHINE trials. For the comparator arms, the annual probability of treatment discontinuation was assumed to be equivalent to that of the faricimab arm in year 1 to year 5.

ERG conclusions: We have reservations about the company's assumption of the same probability of discontinuation in years 2 to 5. Advice from our clinical experts suggest that patients who discontinue treatment either due to efficacy (i.e. resolution of DMO) or lack of efficacy might experience recurrence or need to restart treatment. Furthermore, the probability of discontinuation in each of the following years is likely to be higher due to fewer injections. However, we have not conducted a scenario exploring this assumption due to data constraints.

With respect to treatment duration, the company assume a maximum duration of 5 years from baseline for the study eye for treatment with faricimab, ranibizumab and aflibercept. After this, 85% of those who were alive and on treatment are assumed to discontinue treatment. The remaining 15% remain on treatment beyond year 5 to reflect the fact that some people with DMO require long-term treatment. Expert clinical advice to the ERG is that the company's assumption aligns more with neovascular oedema than DMO. The ERG's clinical experts advised that, in DMO, the on/off treatment cycle could go back and forth. For example, a study by Elman et al.[55] indicates that at 5 years, 50% of people were still receiving treatment. Based on our clinical experts' advice and the

study by Elman et al. we view the assumption that 50% of people who are alive would discontinue treatment after 5 years reflects clinical practice. The company have conducted a scenario analysis for this assumption (shown in CS Table 40) which indicated that at the patient access scheme (PAS) price for faricimab and list prices for the two comparators, [redacted].

For those developing DMO in their second eye, a maximum treatment duration of 5 years from the point of DMO development in the second eye is assumed. The ERG's clinical experts suggested that this assumption may be reflective of patients with AMD, but not those with DMO. In clinical practice, 50% of those developing DMO in the second eye would still receive treatment at 5 years as observed in the DRCR Protocol T trial.[4].

The company conducted a range of scenario analyses where they explore the impact of alternative assumptions for treatment discontinuation:

- Varying the treatment duration between 3 and 10 years
- Varying the proportion of people discontinuing treatment after year 5
- Varying the positive discontinuation probabilities differently for faricimab, aflibercept ad ranibizumab after year 1 whereby it was assumed that [redacted] receiving faricimab and [redacted] receiving aflibercept would stop treatment after 1 year. These are based on the outcome in YOSEMITE and RHINE. The discontinuation proportion for ranibizumab was assumed equivalent to that applied for aflibercept.

ERG conclusion: We view that the company have provided a reasonable range of scenarios for treatment discontinuation. Across all their scenarios, [redacted] (as shown in CS Table 40). Overall, we view that their scenario where 50% of people discontinue treatment after 5 years is more reflective of the UK clinical practice. We explore the impact of this assumption in conjunction with other ERG preferred assumptions in ERG additional analyses. These are discussed in Section 4.6 below.

4.3.2 Mortality

The model uses general population mortality rates, adjusted for the age and sex of the modelled cohort (England and Wales 2017-2019, ONS 2019). Furthermore, mortality was adjusted by applying a diabetes specific hazard ratio (HR 1.95, Preis 2009[56]) for the entire population as well as health state mortality risks from being blind and visually impaired (HR 1.5 and 1.2). These assumptions are consistent with the previous aflibercept appraisal (TA346[3]). The company do not assume an increase

in mortality from bilateral disease. Furthermore, the annual mortality rate is assumed to be equivalent regardless of DMO treatment.

ERG conclusion: We agree with the company's assumptions.

4.3.3 Costs

- **Acquisition costs**

The company set out the dosing assumptions and list prices for the calculation of acquisition costs for faricimab and the comparators in CS Table 28.

- **Treatment Dosing**

In the model base case, the dosing regimen for faricimab aligned with the personalised treatment interval (PTI) arm in the YOSEMITE and RHINE trials and with the anticipated marketing authorisation for faricimab. This included a loading phase of 4 injections (one per month for 4 months). Dosing included a protocol-driven treat- and- extend regimen in which treatment intervals are adjusted based on individualised treatment response, measured by central subfield thickness (CST) and visual acuity. The dosing intervals in the PTI could extend up to every 16 weeks, in increments of 4 weeks.

For the comparator arms, the company assume treatment dosing is administered using a PRN regimen in which patients receive treatment in response to disease activity. Prior to commencing the PRN regimen, patients are assumed to receive five injections of aflibercept or ranibizumab (one per month for 5 months) in a treatment loading phase (aflibercept 2 mg LP → PRN, ranibizumab 0.5 mg LP → PRN). This is based on the treatment and monitoring schedule in the DRCR Protocol T trial,[4] which compared visual acuity loss for people receiving aflibercept, bevacizumab or ranibizumab.

The company explored alternative dosing regimens for the comparator treatments in their scenario analyses (e.g. ranibizumab on a treat and extend dosing regimen) by varying the frequencies of injections and monitoring visits. However, they did not explore the impact on the cost comparison of a treat and extend regimen for aflibercept. Their scenarios indicated that the changes in dosing regimen did not change the overall conclusions.

ERG conclusion: Following a treat-and-extend regimen in the first years of treatment is reflective of the UK NHS clinical practice. Therefore, we view the company's approach to the dosing regimen for faricimab is reasonable. We have conducted a range of exploratory scenario analyses on alternative dosing regimens for aflibercept and faricimab (see section 4.6).

- **Healthcare resource use and costs**
    - **Diagnosis using optical coherence tomography**

The company's analyses assume that patients with DMO are diagnosed using optical coherence tomography (OCT). The cost of OCT, sourced from
the 2019/2020 NHS reference costs schedule, is applied:

- across all patients at cycle one
- in the first model cycle after patients develop DMO in their second eye and
- in subsequent injection and monitoring visits.

ERG conclusion: We agree that DMO diagnosis using OCT is reflective of UK NHS clinical practice. We noted an inconsistency in the OCT cost used in the company's analyses, which the company corrected as part of their response to clarification question B4. The correction did not have any significant impact on the overall results.

- **Injection administration**

The company discuss their base case assumptions for estimating the annual mean number of injection administration visits in CS Section B.4.2.8 and CS Table 30. Briefly, the frequency of injection administrations for faricimab in years 1 and 2 is derived from data pooled from the YOSEMITE and RHINE trials. The frequency of aflibercept and ranibizumab injections is informed by the results of the NMA assuming a PRN regimen in year 1. For year 2, both comparators used the number of injections received considering the DRCR Protocol T trial.[4]. Alternative assumptions about the injection administration visits for the two comparator treatments aflibercept and ranibizumab were explored by the company in scenario analyses (CS Table 39).

With respect to resource use, for their base case the company assume:

- Intravitreal (IVT) injections are administered in consultant-led outpatient appointments
- Additional resource use and costs associated with IVT injections would apply at each injection administration visit.
- The cost of an injection administration visit comprised of an outpatient consultant-led visit, an injection administration cost, and an OCT procedure.

ERG conclusion: We have several concerns with the company's assumptions, as follows:

- The number of injection administration visits assumed by the company do not reflect clinical practice and the existing evidence (Egan et al.[57]). Advice from our clinical experts suggests

that there are less than 9 injection administration visits in year 1 and fewer thereafter, reflecting NHS capacity limitations. We conducted a range of scenario analyses whereby the number of visits were varied between 6 and 8 in year 1 and between 2 and 4 in year 2 and are assumed to be similar across the DMO treatments. As discussed previously in Section 3.1.2, we note from the Committee papers and the ERG report for the aflibercept appraisal TA346[3] that the cost-utility model was particularly sensitive to injection frequency. The NICE guidance on the appraisal concluded that it is reasonable to conduct sensitivity analyses that included equal numbers of injections for aflibercept and ranibizumab in year 2. We explore this assumption in our scenario analyses (see section 4.6). We prefer to base the number of injection administration visits on the estimates from our clinical experts and TA346.

- In UK clinical practice, a majority of the IVT injections are administered by staff such as specialist nurses and optometrists. The company conducted a scenario analysis (CS Table 40) exploring the impact of non-consultant led outpatient visits; this increases the incremental costs versus aflibercept and ranibizumab by [redacted] and [redacted] respectively, compared to the base case results. We view this scenario better reflects UK NHS clinical practice.
- Furthermore, an OCT procedure is unlikely to be performed during an injection administration visit in the initial doses. Often vision testing and OCT are performed prior to an injection. We have conducted a scenario to explore this assumption (see section 4.6).

- **Monitoring visits**

The company detail their approach for estimating the monitoring visits in CS Section B.4.2.8 and in CS Table 32 (reproduced below in **Error! Reference source not found.**). They made the following assumptions:

- In the faricimab arm, there are no additional monitoring visits in years 1 and 2. In year 3 and beyond, people in this arm would transition to a PRN type regimen where there will be separate monitoring visits. The total number of visits in year 3 and beyond is based on the total visit numbers observed for patients treated with aflibercept and ranibizumab in years 3-5 of the DRCR Protocol T trial.[4]
- For those receiving the comparator treatment regimens, monitoring visits are applied in all years of the model as they are administered using a PRN regimen.
- The cost of a separate monitoring visit comprised of an outpatient-led visit and an OCT procedure.

ERG conclusion: Our clinical experts viewed that faricimab would be administered in a similar way to the other anti-VEGFs. Therefore, faricimab is likely to have the same monitoring visits as the comparators. Secondly, the company's number of monitoring visits for aflibercept and ranibizumab

appear to be lower than observed in UK clinical practice. We conducted scenario analyses varying the number of these visits based on the previous appraisal TA346 and our experts' opinion, as shown in section 4.6.

- **Bilateral treatment multipliers**

To account for additional costs for treating two eyes instead of one, the company use bilateral cost multipliers for the drug, administration, and monitoring costs in their base case analysis (see CS Table 33). Their assumptions for the cost multipliers are based on the NICE clinical guideline for AMD NG82 and previous technology appraisals for DMO (TA346) and AMD (TA672).

ERG conclusion: We have no concerns with these assumptions.

- **Other: adverse events and miscellaneous**

In the company's analyses, adverse events are assumed to be equivalent across all the three treatments. We view this as a reasonable simplification based on the safety results from the YOSEMITE and RHINE trials where the incidence of AEs was comparable across the treatment arms (section 3.3.1). While the incidences of serious AEs were higher in both the arms of faricimab compared to that of the aflibercept arm, the company argued that these are unlikely to have a significant impact. We agree with the company as the overall frequency was low and therefore unlikely to influence the overall results.

The company model has the provision to include the wider societal impact of visual impairment and anti-VEGF treatment burden such as reduced productivity of the patients and that of the carer for disruption to their workday. These scenarios are explored in the company's scenario analyses (CS Table 40).

ERG conclusion: We agree with the company's approach to exclude adverse events from the cost comparison analyses.

4.4 ERG model checks

The ERG conducted a range of checks on the company's cost-comparison model. This included verification that all input parameters and model results matched the values cited in the CS and, where available, values in published sources. We also inspected formulae in the Markov trace and intermediate calculations ('white box' verification) and checked that changes to input parameters had a plausible impact on results ('black box' verification). Furthermore, the ERG re-ran all the company's sensitivity and scenario analyses.

We identified the following issues, although these do not affect the overall model conclusions.

- There is a small discrepancy in reporting the cost for retinal tomography which the company addressed as their response to clarification question B4.
- For five of the company's scenario analyses (shown below in Table 5) there are slight discrepancies in the results reported by the company and those obtained by the ERG.

Table 5 Inconsistency in the cost comparison results obtained by the company and the ERG (PAS price for faricimab and list price for the comparators) (based on the company's revised model submission as part of the clarification response)

Scenario		Incremental cost vs aflibercept		Incremental cost vs ranibizumab	
		Company	ERG	Company	ERG
Ranibizumab dosing regimen	LP→q4w	N/A	N/A	-£7,966	-£7,976
	LP→T&E	N/A	N/A	-£6,473	-£6,484
Aflibercept dosing regimen	LP→q4w	-£21,366	-£21,382	N/A	N/A
	LP→q8w	-£17,774	-£17,658	N/A	N/A
Treatment and monitoring setting costs	£89.13	-£15,995	-£15,955	No discrepancy	

LP: Loading Phase; T&E: Treat and extend

4.5 Cost comparison analysis results

The company base case cost comparison results are presented in CS Table 35. The analyses are based on the PAS discount for faricimab and the list prices for the comparators. Uncertainty over model assumptions was assessed with one-way sensitivity analyses (presented in CS Figures 25-26) and scenario analyses (CS Table 40).

The cost-comparison analyses and their results reported in this report are conducted with the PAS discount for faricimab and the two comparators at list price. We present the cost-comparison results with the available PAS discounts for faricimab and ranibizumab and Commercial Medicines Unit (CMU) discount for aflibercept in a confidential addendum to this report.

4.6 ERG analyses

We summarise the results of the company's base case at the PAS price for faricimab and list price for the comparators in Table 6 below. These results are based on the company's revised submission provided in response to the ERG's clarification questions. The company also conducted a threshold

analysis that explored the impact of varying the level of discounts for the comparators aflibercept and ranibizumab (in CS Table 36). We present the cost comparison results for the company's assumption that the PAS prices for aflibercept and ranibizumab are [redacted] and [redacted] respectively in

Table 7 below. In line with NICE methodological guidance for FTA cost-comparisons, the company did not report a probabilistic sensitivity analysis. All results are therefore deterministic.

Table 6 Company's base case results – PAS price for Faricimab and comparators

Cost	Faricimab 6 mg LP → q16w/q12w	Aflibercept 2 LP → PRN	Ranibizumab 0.5 LP → PRN
Mean total cost	[redacted]	£44,476	£34,675
Incremental cost vs faricimab	N/A	[redacted]	[redacted]
Source: Results from the cost-comparison model in Excel			

Table 7 PAS price for Faricimab and assumed discounts for ranibizumab and aflibercept at [redacted] and [redacted] respectively

Cost	Faricimab 6 mg LP → q16w/q12w	Aflibercept 2 LP → PRN	Ranibizumab 0.5 LP → PRN
Mean total cost	[redacted]	[redacted]	[redacted]
Incremental cost vs faricimab	N/A	[redacted]	[redacted]
Source: Results produced by ERG from the company's model			

4.6.1 Scenario analyses conducted by the ERG on the company's model

In addition to the company's scenario analyses, the ERG conducted a range of additional scenarios on the company's revised base case model, varying the annual mean number of injections and monitoring visits. These scenarios (ERG Scenarios 1 to 7) are detailed below in Table 8 and Table 9. Furthermore, we conducted a scenario assuming no OCT procedure is performed during an injection administration (ERG Scenario 8). The results of our analyses are summarised in Table 10.

Table 8 Different dosing regimens

	Dosing regimen	Year 1	Year 2	Year 3+
Annual mean number of	**ERG scenario 1 (exploratory scenario)**			
	Faricimab (6 LP → Q16W/Q12W [T&E] → PRN)	6	2	2

injections	Aflibercept (2 LP → PRN)	6	2	2
	Ranibizumab (0.5 LP → PRN)	6	2	2
	ERG Scenario 2 (based on clinical experts' opinions and TA346)			
	Faricimab (6 LP → Q16W/Q12W [T&E] → PRN)	8.42	4.73	1.90
	Aflibercept (2 LP → PRN)	8	4	2.3
	Ranibizumab (0.5 LP → PRN)	8	4	2.3
Separate monitoring visits	**ERG scenario 3 (based on clinical experts' opinions and TA346)**			
	Faricimab (6 LP → Q16W/Q12W [T&E] → PRN)	4	2.3	1.7
	Aflibercept (2 LP → PRN)	4	2.3	1.7
	Ranibizumab (0.5 LP → PRN)	4	2.3	1.7
LP: loading phase; PRN pro re nata (administer as needed); T&E: treat and extend (increase dosing interval) Numbers (e.g. as in "6 LP") reflect the loading phase dose in mg				

Table 9 Different combinations of injection and monitoring visits

Dosing regimen	**Injections**			**Separate Monitoring visits**		
	Year 1	**Year 2**	**Year 3+**	**Year 1**	**Year 2**	**Year 3+**
ERG Scenario 4: Aflibercept on a T&E regimen (assumed same as that of ranibizumab T&E regimen)						
Aflibercept (2 LP → T&E)	9.53	5.40	2.17	3.13	3.90	1.83
ERG Scenario 5: No monitoring visits for aflibercept and ranibizumab in Years 1 & 2						
Faricimab (6 LP → Q16W/Q12W [T&E] → PRN)	8.42	4.73	1.90	0	0	2.10
Aflibercept (2 LP → PRN)	9.20	5.00	2.37	0	0	1.63
Ranibizumab (0.5 LP → PRN)	9.40	5.40	2.17	0	0	1.83
ERG Scenario 6: Similar dosing regimens for faricimab and aflibercept						
Faricimab (6 LP → Q16W/Q12W [T&E] → PRN)	6	2	2	4	2.3	1.7
Aflibercept (2 LP → PRN)	6	2	2	4	2.3	1.7
Ranibizumab (0.5 LP → PRN)	6	2	2	4	2.3	1.7
ERG Scenario 7: Injection dosing visits and monitoring visits based on clinical experts' opinions and TA346 (Scenario 2 + 3)						
Faricimab (6 LP → Q16W/Q12W [T&E] → PRN)	8.42	4.73	1.90	4	2.3	1.7
Aflibercept (2 LP → PRN)	8	4	2.3	4	2.3	1.7
Ranibizumab (0.5 LP → PRN)	8	4	2.3	4	2.3	1.7
ERG Scenario 8: No OCT performed during injection procedure						
Injections and monitoring visits as per the company's base case						
LP: loading phase; PRN pro re nata (administer as needed); T&E: treat and extend (increase dosing interval) Numbers (e.g. as in "6 LP") reflect the loading phase dose in mg						

Table 10 Results from the scenarios conducted by the ERG on the company's revised base case model (PAS price for faricimab and list prices for comparators)

	Incremental cost vs aflibercept	Incremental cost vs ranibizumab
Company base case	[redacted]	[redacted]
ERG scenario 1	[redacted]	[redacted]
ERG scenario 2	[redacted]	[redacted]
ERG scenario 3	[redacted]	[redacted]
ERG scenario 4	[redacted]	[redacted]
ERG scenario 5	[redacted]	[redacted]
ERG scenario 6	[redacted]	[redacted]
ERG scenario 7	[redacted]	[redacted]
ERG scenario 8	[redacted]	[redacted]

4.6.2 ERG's preferred assumptions

The ERG's preferred assumptions are as follows:

- The proportion of patients discontinuing treatment after 5 years is 50%
- Injection dosing visits and monitoring visits based on clinical experts' opinions and TA346 (section 4.6.1, ERG Scenario 7)
- Appointments for treatment and monitoring are non-consultant led (£89.13)
- No OCT procedure performed during an injection administration (section 4.6.1, ERG Scenario 8)

The cumulative results of the ERG's preferred assumptions are shown below in Table 11. The incremental cost for faricimab versus aflibercept [redacted] from [redacted] (company's revised base case) to [redacted] (ERG's preferred case) and that for faricimab versus ranibizumab [redacted] from [redacted] to [redacted].

Table 11 Results from the ERG's preferred assumptions (PAS price for faricimab and list prices for comparators)

Analysis	Incremental cost vs aflibercept	Incremental cost vs ranibizumab
Company's base case	[redacted]	[redacted]
+ 50% treatment discontinuation at 5 years	[redacted]	[redacted]
+ Injection dosing visits and monitoring visits based on clinical experts' opinions and TA346 (ERG Scenario 7)	[redacted]	[redacted]
+ Non-consultant led appointments for treatment and	[redacted]	[redacted]

monitoring (£89.13)		
+ No OCT procedure for injection administration	[redacted]	[redacted]
ERG preferred case	[redacted]	[redacted]

We also conducted two additional scenarios on the ERG preferred case:

- No monitoring visits for aflibercept and ranibizumab in years 1 & 2
- Similar dosing regimens for faricimab and aflibercept

The cost comparison results of these two scenarios are presented below in Table 12.

Table 12 Scenarios conducted on the ERG's preferred model (PAS price for faricimab and list prices for comparators)

Analysis	Incremental cost vs aflibercept	Incremental cost vs ranibizumab
ERG's preferred case	[redacted]	[redacted]
No monitoring visits for aflibercept and ranibizumab in Years 1 & 2	[redacted]	[redacted]
Similar dosing regimens for faricimab and aflibercept	[redacted]	[redacted]

5 ERG conclusions on the cost comparison

- The model structure and key assumptions of the company's cost-comparison model are appropriate, and consistent with the previous NICE aflibercept appraisal TA346.
- The model assumes equal clinical efficacy for all three drugs. However, limitations in in the NMA comparing faricimab against ranibizumab (as discussed in section 3.5) mean that the appropriateness of assuming equal efficacy of faricimab and ranibizumab is uncertain.
- With the PAS price for faricimab and list prices for aflibercept and ranibizumab, faricimab is estimated to be [redacted] than the two comparators. This applies for the company's revised base case analysis and for all the company and ERG scenario analyses. Results with the PAS discounts for faricimab and ranibizumab and the CMU discount for aflibercept are shown in a confidential addendum to this report.
- For the ERG's preferred assumptions, while faricimab is estimated to be [redacted] than the two comparators (at the PAS price for faricimab and list prices for the comparators), there is a [redacted] in the incremental costs of faricimab versus the two comparators compared to the company's revised base case results. For example, the incremental cost for faricimab versus aflibercept [redacted] by [redacted] ([redacted] in the company's revised base case versus [redacted] in the ERG's preferred case) and that for faricimab versus ranibizumab

[redacted] by [redacted] ([redacted] in company's revised base case versus [redacted] in the ERG's preferred case).

- The cost difference between faricimab and the two comparators is most sensitive to assumptions about different treatment regimens and the duration of maximum treatment.

6 References

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National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

ERG report – factual accuracy check and confidential information check

Faricimab for treating diabetic macular oedema [ID3899]

‘Data owners will be asked to check that confidential information is correctly marked in documents created by others in the technology appraisal process before release; for example, the technical report and ERG report.‘ (Section 3.1.29, Guide to the processes of technology appraisals).

You are asked to check the ERG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by 5pm on Friday 14 January 2022 using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as ’commercial in confidence’ in turquoise, all information submitted as ‘academic in confidence’ in yellow, and all information submitted as ‘depersonalised data’ in pink.

Issue 1

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ID3899 faricimab Final ERG report v2.0 10122021 IC [ACIC]_Section 3.2.3_page 11	"One of the ERG's clinical experts expressed concern that relatively limited evidence has been provided for the target population with CRT ≥400 µm given that this is the population for whom NICE recommend the comparator therapies and is the population for which the company are positioning faricimab." This passage should be amended to include the views of the other experts it consulted in relation to this point, or to make it explicit that this was the view of one of four experts.	This statement fails to capture the views of the four experts consulted by the ERG. Excluding the views of other experts could bias the committee's conclusions around this point.	Not a factual inaccuracy. However, in the interests of clarity we have amended the text to indicate that there were four experts. Three experts did not provide views; the expert in question offered their opinion unsolicited.

Issue 2

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ID3899 faricimab Final ERG report v2.0 10122021 IC [ACIC]_Section 3.3.1_page 14	"Two of the ERG's clinical experts commented that careful monitoring of adverse events will be important, given the experience with brolucizumab for AMD in which intraocular inflammation emerged during post-market monitoring." These views should be removed from the ERG's report. At a minimum, the ERG should highlight that the experience of broluciuzmab, a treatment not licensed for use in DMO, are not relevant to the safety of faricimab for DMO.	The experience of brolucizumab in AMD is not relevant to the appraisal of faricimab in DMO and should not included in the ERG's report.	Not a factual inaccuracy. The statement clearly and accurately reflects a concern which was independently raised by the experts, unsolicited by the ERG. The experts were fully aware that brolucizumab is not licensed for DMO and were highlighting general safety concerns relating to intravitreal anti-VEGF therapies. No change made.

Issue 3

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ID3899 faricimab Final ERG report v2.0 10122021 IC [ACIC]_Section 3.4.6_page 22	"As with the base case NMAs, these results should be regarded as illustrative only, since 0.3 and 0.5 mg ranibizumab doses were pooled in the analyses." This statement should be amended to "As with the base case NMAs, these results should be interpreted with caution, since 0.3 and 0.5 mg ranibizumab doses were pooled in the analyses."	In the ERG's view, the pooling of these doses may introduce uncertainty into the analysis. However, the view of 1 expert consulted by the ERG, and those consulted by Roche, suggested that efficacy and safety outcomes would be similar across the 2 doses, and pooling these data would be acceptable. It is inappropriate to suggest that the results are illustrative only. If the ERG has concerns about these particularly analysis, it should be stated in an alternative way.	Not a factual inaccuracy since the results are illustrative of a hypothetical situation (which assumes there is no uncertainty relating to pooling the two doses). However, as the company's alternative wording is acceptable to the ERG we have amended the text as suggested.

Issue 4

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ID3899 faricimab Final ERG report v2.0 10122021 IC [ACIC]_Section 3.4.6_page 23	"The 0.3 mg ranibizumab dose which is not relevant to clinical practice." This should be amended to "The 0.3 mg ranibizumab dose which is not used in UK clinical practice."	Although the 0.3 mg dose of ranibizumab is not used in UK clinical practice, views expressed by clinical experts consulted by Roche and the ERG, suggest outcomes will be the same when treating with 0.3 mg or 0.5 mg doses. As such, it is not factually accurate to state that results based on studies which included the 0.3 mg ranibizumab dose are not irrelevant to this appraisal. It would be more factually accurate to state that	Not a factual inaccuracy. The 0.3mg ranibizumab dose is neither licensed for use nor used in the UK for DMO. However, as the company's alternative wording is acceptable to the ERG we have amended the text as suggested.

		the 0.3 mg dose is not used in UK clinical practice.	

Issue 5

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ID3899 faricimab Final ERG report v2.0 10122021 IC [ACIC]_Section 3.4.6_page 23	"BOULEVARD included 0.3 mg ranibizumab which is not a relevant dose for UK NHS practice" This should be amended to "BOULEVARD included 0.3 mg ranibizumab, a dose not used in UK NHS practice"	Although the 0.3 mg dose of ranibizumab is not used in UK clinical practice, views expressed by clinical experts consulted by Roche and the ERG, suggest outcomes will be the same when treating with 0.3 mg or 0.5 mg doses. As such, it is not factually accurate to state that results based on studies which included the 0.3 mg ranibizumab dose are not irrelevant to this appraisal. It would be more factually accurate to state that the 0.3 mg dose is not used in UK clinical practice.	As with Issue 4 above this is not a factual inaccuracy. However, the company's alternative wording is acceptable to the ERG so we have amended the text as suggested.

Issue 6

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ID3899 faricimab Final ERG report v2.0 10122021 IC [ACIC]_Section 4.4_page 33	The "treatment and monitoring setting costs" row of table 5 inaccurately reports the company results in the incremental cost vs aflibercept section. The company result (see Table 40 company submission_version161121) is consistent	The information presented in Table 5 is incorrect. This table should be corrected to accurately represent the results presented in the company submission.	In CS Table 40, the incremental cost vs aflibercept for 'treatment and monitoring setting costs' is reported as **-£15,995** whereas the ERG obtain the value of **-£15,955** (that is, a difference of £40). We have therefore not removed this row from the table. The treatment and monitoring setting costs

	with the ERG's, and therefore the entire row should be removed from Table 5.		row had an error where -£15,995 was missing the minus symbol. This has been corrected.

ID3899 faricimab Final ERG report v2.0 10122021 IC [ACIC]_Section 4.3.1_~~Table 2~~_page 28	Pooled study data on the percentages of study patients achieving an absence of DMO at 1 year are academic in confidence.	"Varying the positive discontinuation probabilities differently for faricimab, aflibercept and ranibizumab after year 1 whereby it was assumed that [redacted] receiving faricimab and [redacted] receiving aflibercept would stop treatment after 1 year."	We have added the academic in confidence marking as suggested.