NICE National Institute for Health and Care Excellence

Fast Track Appraisal

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

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

FAST TRACK APPRAISAL

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

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**

4. **Patient group, professional group and NHS organisation submission** from:
   a. Macular Society
   b. The College of Optometrists
   c. Royal College of Ophthalmologists

5. **Expert personal perspectives** from:
   a. Dr Clare Bailey – clinical expert, nominated by Roche Products
   b. Professor Ian Pearce – clinical expert, nominated by Roche Products
   c. Mr Brian Naylor– 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 Warwick Evidence
   a. ERG report
   b. ERG addendum re KM TTD data

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 wet age-related macular degeneration [ID3898]

Document B

Company evidence submission

November 2021

File name	Version	Contains confidential information	Date
ID3898_Faricimab for wet AMD_Doc B_REDACTED	1.0	No	23 November 2021

Contents

Tables and figures

Tables

Figures

Abbreviations

AE	Adverse events
AESI	Adverse events of special interest
ALT	Alanine aminotransferase
(n)AMD	(Neovascular) 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
CNV	Choroidal neovascularisation
CPT	Central point 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
FFA	Fundus fluorescein angiography
FTA	Fast track appraisal
IADL	Instrumental activities of daily living
ICGA	Indocyanine green angiography
ILM	Internal limiting membrane
IOI	Intraocular inflammation
IRF	Intraretinal fluid
ITC	Indirect treatment comparison
ITT	Intention to treat
IVT	Intravitreal injection
LLD	Low luminence deficit
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
OCTA	Optical coherence tomography-angiography
ONS	Office for National Statistics
PAS	Patient access scheme
PCV	Polypoidal choroidal vasculopathy
PDR	Proliferative diabetic retinopathy
PED	Pigment epithelial detachment
PRN	Pro re nata (treatment as needed)
PSS	Personal social services
PTI	Personalised treatment interval
QXW	One injection every x weeks
RAP	Retinal angiomatous proliferation
RCT	Randomised clinical trial
RPE	Retinal pigment epithelial
RWD	Real-world data
SAE	Serious adverse event
SAP	Statistical analysis plan
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	Adults with choroidal neovascularisation secondary to age related macular degeneration	Adults with choroidal neovascularisation secondary to age-related macular degeneration	N/A in line with NICE final scope
Intervention	Faricimab	Faricimab	N/A in line with NICE final scope
Comparator(s)	• Aflibercept • Ranibizumab • Brolucizumab • Bevacizumab (does not currently have a marketing authorisation in the UK for this indication) • Best supportive care	• Aflibercept • Ranibizumab	Bevacizumab is not a relevant comparator for this appraisal because: 1. it is not licensed for neovascular AMD (nAMD) in the UK 2. it is used infrequently in clinical practice to treat nAMD in the population which will be the focus of the appraisal. [redacted] 3. as per the cost-comparison methods guide, it will be excluded from the appraisal on the basis of having no associated or published NICE guidance in nAMD. Brolucizumab has been excluded as clinical experts have confirmed to Roche it is not routinely used in clinical practice, as reflected by the January- April 2021 report which indicated a [redacted] market share [redacted]. Best supportive care is also not considered to be a relevant comparator, as patients should be

			offered treatment with established anti-VEGF technologies (such as aflibercept or ranibizumab) (1, 2).
Outcomes	• Visual acuity (the affected eye) • Overall visual function • Central subfield foveal thickness (CSFT) • Adverse effects of treatment • Health-related quality of life	• Visual acuity (the affected eye) • Overall visual function • Central subfield foveal thickness (CSFT) • Adverse effects of treatment • Health-related quality of life	In line with TA155 (1), loss and gain of letters in BCVA outcomes from baseline over time will be presented. In line with TA294 (2), visual outcomes related to loss, gain and change of letters in BCVA will be presented. Total area of choroidal neovascularisation has been measured as an outcome within the pivotal trials.
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	As faricimab is considered 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 case is presented comparing the cost per patient per year of faricimab versus aflibercept and ranibizumab. The base-case time horizon of the model is 25 years. A 25-year time horizon is considered to be a lifetime time horizon for these patients and be sufficiently long enough to capture any important differences in costs between the technologies being compared. Costs will be considered from a National Health Service (NHS) and Personal Social Services perspective.	Faricimab should be appraised through the NICE FTA cost-comparison process, with aflibercept and ranibizumab as the existing licensed and NICE recommended comparators. The results of the TENAYA and LUCERNE trials demonstrate faricimab to be associated with comparable vision outcomes versus aflibercept that is achieved with a lower injection frequency, as well as a comparable safety profile. 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 all comparators.

	sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. 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.	A discount rate of 3.5% will be applied to the costs in the model. The methodology aligns with that stated the addendum to the guide to the methods of technology appraisal.	
Subgroups to be considered	If the evidence allows the following subgroups will be considered: • Lesion is classic or occult neovascularisation in nature.	Change from baseline in BCVA at Week 40/44/48 across various baseline demographic subgroups (e.g. by age, gender, race, baseline LLD, CNV lesion subtype [classic, minimally classic, and occult] and size).	No economic subgroup analyses are considered relevant to this appraisal.
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

Age-related macular degeneration (AMD) is a chronic, progressive disease of the macula, the functional central area of the retina responsible for visual acuity (VA) and colour vision. The condition can be classified into early- and late-stage AMD (4). Failure to treat late-stage AMD with choroidal neovascularisation or neovascular age-related macular degeneration (nAMD) can lead to rapid progression of the disease, resulting in irreversible central vision loss (5). Worldwide, AMD accounts for 5.6% of all blindness and 3.0% of moderate and severe vision impairment (6). AMD is the leading cause of severe vision loss and legal blindness in individuals aged >65 years in Europe, North America, Australia, and Asia (7, 8)

nAMD is one of the advanced stages of AMD, the other being geographic atrophy (GA). In nAMD, new and abnormal blood vessels grow uncontrollably under the macula, causing swelling, bleeding and/or fibrosis. Untreated nAMD eventually leads to irreversible vision loss and blindness, and it is the most debilitating form of AMD (9).

In Europe, nAMD was estimated to affect 2.7 million people in 2016, and this is expected to increase by 44% to 3.9 million in 2040 (10). A meta-analysis applied to the UK 2007–2009 population data estimated the prevalence of AMD in the UK among people aged 50 years or over to be 2.4% (11). This increases to 4.8% in people aged 65 years or over, and 12.2% in people aged 80 years or over. The same study found the prevalence of nAMD to be 1.2 to 6.3%. Estimates indicate that around 40,000 people develop nAMD in the UK each year, which based on a UK population of 67 million equates to approximately 600 new cases per million per year (11, 12).

While the development of nAMD typically manifests initially in one eye, the presence of nAMD in one eye is a major risk factor for the development of nAMD in the fellow eye (13). Data from the UK AMD database as reported in the NICE AMD guidelines (NG82) demonstrates that 42% of patients developed nAMD in the fellow eye over 3 years, equating to a monthly incidence of 1.39% (12).

Pathogenesis

nAMD is a rapidly progressive, degenerative disease of the macula (4). nAMD is characterised by choroidal neovascularisation (CNV), the formation of new blood vessels due to high levels of angiogenic and inflammatory factors, including angiopoietin-2 (Ang-2) (14, 15) and vascular endothelial growth factor (VEGF) (4, 16). This occurs in the choroid, the thin, vascular tissue layer located behind the retina.

nAMD is a multifactorial disease and many pathological processes (including angiogenesis, oxidative stress, and inflammation) are known to contribute to its development (4). Retinal pigment epithelial (RPE) abnormalities are central to all hypothesised mechanisms of nAMD pathogenesis (17). Stress or damage to the RPE, and the immune responses associated with this, may promote the production of the pro-angiogenic factors that drive CNV (17). Degenerative changes in the choroidal vasculature, resulting from pathological alterations

that occurred in early life, may lead to hypoxia and upregulation of angiogenic factors in the choroid, and subsequent CNV (4).

The pathogenesis of nAMD involves concomitant degeneration of proteins within Bruch's membrane, stimulating a chronic inflammatory process that contributes to the development of drusen and activation of the complement pathway (18). The accumulation of drusen results in pathological alteration and dysfunction of the RPE, which in turn results in the upregulation of proangiogenic factors, such as Ang-2 and VEGF-A, leading to the growth of new vessels from the choroid into the outer retina. These new vessels are highly permeable and unstable and leak blood and fluid into the macular tissue. The resultant lipidic, haematic, and inflammatory cell extravasation into the macular tissue threatens the survival of photoreceptors and retinal neuroglia.

The angiopoietin/Tie pathway plays a key role in regulating vascular stability and inflammation under healthy and pathological conditions (19). Angiopoietins Ang-1 and Ang-2 are growth factors that compete for binding to the Tie2 receptor (14). Under normal conditions, Ang-1 binds to and activates Tie2 on vascular endothelial cells, leading to Tie2 autophosphorylation (20). Activated Tie2 promotes survival of endothelial cells and stability of cell junctions, thereby stabilising vasculature (21).

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 (14, 19, 22, 23).

In nAMD, 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 (22), while Ang-2 binding to integrin receptors promotes endothelial cell destabilisation and pericyte apoptosis (24). Ang-2 also promotes inflammation via upregulation of pro-inflammatory cytokines and by enhancing cytokine-induced leukocyte adhesion and transmigration (25). Moreover, monocytes and neutrophils adhere to the vascular endothelium (leukostasis) in an integrin-dependent manner, resulting in endothelial dysfunction and capillary non perfusion (15, 26).

Clinical signs and symptoms

Initial clinical signs of AMD in the aging eye can be found in the macula, where drusen aggregate in the retina. Upon progressing to nAMD, the presence of CNV is the main clinical sign of the disease (17, 27, 28). Symptoms of nAMD include a general haziness in overall vision, and abrupt onset and worsening of AMD symptoms (29, 30). Detachment of the RPE caused by fluid accumulation disturbing the photoreceptors causes image distortion known as metamorphopsia, where straight lines appear distorted (28). The development of a dark patch (scotoma) causing blurriness in central vision, alongside metamorphopsia, can affect patient mobility, reading, facial recognition, driving, and other daily activities, including self-care (31). The presence of sub-retinal scar tissue is also a key marker of the disease (31). Photopsia, the presence of rapid, temporally-located white flashes, are also associated with nAMD (32).

Burden of disease on patients

nAMD is a chronic, debilitating condition, with a substantial impact on the quality of life (QoL) and independence of patients (33). Currently approved treatment options require chronic treatment at regular intervals and frequent eye examinations and clinic visits, representing significant burden for patients, caregivers, and clinicians alike.

In the absence of treatment, patients with nAMD on average experience a loss of 5, 15, and 20 letters at 3 months, 1 year, and 2 years from diagnosis, respectively (34). Declining VA has implications on patient self-sufficiency and self-care in patients with chronic comorbidities, due to impacting their ability to monitor and manage their disease (35). While the introduction of anti-VEGF therapy has revolutionised treatment of nAMD and reduced the number of patients becoming legally blind after 2 years (36), nAMD continues to be associated with burden due to vision loss, which is often significantly underestimated by both clinicians and members of the general public (37).

nAMD causes a severity-dependent decrease in patient QoL (38-40), associated with reduced overall well-being, poorer life satisfaction, more emotional problems, greater social dysfunction, and resulting isolation (41, 42). Furthermore, the QoL of patients with chronic nAMD is significantly lower than the QoL of patients diagnosed with nAMD in the past year (43). The loss in visual acuity results in a reduced ability to perform basic activities of daily living (ADLs), such as self-care and eating, as well as instrumental ADLs (IADLs), which include more cognitively demanding tasks necessary for maintaining independence such as administrative tasks, reading, and driving (40, 44). Of particular importance is the inability to drive or complete near activities such as cooking and doing housework, as these are fundamentally linked with mobility and independence (33, 41). Both baseline IADL levels and changes in IADL levels are significant predictors of mortality. Accordingly, for the average person with nAMD, 6/12 VA is associated with a long-term increase of 5% in length of life vs 6/24 VA (45). In addition, declining IADLs have a profound impact on social isolation and depression and have also been linked to an increased risk for cognitive decline and dementia (46, 47). Patients with nAMD experience increased levels of anxiety and depression (40, 48) and multiple studies have reported an association between vision loss or impairment and suicidal ideation (49-52).

In addition, those diagnosed with nAMD also have an increased risk of falls and fractures (40, 41), with older women experiencing almost twice the risk of injurious falls (self-reported) than matched controls (53). Accordingly, AMD has been associated with a fear of falling, which results in activity limitation (54-56), and this is considered to play a part in mediating the relationship between eye disease and depression (57). As a result, patients with nAMD rely heavily on providers of long-term informal care (e.g. family members) (44), or institutional or residential care (41, 58).

Caregiver burden

The level of care required for patients with nAMD is substantial and is considered to be equivalent to that required for patients with rheumatoid arthritis and multiple sclerosis, and higher than for patients with colorectal cancer (44). Approximately 50% of patients with nAMD require caregiver assistance with IADLs and >10% of patients rely on caregivers for help with basic self-care such as bathing and feeding (44).

Caregivers may take responsibility for duties previously performed by the patient such as household duties and driving, and may experience financial or time pressures (including time away from work or family) in their role (33). Driving is not recommended for patients after treatment (59), even in patients whose VA does not prevent them from driving routinely; patients are therefore reliant on caregiver support to attend treatment or monitoring visits. The caregiver burden associated with regular treatment visits is also substantial, with 70% of caregivers reporting that they spend at least half a day every 4–6 weeks assisting patients with their clinic appointments (44).

The majority of caregiver support for nAMD patients is provided by informal caregivers such as family members or friends (44), and can often include a child or grandchild of the patient (43, 60). These data highlight that the burden of care often falls on younger family members, who are likely to be in full-time employment and may therefore experience greater disruption to their daily routine.

Moreover, there are considerable emotional and psychological impacts on caregivers of patients with nAMD, with many reporting the time spent accompanying patients to treatment or monitoring visits as stressful (61) and the level of depression reported in caregivers is comparable to that experienced by the patients themselves (62). The degree of emotional distress experienced by the caregiver of a patient with nAMD increases with the degree of visual impairment experienced by the care recipient (43).

B.1.3.2 Clinical management

Following a diagnosis of nAMD, the aim of treatment is to provide significant recovery of vision and subsequent maintenance of that vision, while reducing the likelihood of blindness (39, 43, 63-66). IVT injection of anti-VEGF agents is the current standard of care for nAMD as significant gains and maintenance of vision are realised with this approach (67, 68).

Three anti-VEGF agents are currently recommended by NICE for nAMD: brolucizumab (TA672) (69), aflibercept (TA294) (2) and ranibizumab (TA155) (1). Market share data collected from January to April 2021 suggest that [redacted] of patients currently receive aflibercept, with [redacted] and [redacted] receiving ranibizumab and brolucizumab, respectively (70). The market share data for brolucizumab indicates that this regimen is not routinely used in UK clinical practice ([redacted]) (70), which has also been verified by UK clinical experts, therefore brolucizumab is excluded as a comparator for the current submission. Moreover, brolucizumab has been associated with potentially serious adverse events that are not commonly associated with IVT VEGF agents (71, 72), which may result in its use as a first-line therapy being limited to patients who do not respond at all, or are very poor responders to the currently available anti-VEGF treatments (73).

Table 3: Aflibercept and ranibizumab dosing regimens

	Aflibercept	Ranibizumab
Loading dose	Monthly injection for 3 consecutive doses (3 x Q4W) Treatment interval is then extended to every 2 months	Minimum 3 monthly injections (≥3 x Q4W) Monthly injection until maximum VA is achieved and/or no signs of disease activity

Flexible dosing regimen	T&E regimen: Based on the physician's judgement of visual and/or anatomic outcomes, the treatment interval may be maintained at two months or further extended using a T&E dosing regimen, where injection intervals are increased in 2- or 4-weekly increments to maintain stable visual and/or anatomic outcomes. If visual and/or anatomic outcomes deteriorate, the treatment interval should be shortened accordingly.	PRN regimen: Monitoring and treatment intervals should be determined by the physician and should be based on disease activity T&E regimen: once maximum VA is achieved and/or there are no signs of disease activity, the treatment intervals can be extended stepwise until signs of disease activity or visual impairment recur. The treatment interval should be extended by no more than two weeks at a time for wet AMD

AMD, age-related macular degeneration; PRN, pro re nata; Q4W, every 4 weeks; T&E, treat and extend; VA, visual acuity

Bevacizumab is not licensed or formulated for intraocular use and would require compounding of vials. While no major safety issues have been reported with off-label use of bevacizumab for ophthalmological conditions (74), there are potential safety risks with using a drug off-label. Furthermore, as it is not routinely used in UK clinical practice, bevacizumab is therefore not considered a relevant comparator for this submission.

Photodynamic therapy is reserved as an option for those patients who do not respond to anti-VEGF agents. However, NICE guidelines state that photodynamic therapy should only be offered as an adjunct to anti-VEGF as a second-line treatment (and not as a first-line treatment) for nAMD in the context of a randomised trial (12).

Limitations of current treatment and unmet need

While the efficacy of IVT anti-VEGF agents for nAMD is well established (16, 68), best-achievable long-term outcomes require frequent injections and patient monitoring as often as once a month (75, 76), which places a high burden on patients, their caregivers, and healthcare providers (43, 44, 77).

Real-world data suggest that the overall burden of frequent injections and monitoring creates a barrier to effective anti-VEGF treatment that contributes to many patients not achieving or maintaining vision outcomes seen in randomised clinical trials (16, 65, 78-80). Patients must receive sufficient treatment to achieve and maintain consistent vision gains (81). In real-world clinical practice, many patients are treated less frequently than in clinical trials and, as a consequence, may experience unsustained vision outcomes that decline over time (65, 75, 78, 82, 83), as visual outcomes have been shown to be proportional to injection frequency (75, 82, 84).

This difference in outcomes clearly demonstrates the need for more durable treatments that enable efficacy to be sustained with less frequent dosing and visits. This need is echoed by patients, who desire new treatments to have long-lasting efficacy and less frequent injections, without compromising efficacy and safety (33). Similarly, physicians also see improved treatment durability as one of the greatest unmet needs in the treatment of retinal diseases (85, 86).

In addition to the burden on patients and caregivers, the current resource burden on ophthalmology clinics is also substantial due to the onerous schedule of frequent injections with current treatments and is expected to increase further with the growing prevalence of nAMD. nAMD is a chronic condition, and once diagnosed, patients require lifelong care, attending clinics for both monitoring and treatment to avoid vision loss. 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 (86). The frequency of anti-VEGF injections may also result in resources (including funds and/or personnel) being redirected from other eye care services to support anti-VEGF clinic appointments (86-88).

Prior to the COVID-19 pandemic, ophthalmology was the busiest specialty in England with the highest number of attendances for outpatient appointments (89), with delays in hospital eye care services resulting in permanently reduced vision in some patients (90). The COVID-19 pandemic brought additional pressures on the system and a desire among higher-risk patients, which included those patients with nAMD, to attend hospital less frequently. For instance, Wickham et al. demonstrated that the number of both first eye and follow up injections performed across Moorfields Eye Hospital Trust fell significantly in April 2020 following the introduction of isolation measures (91).

COVID-19 has also brought the requirement for more efficient use of healthcare resources and the impact of delayed or under-treatment into urgent focus. It has been estimated that a treatment delay of 3 months could lead to a >50% relative increase in the number of eyes with vision ≤6/60 and a 25% decrease in the number of eyes with driving vision at one year (92). One study found that patients requiring IVT injections (i.e. patients with diabetic macular oedema, proliferative diabetic retinopathy, or both, nAMD, or retinal vein occlusion) had a delay in treatment of 5.34 weeks during the initial lockdown period (March–May 2020). These patients experienced vision loss by their next scheduled visit to ophthalmologic services (93). A separate study also found that patients with nAMD experienced the greatest loss of vision with treatment delay, and these patients were also less likely to return to baseline upon restarting treatment (94). A more durable treatment than current anti-VEGF therapies that extends the duration of the treatment-free interval may reduce the risk of vision loss. The implementation of home monitoring tools may also complement a more durable treatment by supporting patients to monitor their vision between visits and alerting them if they need to seek medical review.

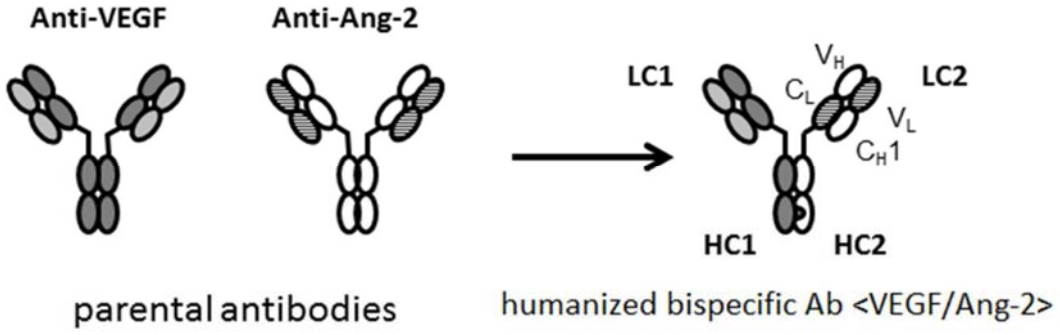
In summary, although IVT anti-VEGF therapy is efficacious for many patients (16, 95), there is still a substantial need for long-lasting efficacy with less frequent injections. As nAMD is a multifactorial disease, novel mechanisms of action targeting pathways in addition to VEGF provide the potential for sustained efficacy and improved durability compared with VEGF inhibition alone. This provides the rationale for developing new treatments, which may facilitate reduced treatment burden and sustained clinical outcomes that are maintained for longer periods.

B.1.3.3 Faricimab for the treatment of nAMD

Faricimab is a humanised bispecific immunoglobulin G1 (IgG1) antibody that acts through inhibition of two distinct pathways by neutralisation of both Ang-2 and 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 (14, 96, 97). 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



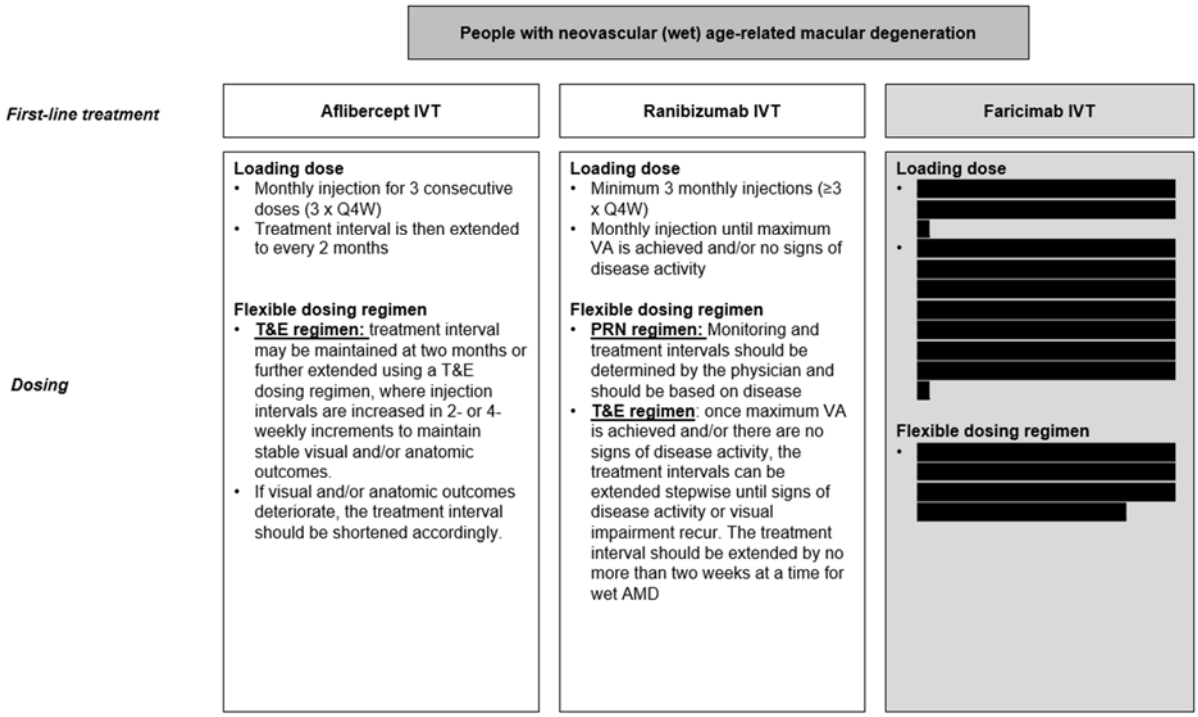
Ab, antibody; Ang-2, angiopoietin-2; HC, heavy chain; LC, light chain; VEGF, vascular endothelial growth factor.
Source: Investigator's Brochure RO686746

The combined evidence from the Phase II studies BP29647 (AVENUE) and CR39521 (STAIRWAY) in nAMD indicated that the 6 mg faricimab dose delivered comparable efficacy with monthly ranibizumab administration but importantly, had the potential to be given at substantially less-frequent treatment intervals (up to Q16W) (98, 99).

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 AMD, as presented below.

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



AMD, age-related macular degeneration; 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)

B.2.1 Clinical outcomes and measures

The comparators for 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 nAMD in NICE TA294 (aflibercept, published 2013) and NICE TA155 (ranibizumab, published 2020).

Aflibercept (TA294)

The pivotal studies for aflibercept considered in TA294 were VIEW 1 and VIEW 2 (100).

- VIEW 1 (n=1217) was a prospective, double blind, randomised (1:1:1:1), active controlled, parallel group, international and multisite, non-inferiority phase III clinical trial carried out at 154 sites in the United States and Canada.
- VIEW 2 (n=1240) was a similarly designed study with patients randomised at 172 sites across Europe, the Middle East, Asia-Pacific and Latin America.

Both trials enrolled patients with active primary subfoveal CNV lesions secondary to AMD, who were then randomised into one of four treatment arms: aflibercept 2 mg q4w, aflibercept 0.5 mg q4w, aflibercept 2 mg q8w, and ranibizumab 0.5 mg q4w. The primary endpoint for both studies was the proportion of patients who maintained vision at Week 52; defined as a loss of <15 ETDRS letters versus baseline.

Ranibizumab (TA155)

Ranibizumab technology appraisal (TA155), presented data from the MARINA (101), ANCHOR (102) and PIER (103, 104) pivotal trials. All three studies were two-year, multi-centre, randomised, double-blinded studies investigating the efficacy and safety of ranibizumab 0.3mg and 0.5mg.

- MARINA (n=716) investigated nAMD patients with either minimally classic or occult choroidal neovascularization (CNV), randomised to receive either ranibizumab (0.3mg or 0.5mg) or sham injection over 24 months on a Q4w treatment basis. The primary end point was the proportion of patients losing fewer than 15 letters from baseline visual acuity at 12 months.
- ANCHOR (n=423) ranibizumab (0.3mg or 0.5mg) was compared to photodynamic therapy, in patients with predominately classic nAMD, who were randomised 1:1:1 across treatment arms and treated on a Q4w basis. The primary, intent-to-treat efficacy analysis was at 12 months measuring the percentage of patients losing <15 letters from baseline visual acuity score.
- PIER (n=184) evaluated ranibizumab (0.3mg or 0.5mg) vs sham in patients with predominately or minimally classic or occult with no classic CNV lesions. Patients were treated Q4w during the loading phase, following by Q12w treatment intervals The primary efficacy endpoint was mean change from baseline visual acuity at month 12.

Table 4 presents the key clinical outcomes and measures considered in TA294 and TA155 (1, 2).

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 nAMD [TA294] (2)	Visual acuity (study eye)	Proportion of patients losing <15 ETDRS letters from baseline at Week 52 (and Week 96)	Yes	VIEW 1, VIEW 2
		Mean change in BCVA from baseline at Week 52 (and Week 96)	Yes	VIEW 1, VIEW 2
		Proportion of patients gaining ≥15 letters from baseline to Week 52 (and Week 96)	Yes	VIEW 1, VIEW 2
	Visual function	Change in CNV area from baseline to Week 52 (and Week 96)	No	VIEW 1, VIEW 2
		Mean change in CSFT from baseline to Week 52 (and Week 96)	No	VIEW 1, VIEW 2
	Adverse events	Ocular AEs; non-ocular AEs	No (inclusion of ocular AEs explored in a scenario analysis only)	VIEW 1, VIEW 2
	HRQoL	Change in total NEI VFQ-25 from baseline to Week 52 (and Week 96)	No	VIEW 1, VIEW 2
		Change in EQ-5D from screening	Yes	VIEW 2 only
Ranibizumab for nAMD [TA155] (1)	Visual acuity (study eye)	Proportion of patients losing <15 ETDRS letters from baseline to 12 months (and 24 months)	Yes	MARINA, ANCHOR, PIER
		Gain of more than 15 ETDRS letters of visual acuity from baseline to 12 months (and 24 months)	Yes	MARINA, ANCHOR, PIER
		Mean change in visual acuity (mean number of ETDRS letters lost or gained) from baseline to 12 months (and 24 months)	Yes	MARINA, ANCHOR, PIER
	Visual function	Mean change in area of leakage from CNV and total area of CNV from baseline over time	Yes	MARINA, ANCHOR, PIER
	Adverse events	Ocular AEs; non-ocular AEs	Yes (only ocular AEs deemed clinically and economically important)	MARINA, ANCHOR
	HRQoL	Change in total NEI VFQ-25 from baseline over time	No	MARINA, ANCHOR, PIER

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; 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 aflibercept cost-effectiveness analysis, as described in TA294 included: the cost of aflibercept and ranibizumab injections; the risk ratio of gaining vision as the main determinant of treatment effect; the frequency of monitoring and the proportion of patients in a one-stop and two-stop model; and the number of injections.

Within the ranibizumab cost-effectiveness analysis, as described in TA155, the key drivers included: the costs of blindness, the costs of injection administration, the number of injections of ranibizumab and the utility values.

The key drivers of the cost-effectiveness from TA294 and TA155, 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.

Table 5: Clinical effectiveness evidence

Study	TENAYA/GR40306, NCT03823287 (105)							LUCERNE/GR40844, NCT03823300 (106)		
Study publications	Primary clinical study report (107) Phase 3 trial design (108) One year efficacy, safety, and durability (Week 48) (109, 110) Primary results (pooled analysis [Week 48]) (111)							Primary clinical study report (112) Phase 3 trial design (108) One year efficacy, safety, and durability (Week 48) (109, 110) Primary results (pooled analysis [Week 48]) (111)		
Study design	Phase III, multicentre, randomised, active comparator-controlled, double-masked, parallel-group, 112-week study to investigate the efficacy, safety, durability, and pharmacokinetics of faricimab administered at up to 16-week intervals to treatment-naive patients with nAMD.									
Population	Adults aged 50 years and older with treatment-naïve choroidal neovascularisation (CNV) secondary to nAMD in the study eye.									
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 2.0 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	TENAYA and LUCERNE are Phase III trials providing efficacy, safety and durability evidence for faricimab in patients with nAMD. Data from TENAYA and LUCERNE were used to inform the efficacy and safety of faricimab in the economic model.									
Reported outcomes specified in the decision problem	• Visual acuity (affected eye) • Overall visual function (both eyes) • Central subfield foveal thickness • Adverse effects of treatment • Health-related quality of life									

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

Unless otherwise stated, information on the TENAYA and LUCERNE studies were sourced from the primary clinical study reports (107, 112).

B.3.3.1 Study design

The TENAYA and LUCERNE studies are ongoing, identical Phase III, multi-centre, randomised, active-comparator controlled, double-masked, parallel-group, 112-week studies, evaluating the efficacy, safety, durability, and pharmacokinetics of the 6 mg dose of faricimab administered at up to 16-week intervals compared with aflibercept monotherapy every 8 weeks (Q8W) in treatment-naive patients with nAMD.

Only one eye was assigned as the study eye. If both eyes were considered eligible (per the inclusion and exclusion criteria), the eye with the worse BCVA, as assessed at screening, was selected as the study eye (unless, based on medical reasons, the investigator deemed the other eye to be more appropriate for treatment in the study).

The studies consisted of a screening period of up to 28 days (Days –28 to –1) in length and has an approximately 108-week treatment period, followed by a final study visit at Week 112 (at least 28 days after the last study treatment administration). A unique screening number was assigned to each screened patient through an interactive web based response system (IxRS). The primary analysis was performed when all patients from the global enrolment phase had either completed the study through Week 48 or had discontinued from the study prior to Week 48. At the time of the primary analysis (CCOD of 20 October 2020 [TENAYA] and 05 October 2020 [LUCERNE]), the study was ongoing.

The primary endpoint was change from baseline in BCVA (as measured on the ETDRS chart at a starting distance of 4 metres) averaged over Weeks 40, 44, and 48. Measuring BCVA change from baseline as an average of weeks 40, 44 and 48, controlled for differences in time from last treatment, and averaging the BCVA over 3 time-points reduced the impact of measurement variability in between tests, and thus provides a more accurate measure of treatment effect on BCVA over a single timepoint measurement.

Study population and randomisation

A total of 671 and 658 patients were enrolled globally in TENAYA and LUCERNE respectively and were randomised in a 1:1 ratio to one of two treatment arms:

- Arm A (faricimab up to Q16W) (n=334 [TENAYA] and n=331 [LUCERNE]): Patients randomised to Arm A received 6 mg of intravitreal faricimab every 4 weeks (Q4W) up to Week 12 (four injections). At Week 20, following a protocol-defined assessment of disease activity, patients in Arm A with active disease received faricimab at that visit and continued on a Q8W dosing regimen. At Week 24, following a second protocol-defined assessment of disease activity, patients in Arm A with active disease (excluding those with active disease at Week 20) received faricimab at that visit, and continued on a Q12W dosing regimen. Patients in Arm A who did not have active disease at Week 20 and Week 24 according to the protocol-defined criteria were treated with on a fixed-Q16W dosing regimen of faricimab. These faricimab dosing

regimens continued until Week 60, and no supplementary therapy was allowed

From Week 60 (when all patients in Arm A are scheduled to receive faricimab) onward, all patients in Arm A are treated according to a personalised treatment interval (PTI) dosing regimen up to Week 108

- Arm B (comparator arm) (Q8W) (n=337 [TENAYA] and n=327 [LUCERNE]): Patients randomised to Arm B received 2 mg of intravitreal aflibercept Q4W up to Week 8 (three injections), followed by 2 mg of intravitreal aflibercept Q8W up to Week 108

Randomisation was stratified by the following baseline factors:

- Baseline best corrected visual acuity (BCVA) Early Treatment Diabetic Retinopathy Study (ETDRS) letter score (≥74 letters, 73–55 letters, ands ≤54 letters);
- Low luminance deficit (LLD) (<33 letters, and ≥33 letters)
- Region (United States and Canada, Asia, and the rest of the world).

A sham procedure was administered to patients in both treatment arms at study visits with no study treatment administration to maintain masking among treatment arms.

The 6 mg dose of faricimab was administered to patients as initiating and maintenance doses in treatment Arm A. The combined evidence from the Phase II studies BP29647 (AVENUE) and CR39521 (STAIRWAY) in nAMD indicated that the 6 mg faricimab dose delivered comparable efficacy with monthly ranibizumab administration but importantly, had the potential to be given at substantially less-frequent treatment intervals (up to Q16W) (98, 99).

The dosing schedule in Year 1 of the TENAYA and LUCERNE studies was based primarily on clinical data from the Phase II study STAIRWAY (98) and was designed to allow the assessment of efficacy of the 6 mg faricimab dose administered at intervals of up to Q16W, as outlined in Figure 3.

Data from the STAIRWAY study suggested that nAMD disease activity could be managed adequately with a faricimab Q12W or Q16W regimen in the majority of patients with nAMD. The option for Q8W dosing (which was shown to be effective in the AVENUE study) was included in the Phase III study design to help ensure that individual treatment needs were met by allowing dosing according to the most appropriate frequency, ranging between Q8W and Q16W.

Weeks 20 and 24 disease activity criteria

Determination of active disease at Weeks 20 and 24 in patients randomised to receive faricimab in TENAYA and LUCERNE were made if any of the following criteria were met:

- Increase >50 µm in central subfield thickness (CST) compared with the average CST value over the previous two scheduled visits (Weeks 12 and 16 for the Week 20 assessment and Weeks 16 and 20 for the Week 24 assessment)

Or

- Increase ≥75 µm in CST compared with the lowest CST value recorded at either of the previous two scheduled visits

Or

- Decrease ≥5 letters in BCVA compared with average BCVA value over the previous two scheduled visits, owing to nAMD disease activity (as determined by the investigator)

Or

- Decrease ≥10 letters in BCVA compared with the highest BCVA value recorded at either of the previous two scheduled visits, owing to nAMD disease activity (as determined by the investigator)

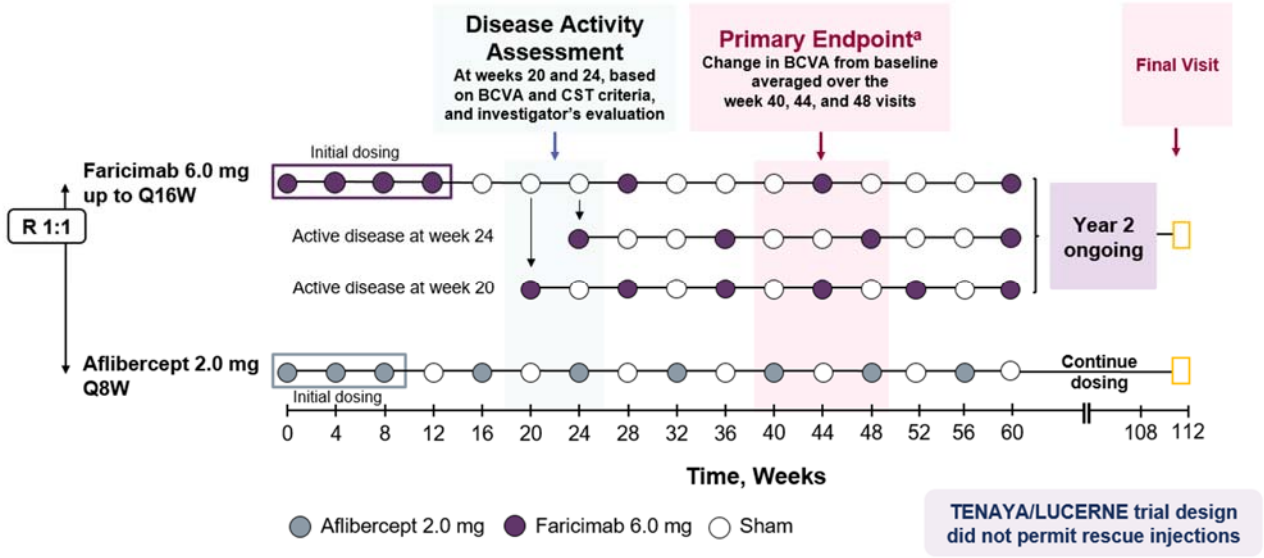
Or

- Presence of new macular haemorrhage (as determined by the investigator), owing to nAMD activity

Patients randomised to faricimab (Arm A) who met the disease activity criteria at Week 20 were treated at this visit and continued with a Q8W dosing regimen of faricimab until Week 60. Patients randomised to faricimab who met the disease activity criteria at Week 24 were treated at this visit and continued with a Q12W dosing regimen of faricimab until Week 60. The remaining patients randomised to faricimab who did not have active disease at Week 20 or Week 24 were treated with a Q16W dosing regimen of faricimab until Week 60.

Additional considerations at Week 24: If there was significant nAMD disease activity at Week 24 that did not meet the above criteria, but which, in the opinion of the investigator, warranted treatment, then these patients received treatment at Week 24 and continued with a faricimab Q12W dosing regimen until Week 60.

Figure 3: Study schema for TENAYA and LUCERNE



BCVA, best-corrected visual acuity; CST, central subfield thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; Q8W, every 8 weeks; Q16W, every 16 weeks; R, randomised.
Screening period from day -29 to day -1.
[a] BCVA was measured using the ETDRS visual acuity chart at a starting distance of 4 m.

B.3.3.2 Summary of study methodology

	TENAYA/GR40306, NCT03823287 (105)	LUCERNE/GR40844, NCT03823300 (106)
Settings and locations of data collection	TENAYA was conducted at 149 sites that enrolled patients in 15 countries: United States (332 sites), United Kingdom (15 sites), Japan (29 sites), Canada (9 sites), Poland (7 sites), Spain (8 sites), Israel (5 sites), Hungary (4 sites), Russia (3 sites), Italy (3 sites), Turkey (3 sites), Germany (3 sites), Mexico (3 sites), Netherlands (2 sites), and Switzerland (2 sites).	LUCERNE was conducted at 122 sites that enrolled patients in 20 countries: United States (41 sites), Australia (9 sites), France (9 sites), Republic of Korea (8 sites), Argentina (7 sites), Italy (6 sites), Spain (6 sites), Germany (4 sites), Poland (4 sites), Russia (4 sites), Turkey (4 sites), Hungary (3 sites), Taiwan (3 sites), Austria (2 sites), Brazil (2 sites), Bulgaria (2 sites), Denmark (2 sites), Hong Kong (2 sites), Portugal (2 sites), Singapore (2 sites).
Trial design	Phase III multicentre, randomised, double-masked, active comparator-controlled study to evaluate the efficacy and safety of faricimab in patients with nAMD.	
Eligibility criteria	**Key inclusion criteria** Patients, aged ≥50 years of age with the following ocular inclusion criteria: • Treatment-naive choroidal neovascularisation (CNV) secondary to nAMD • Subfoveal CNV or juxtafoveal/extrafoveal CNV with a subfoveal component related to the CNV activity identified by FFA or OCT (where CNV activity was defined as showing evidence of subretinal fluid, subretinal hyper-reflective material, or leakage) • CNV lesion of any type (i.e., predominantly classic, classic, minimally classic, or occult [including polypoidal choroidal vasculopathy and retinal angiomatous proliferation]) that exhibited all of the following characteristics: total lesion size of ≤9 disc areas on FFA, CNV component area of ≥50% of the total lesion size (including blood, atrophy, fibrosis and neovascularisation) on FFA, active CNV confirmed on FFA, and CNV exudation confirmed on OCT. • BCVA of 78–24 letters using the Early Treatment Diabetic Retinopathy Study (ETDRS) protocol and assessed at the initial testing distance of 4 meters on Day 1 • Sufficiently clear ocular media and adequate pupillary dilation to allow acquisition of good quality retinal images to confirm diagnosis. **Key ocular exclusion criteria (see CSRs for further details)** Patients who met any of the following ocular exclusion criteria for the study eye were excluded from study entry: • CNV due to causes other than AMD, such as ocular histoplasmosis, trauma, pathological myopia, angioid streaks, choroidal rupture, or uveitis • Any history of macular pathology unrelated to AMD affecting vision or contributing to the presence of intraretinal fluid or subretinal fluid • Presence at screening of central serous chorioretinopathy	

	• RPE tear involving the macula on Day 1 • On FFA/colour fundus photograph (CFP): - Subretinal haemorrhage of >50% of the total lesion area and/or that involved the fovea - Fibrosis or atrophy of >50% of the total lesion area and/or that involved the fovea • Any concurrent intraocular condition that in the opinion of the investigator could either reduce the potential for visual improvement or require medical or surgical intervention during the study • Current vitreous haemorrhage on Day 1 • Uncontrolled glaucoma • Spherical equivalent of refractive error demonstrating more than 8 dioptres of myopia - For patients who had undergone prior refractive or cataract surgery, the preoperative refractive error should not have exceeded -8 dioptres of myopia • Any prior or concomitant treatment for CNV or vitreomacular-interface abnormalities, including, but not restricted to, intravitreal treatment (e.g., anti-VEGF, steroids, tissue plasminogen activator, ocriplasmin, C3F8, air), periocular pharmacological intervention, argon laser photocoagulation, verteporfin photodynamic therapy, diode laser, transpupillary thermotherapy, or ocular surgical intervention • Any cataract surgery or treatment for complications of cataract surgery with steroid or yttrium-aluminum-garnet laser capsulotomy within 3 months prior to Day 1 • Any other intraocular surgery • Prior periocular pharmacological or intravitreal treatment (including anti-VEGF medication) for other retinal diseases Patients who met the following exclusion criterion for the fellow eye (non-study eye) at both the screening and Day 1 visits were excluded from study entry: - Non-functioning non-study eye, defined as either: - BCVA of hand motion or worse - No physical presence of non-study eye (i.e., monocular) Patients who met the following exclusion criteria for either eye were excluded from study entry: • Prior intravitreal administration of faricimab in either eye • History of idiopathic or autoimmune-associated uveitis in either eye • Active ocular inflammation or suspected or active ocular or periocular infection in either eye on Day 1
Trial drugs and concomitant medications	**<u>Trial drugs</u>** • Arm A (faricimab up to Q16W) (n=334 [TENAYA] and n=331 [LUCERNE]): Patients randomised to Arm A received 6 mg of intravitreal faricimab every 4 weeks (Q4W) up to Week 12 (four injections). - At Week 20, patients in Arm A with active disease according to protocol defined criteria received faricimab at that visit and continued on a Q8W dosing regimen. - At Week 24, patients in Arm A with active disease according to protocol defined criteria (excluding those with active disease at Week

	20) received faricimab at that visit, and continued on a Q12W dosing regimen. - Patients in Arm A who did not have active disease at Week 20 and Week 24 according to the protocol-defined criteria were treated with a fixed-Q16W dosing regimen of faricimab. - These faricimab dosing regimens continued until Week 60, and no supplementary therapy was allowed • Arm B (comparator arm) (Q8W) (n=337 [TENAYA] and n=327 [LUCERNE]): Patients randomised to Arm B received 2 mg of intravitreal aflibercept Q4W up to Week 8 (three injections), followed by 2 mg of intravitreal aflibercept Q8W up to Week 108 **<u>Sham procedure</u>** • A sham procedure was administered to patients in both treatment arms at study visits with no study treatment administration to maintain masking among treatment arms. **<u>Concomitant medications</u>** **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., dexamethasone, fluocinolone acetonide), or chronic topical ocular corticosteroids in study eye • Concurrent use of any macular photocoagulation or photodynamic therapy with verteporfin in the study eye • Other experimental therapies (except those comprising vitamins and minerals) **Permitted concomitant medications:** Patients could continue to receive medications and standard treatments administered for other conditions. 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 (YAG) capsulotomy, peripheral iridotomy, argon/selective laser trabeculoplasty, or ocular allergic conditions • Patients who required anti-VEGF treatment for their fellow eye could continue or have fellow eye treatment initiated
Primary outcome	**Primary endpoint:** • Change from baseline in BCVA (as measured on the ETDRS chart at a starting distance of 4 metres) averaged over Weeks 40, 44, and 48
Other outcomes used in the economic	**Secondary endpoints:** • Change from baseline in BCVA over time

model/specified in the scope	• Proportion of patients gaining ≥15 or ≥10 letters in BCVA from baseline averaged over Weeks 40, 44, and 48 and over time • Proportion of patients avoiding loss of ≥15 or ≥10 letters in BCVA from baseline averaged over Weeks 40, 44, and 48 and over time • Proportion of patients gaining ≥15 letters from baseline or achieving BCVA of ≥84 letters averaged over Weeks 40, 44, and 48 and over time • Proportion of patients in the faricimab arm on a Q8W, Q12W, and Q16W treatment interval at Weeks 48, 60, and 112 • Number of study drug injections received through Weeks 48, 60, and 112 • Change from baseline in CST at Week 52/56/60 • Change from baseline in CST over time • Change from baseline in total area of CNV lesion at Week 48 • Change from baseline in total area of leakage at Week 48 **Exploratory objectives:** • Change from baseline in NEI VFQ-25 composite over time **Safety endpoints** • Incidence and severity of ocular adverse events • Incidence and severity of non-ocular adverse events
Pre-planned subgroups	The primary endpoint of the adjusted mean change from baseline in BCVA at Week 40/44/48 was analysed across subgroups including: • Baseline BCVA (≥74 letters, 73–55 letters, and ≤54 letters) • Region (United States and Canada, Asia, and the rest of the world) • LLD (<33 letters and ≥33 letters) • CNV lesion subtype (classic, minimally classic, and occult) • Total CNV lesion area (<1 mm^2, 1–3 mm^2, and >3 mm^2) • CNV lesion size (<1 mm^2, 1–3 mm^2, and >3 mm^2) • Age (<75 years and ≥75 years) • Gender • Race (White, Asian, and other)

AMD, age-related macular degeneration; BCVA, best corrected visual acuity; BM, Bruch's membrane; CFP, colour fundus photograph; CNV, choroidal neovascularisation; CST, central subfield thickness; ETDRS Early Treatment Diabetic Retinopathy Study; FFA, fundus fluorescein angiography; ILM, internal limiting membrane; LLD, low luminance deficit; NEI VFQ-25, National Eye Institute 25-Item Visual Function Questionnaire; OCT, optical coherence tomography; OCTA, optical coherence tomography-angiography; RPE, retinal pigment epithelial; VEGF vascular endothelial growth factor.

B.3.3.3 Patient demographics and baseline characteristics

Patient demographics were comparable across the two studies, with the exception that the majority of patients were predominantly from North America in TENAYA (~54.5%), and Rest of the World (i.e. not North America or Asia) in LUCERNE (~49.1%). The majority of patients were female (~60%) and White (>86%). In the pooled ITT population, patient ages ranged from 50 to 99 years, with a mean of 75.9 years.

At the time of screening, patient-reported time since AMD diagnosis was comparable between treatment arms in TENAYA and LUCERNE, and in the pooled ITT population. In the pooled ITT population, the mean (median [minimum–maximum]) time since nAMD diagnosis was 2.4 (0.6 [0–187]) months in the faricimab arm and 1.4 (0.7 [0–51]) months in the aflibercept arm.

At baseline, ocular characteristics were generally comparable between treatment arms in TENAYA and LUCERNE, comparable across studies, and comparable between treatment arms in the pooled ITT population.

In the pooled ITT population, mean BCVA values at baseline were 60.0 and 60.2 letters and mean LLD values at baseline were 25.1 and 25.9 letters in the faricimab and aflibercept arms, respectively. Overall, 56.6% of patients had a lens status of phakic and 43.4% were pseudophakic.

In the pooled ITT population, mean baseline CST was 356.8 µm in the faricimab arm and 357.5 µm in the aflibercept arm. Overall, intraretinal fluid (IRF) was absent in 53.6% of patients, subretinal fluid (SRF) was absent in 32.4% of patients, and pigment epithelial detachment (PED) was absent in 7.9% of patients. CNV lesion location (determined by FFA) was most commonly subfoveal (59.2%), followed by juxtafoveal (25.1%) and extrafoveal (13.7%). The most common CNV lesion types were occult (49.8%), classic (27.4%), and minimally classic (9.3%). Mean total area of CNV lesion (determined by FFA) was 4.7 mm2 in the faricimab arm and 4.4 mm2 in the aflibercept arm.

At baseline, the number of patients who participated in optional indocyanine green angiography (ICGA) and OCTA imaging was low. In the pooled ITT population, 16 out of 311 patients (5.1%) with ICGA imaging had polypoidal choroidal vasculopathy (PCV), and 34 out of 310 patients (11.0%) had evidence of retinal angiomatous proliferation (RAP). Among the 235 patients who had OCTA performed, the majority had either type 1 (120 patients, 51.1%) or mixed type CNV (86 patients, 36.6%).

Table 6: Baseline demographics and patient characteristics: TENAYA and LUCERNE

	TENAYA		LUCERNE		Pooled (TENAYA and LUCERNE)		
	Fari 6.0 mg n=334	Afli 2.0 mg n=337	Fari 6.0 mg n=331	Afli 2.0 mg n=327	Fari 6.0 mg n=665	Afli 2.0 mg n=664	All patients N=1329
Region, n (%)							
US and Canada	182 (54.5)	184 (54.6)	135 (40.8)	132 (40.4)	317 (47.7)	316 (47.6)	633 (47.6)
Rest of the World	126 (37.7)	127 (37.7)	161 (48.6)	162 (49.5)	287 (43.2)	289 (43.5)	576 (43.3)
Asia	26 (7.8)	26 (7.7)	35 (10.6)	33 (10.1)	61 (9.2)	59 (8.9)	120 (9.0)
Age, years							
Median	77.0	77.0	75.0	76.0	76.0	77.0	76.0
Min–Max	50–99	51–95	50–95	50–95	50–99	50–95	50–99
≥75, n (%)	204 (61.1)	213 (63.2)	175 (52.9)	186 (59.9)	379 (57.0)	409 (61.6)	788 (59.3)
Sex, male, n (%)	143 (42.8)	126 (37.4)	128 (38.7)	139 (42.5)	271 (40.8)	265 (39.9)	536 (40.3)
Ethnicity, n (%)							
Not Hispanic or Latino	303 (90.7)	308 (91.4)	287 (86.7)	274 (83.8)	590 (88.7)	582 (87.7)	1172 (88.2)
Hispanic or Latino	26 (7.8)	26 (7.7)	35 (10.6)	46 (14.1)	61 (9.2)	72 (10.8)	133 (10.0)
Unknown	2 (0.6)	2 (0.6)	5 (1.5)	3 (0.9)	7 (1.1)	5 (0.8)	12 (0.9)
Not stated	3 (0.9)	1 (0.3)	4 (1.2)	4 (1.2)	7 (1.1)	5 (0.8)	12 (0.9)
Study eye, right, n (%)	166 (49.7)	178 (52.8)	168 (50.8)	170 (52.0)	334 (50.2)	348 (52.4)	682 (51.3)
Bilateral eligibility, n (%)							
n	7	10	13	7	20	17	37
Eye with worse BCVA selected	5 (1.5)	9 (2.7)	7 (2.1)	6 (1.8)	12 (1.8)	15 (2.3)	27 (2.0)
Eye with better BCVA selected	2 (0.6)	1 (0.3)	6 (1.8)	1 (0.3)	8 (1.2)	2 (0.3)	10 (0.8)
No diff in BCVA between eyes	0	0	0	0	0	0	0
Months since AMD diagnosis, mean (SD)	1.5 (4.8)	1.1 (2.7)	3.2 (4.5)	1.7 (4.5)	2.4 (10.8)	1.4 (3.7)	1.9 (8.1)
BCVA, letters, mean (SD)	61.3 (12.5)	61.5 (12.9)	58.7 (14.0)	58.9 (13.3)	60.0 (13.3)	60.2 (13.1)	60.1 (13.2)
Categories, n (%)							
≥74	47 (14.1)	52 (15.4)	45 (13.6)	39 (11.9)	92 (13.8)	91 (13.7)	183 (13.8)
73–55	200 (59.9)	201 (59.6)	181 (54.7)	183 (56.0)	381 (57.3)	384 (57.8)	765 (57.6)
≤54	87 (26.0)	84 (24.9)	105 (31.7)	105 (32.1)	191 (28.9)	189 (28.5)	381 (28.7)

Missing/invalid	0	0	0	0	0	0	0
Low-luminance visual acuity, letters, mean (SD)	36.0 (15.6)	35.3 (16.4)	33.6 (16.2)	33.2 (16.8)	34.8 (16.0)	34.2 (16.6)	34.5 (16.3)
Low-luminance deficit, letters, mean (SD)	25.3 (12.9)	26.1 (13.2)	25.0 (12.6)	25.8 (13.5)	25.1 (12.7)	25.9 (13.3)	25.5 (13.0)
Categories, n (%)							
<33	236 (70.7)	235 (69.7)	238 (71.9)	234 (71.6)	474 (71.3)	469 (70.6)	943 (71.0)
≥33	95 (28.4)	98 (29.1)	89 (26.9)	93 (28.4)	184 (27.7)	191 (28.8)	375 (28.2)
Missing/invalid	3 (0.9)	4 (1.2)	4 (1.2)	0	7 (1.1)	4 (0.6)	11 (0.8)
Intraocular pressure, mmHg, mean (SD)	15.0 (2.8)	15.0 (2.9)	14.9 (3.0)	14.8 (3.0)	15.0 (2.9)	14.9 (3.0)	14.9 (3.0)
Lens status, n (%)							
Phakic	193 (57.8)	184 (54.6)	190 (57.4)	185 (56.6)	383 (57.6)	369 (55.6)	752 (56.6)
Pseudophakic	141 (42.2)	153 (45.4)	141 (42.6)	142 (43.4)	282 (42.4)	295 (44.4)	577 (43.4)
Aphakic	0	0	0	0	0	0	0
Other	0	0	0	0	0	0	0
CST (ILM-BM), µm, mean (SD)	486.4 (178.6)	473.9 (166.8)	490.3 (194.9)	469.6 (176.4)	488.3 (186.8)	471.8 (171.5)	480.1 (179.4)
CST (ILM-RPE), µm, mean (SD)	360.5 (124.1)	356.1 (107.0)	353.1 (120.1)	359.0 (131.1)	356.8 (122.1)	357.5 (119.4)	357.2 (120.7)
Absence of IRF, yes, n (%)	181 (54.2)	177 (52.5)	184 (55.6)	171 (52.3)	365 (54.9)	348 (52.4)	713 (53.6)
Absence of SRF, yes, n (%)	113 (33.8)	107 (31.8)	107 (32.3)	103 (31.5)	220 (33.1)	210 (31.6)	430 (32.4)
Absence of PED, yes, n (%)	29 (8.7)	26 (7.7)	23 (6.9)	27 (8.3)	52 (7.8)	53 (8.0)	105 (7.9)
CNV location by FFA, n (%)							
Subfoveal	201 (60.2)	186 (55.2)	209 (63.1)	191 (58.4)	410 (61.7)	377 (56.8)	787 (59.2)
Juxtafoveal	88 (26.3)	88 (26.1)	73 (22.1)	84 (25.7)	161 (24.2)	172 (25.9)	333 (25.1)
Extrafoveal	41 (12.3)	55 (16.3)	42 (12.7)	44 (13.5)	83 (12.5)	99 (14.9)	182 (13.7)
Missing/not done	4 (1.2)	8 (2.4)	7 (2.1)	8 (2.4)	11 (1.7)	16 (2.4)	27 (2.0)
CNV lesion type by FFA, n (%)							
Occult	177 (53.0)	174 (51.6)	171 (51.7)	140 (42.8)	348 (52.3)	314 (47.3)	662 (49.8)
Classic	84 (25.1)	73 (21.7)	98 (29.6)	109 (33.3)	182 (27.4)	182 (27.4)	364 (27.4)
Minimally classic	32 (9.6)	30 (8.9)	30 (9.1)	31 (9.5)	62 (9.3)	61 (9.2)	123 (9.3)

RAP	14 (4.2)	27 (8.0)	14 (4.2)	15 (4.6)	28 (4.2)	42 (6.3)	70 (5.3)
Predominantly classic	17 (5.1)	19 (5.6)	6 (1.8)	16 (4.9)	23 (3.5)	35 (5.3)	58 (4.4)
Missing/not done	4 (1.2)	8 (2.4)	7 (2.1)	8 (2.4)	11 (1.7)	16 (2.4)	27 (2.0)
PCV	6 (1.8)	6 (1.8)	5 (1.5)	8 (2.4)	11 (1.7)	14 (2.1)	25 (1.9)
Total area of CNV lesion, mm^2, mean (SD)	4.7 (4.8)	4.5 (4.1)	4.7 (4.7)	4.3 (4.3)	4.7 (4.8)	4.4 (4.2)	4.5 (4.5)
CNV type by OCT-A							
n	55	36	72	72	127	108	235
Type 1	28 (50.9)	14 (38.9)	41 (56.9)	37 (51.4)	69 (54.3)	51 (47.2)	120 (51.1)
Type 2	3 (5.5)	5 (13.9)	9 (12.5)	5 (6.9)	12 (9.4)	10 (9.3)	22 (9.4)
Type 3	0	3 (8.3)	2 (2.8)	5 (2.8)	2 (1.6)	5 (4.6)	7 (3.0)
Mixed	24 (43.6)	14 (38.9)	20 (27.8)	28 (38.9)	44 (34.6)	42 (38.9)	86 (36.6)
Polypoidal	0	0	0	0	0	0	0
PCV status by ICGA,							
n	82	71	85	73	167	144	311
Yes, n (%)	4 (4.9)	3 (4.2)	4 (4.7)	5 (6.8)	8 (4.8)	8 (5.6)	16 (5.1)
Evidence of RAP by ICGA							
n	82	70	85	73	167	143	310
Yes, n (%)	10 (12.2)	7 (10.0)	8 (9.4)	9 (12.3)	18 (10.8)	16 (11.2)	34 (11.0)

AMD, age-related macular degeneration; BCVA, best-corrected visual acuity; BM, Bruch's membrane; CRC, central reading centre; CST, central subfield thickness; CNV, choroidal neovascularisation; FFA, fundus fluorescein angiography; ICGA, indocyanine green angiography; IRF, intraretinal fluid; ILM, internal limiting membrane; OCT-A, optical coherence tomography-angiography; PCV, polypoidal choroidal vasculopathy; PED, pigment epithelial detachment; RAP, retinal angiomatous proliferation; RPE. retinal pigment epithelium; SRF, subretinal fluid.
Baseline is defined as the last available measurement obtained on or prior to randomisation.
CST(ILM-BM) is defined as the distance between ILM and BM as assessed by the CRC.
CST(ILM-RPE) is defined as the distance between ILM and RPE 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 48 or had discontinued from the study prior to Week 48, whichever is later (i.e., timing was defined as the primary analysis last patient last visit [LPLV], and all data collected on or prior to the primary LPLV in the global enrolment 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 112 or have discontinued early from the study, and all data from the global enrolment phase are in the database and have been cleaned and verified.

B.3.4.2 Statistical hypothesis

The primary comparison was to test non-inferiority of faricimab (up to Q16W) compared with aflibercept (Q8W), as measured by the primary endpoint–change from baseline in BCVA averaged over Weeks 40, 44, and 48, in the intent-to-treat (ITT) population. The non-inferiority test was conducted with a non-inferiority margin of 4 letters at the one-sided 0.02485 significance level.

The null hypothesis: H_0: $\mu^{faricimab} - \mu^{aflibercept} \leq -4$ letters, and the alternative hypothesis: H_a: $\mu^{faricimab} - \mu^{aflibercept} > -4$ letters, will be tested, where $\mu^{faricimab}$ and $\mu^{aflibercept}$ are the expected change from baseline in BCVA averaged over Weeks 40, 44, and 48 for the faricimab and aflibercept arms respectively. If the lower bound of a two-sided 95.03% CI for the difference in adjusted means of the two treatments was greater than -4 letters (the non-inferiority margin), then faricimab was considered non-inferior to aflibercept.

B.3.4.3 Planned sample size

Determination of sample size was based on patients enrolled in the global enrolment phase. Enrolment of approximately 640 patients was planned. Patients were randomised in a 1:1 ratio to receive treatment with faricimab (Arm A) or aflibercept (Arm B). The primary comparison was between the active comparator (aflibercept Q8W) and the faricimab up to Q16W arm.

A sample size of approximately 320 patients in each arm provided greater than 90% power to show non-inferiority of faricimab to aflibercept in the change in BCVA averaged over Weeks 40, 44, and 48 in the ITT population, using a non-inferiority margin of 4 letters, and under the following assumptions

- No difference in the mean change from baseline in BCVA between two treatment arms

- Standard deviation of 14 letters for the change from baseline in BCVA averaged over Weeks 40, 44, and 48
- Two-sample t-test
- 2.5% one-sided type I error rate
- 10% dropout rate

As per health authority feedback, for each unmasked iDMC safety review performed prior to the primary analysis (3 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 0.0497. This type I error adjustment was not expected to impact the sample size or power.

B.3.4.4 Analysis populations

Table 7: TENAYA and LUCERNE analysis populations

Population	Description
Intent-to-treat population (ITT)	All patients who were randomised in the study. For analyses based on this patient population, patients were 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. For analyses based on this patient population, patients were grouped according to the actual treatment received. If by error, a patient received a combination of different active study drugs (faricimab and aflibercept) in the study eye, the patient's treatment arm was as randomised. Prior to study unblinding, protocol deviations were reviewed and a determination of the definition of the population for per-protocol analysis was made. Efficacy analysis based on this patient population was supplementary and therefore the PP population is not discussed in detail in this dossier
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, unless otherwise specified. A supplemental analysis based on the PP population was also conducted for the primary endpoint. 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 (≥74 letters, 73–55 letters, and ≤54 letters), LLD (<33 letters and ≥33 letters), and region (United States and Canada, Asia, and the rest of the world). The stratification factors as recorded in IxRS were used.

The primary comparison was between the active comparator (aflibercept Q8W) and the faricimab up to Q16W arm. Continuous outcomes were analysed using a mixed model for repeated measurements (MMRM). Binary endpoints were analysed using stratified

estimation for binomial proportions. The estimates and CIs were provided for the mean (for continuous variables) or proportion (for binary variables) for each treatment arm and the difference in means or proportions between two treatment arms. All CIs were two-sided and at the 95.03% level.

Additional supplemental analyses were performed for the primary efficacy endpoint comparisons using different intercurrent event handling strategies to assess the robustness of assumptions and the impact of the COVID-19 pandemic.

Primary efficacy endpoint and hypothesis testing

The primary efficacy endpoint was the change from baseline in BCVA averaged over Weeks 40, 44, and 48.

The primary estimand was defined as follows:

- Population: Adult treatment-naive patients with nAMD, as defined by the inclusion/exclusion criteria (ITT Population)
- Variable: Change in BCVA score from baseline averaged over Weeks 40, 44, and 48. BCVA score was based on the ETDRS VA chart assessed at a starting distance of 4 meters
- Intercurrent events:
    - Discontinuation of study treatment due to AEs or lack of efficacy not due to COVID-19: A treatment policy strategy was applied where all observed values were used regardless of the occurrence of the intercurrent event.
    - Use of any prohibited systemic treatment or prohibited therapy in the study eye not due to COVID-19: A treatment policy strategy was applied where all observed values were used regardless of the occurrence of the intercurrent event.
    - Discontinuation of study treatment due to COVID-19: A hypothetical strategy was applied where all values were censored after the intercurrent event.
    - Use of any prohibited systemic treatment or prohibited therapy in the study eye due to COVID-19: A hypothetical strategy was applied where all values were censored after the intercurrent event.
    - Missed dose(s) with potentially major impact on efficacy due to COVID-19: A hypothetical strategy was applied where all values were censored after the intercurrent event
    - COVID-19 death: A hypothetical strategy was applied.
- Population-level summary: Difference in adjusted mean between faricimab (up to Q16W) and aflibercept (Q8W) arms

The primary comparison was to test non-inferiority of faricimab (up to Q16W) compared with aflibercept (Q8W) in the ITT population. The non-inferiority test was conducted with a non-inferiority margin of four letters at the one-sided 0.02485 significance level. For the primary efficacy endpoint, if the lower bound of a two-sided 95.03% CI for the difference in adjusted means of the two treatments was greater than -4 letters (the non-inferiority margin), then faricimab was considered non-inferior to aflibercept.

The primary analysis was performed using a MMRM. The model included the change from baseline at Weeks 4–48 as the response variable and included the categorical covariates of

treatment arm, visit, visit-by-treatment arm interaction, baseline BCVA (continuous), as well as randomisation stratification factors as fixed effects. Comparisons between the two treatment arms were made using a composite contrast over Weeks 40, 44, and 48. The MMRM model assumed an unstructured covariance structure, as pre-specified in the SAP. All MMRM analyses used an unstructured covariance structure.

Missing data were implicitly imputed by the MMRM model, assuming a missing at random (MAR) missing data mechanism. Non-standard BCVA data (assessed by ETDRS BCVA testing with prior visit refraction, test performed by unmasked certified ETDRS BCVA assessor, or by uncertified experienced ETDRS BCVA assessor and invalid BCVA data (BCVA testing performed incorrectly) were excluded from the analyses.

Sensitivity/supplemental analyses

The following sensitivity analysis using a different handling of missing data was performed for the primary efficacy endpoint to evaluate the robustness of the primary analysis finding: last observation carried forward (LOCF). The estimand and analysis method was the same as the primary analysis, with the exception that any missing BCVA assessments due to any reason were imputed using the last available post-baseline observation prior to the occurrence of missing data or prior to the occurrence of a COVID-19 related intercurrent event. Additionally, BCVA assessments after the COVID-19 related intercurrent event were censored and were imputed using the last available post-baseline observation prior to the COVID-19 intercurrent event.

A number of supplementary analyses were performed for the primary efficacy endpoint comparisons to provide further understanding of treatment effect. These include PP analysis, analysis using different handling rules for intercurrent events, analysis of covariance (ANCOVA) analysis, trimmed mean analysis, and multiple imputation.

The following supplementary analyses were performed for the primary efficacy endpoint to provide further understanding of treatment effect:

- **Per-protocol analysis**: following the same analysis method as the primary analysis with the exception of analysis based on PP population
- **Analysis using different handling rules for intercurrent events**: populations and definition of intercurrent events were the same as the primary analysis with the exception that:
    - If a patient discontinued from study treatment due to AEs or lack of efficacy and did not receive prohibited therapy after discontinuation, a treatment policy estimand approach was followed where all observed values were used regardless of the occurrence of intercurrent events.

      If a patient received any prohibited systemic treatment or prohibited therapy in the study eye, a hypothetical estimand approach was followed where all values were censored at the time of use of prohibited therapy.
- **Trimmed Mean Analysis:** The analysis was used to assess the difference in BCVA between two treatment arms using a truncated distribution, truncating patients with

the worst outcome, with the assumption that patients have the worst outcome after intercurrent events. The estimand was defined as follows:

1. Population: Adult treatment-naive patients with nAMD, as defined by the inclusion/exclusion criteria
2. Variable: Change in BCVA score from baseline averaged over Weeks 40, 44, and 48. BCVA score was based on the ETDRS VA chart assessed at a starting distance of 4 metres.
3. Intercurrent events: Assume patients have the worst outcome after the following intercurrent events up to Week48: Discontinuation of study treatment due to AEs or lack of efficacy, use of any prohibited systemic treatment or prohibited therapy in the study eye, population-level summary: Difference in adjusted trimmed mean between faricimab (up to Q16W) and aflibercept (Q8W) arms

The trimmed mean analysis was performed using an analysis of covariance (ANCOVA) model with adjustment for covariates. The dependent variable in the ANCOVA model was the average of non-missing values of Weeks 40, 44, and 48 assessments in change from baseline in BCVA score (if at least one assessment is available then the average of the non-missing assessments were used), categorical covariates of treatment arm, baseline BCVA (continuous), as well as randomization stratification factors were used as fixed effects

Secondary endpoints

The 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.

The binary secondary endpoints were analysed using the population, intercurrent events, and handling of intercurrent events, with the following analysis method:

The proportion of patients in each treatment arm and the overall difference in proportions between treatment arms was estimated using the weighted average of the observed proportions and the differences in observed proportions over the strata defined by randomisation stratification factor of baseline BCVA score and region using the Cochran-Mantel-Haenszel (CMH) weights. CIs of the proportion of patients in each treatment arm and the overall difference in proportions between treatment arms were calculated using the normal approximation to the weighted proportions. 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. In addition, the binary endpoints were summarised using descriptive statistics after censoring observations following COVID-19 related intercurrent events.

The primary comparison for the secondary endpoints was faricimab (up to Q16W) versus aflibercept (Q8W).

B.3.4.6 Safety reporting and analysis

Safety analyses were based on the safety-evaluable population. Baseline for safety analyses is defined as the last available measurement prior to first exposure to study drug.

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 48 data in the safety-evaluable population. Laboratory data were summarised descriptively by treatment arm and by timepoint.

B.3.5 Quality assessment of the relevant clinical effectiveness evidence

An overview of the quality assessment for TENAYA and LUCERNE 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	TENAYA (NCT03823287)	LUCERNE (NCT03823300)
Was randomisation carried out appropriately?	Yes	Yes
Was the concealment of treatment allocation adequate?	Yes	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	Yes
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 TENAYA and LUCERNE 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 60 (113).

B.3.6.1 Primary endpoint: change from baseline in BCVA

Week 40/44/48

Both TENAYA and LUCERNE met the primary endpoint of non-inferiority. Patients treated with faricimab had a non-inferior mean change from baseline in BCVA at Week 40/44/48 compared with patients treated with aflibercept, as the lower bound of the 95.03% confidence interval for the adjusted mean difference between the faricimab and aflibercept arms was greater than -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 40/44/48 was 6.2 and 5.9 letters in the faricimab and aflibercept arms, respectively; the difference between the faricimab arm when compared with the aflibercept arm was 0.4 letters (95% CI: -0.9, 1.6) (Table 9).

Week 52/56/60

In both TENAYA and LUCERNE, the adjusted mean change from baseline in BCVA averaged over Weeks 52, 56, and 60 (hereafter represented as Week 52/56/60) in the faricimab arm [redacted].

At Week 52/56/60, the difference in adjusted mean change from baseline in BCVA between the faricimab and aflibercept arms was 0.7 (95% CI: -1.2, 2.7) in TENAYA and -0.6 (95% CI: -2.4, 1.3) in LUCERNE. In the pooled ITT population, the difference between treatment arms was [redacted] at Week 52/56/60 Table 9.

Supplementary analysis

In both TENAYA and LUCERNE, the primary efficacy results were consistent between the ITT and PP populations and were supported by multiple supplementary analyses (Table 10). Note the trimmed mean results are larger for each treatment due to truncating patients with the worst outcome; however, the difference between treatment arms is consistent.

The change from baseline in BCVA at Week 52/56/60 was also consistent between the ITT and PP populations in both studies and was supported by multiple supplementary analyses (Table 11).

Table 9: Change from Baseline in BCVA in the study eye from the individual and pooled Phase III nAMD studies at Week 40/44/48 and at Week 52/56/60: MMRM Method (primary estimand) (ITT population)

	TENAYA		LUCERNE		Pooled TENAYA and LUCERNE	
	Fari 6.0 mg n=334	Afli 2.0 mg n=337	Fari 6.0 mg n=331	Afli 2.0 mg n=327	Fari 6.0 mg n=665	Afli 2.0 mg n=664
Average of week 40, 44 and 48						
n	292	300	302	291	594	591
Adjusted mean (SE)	5.8 (0.64)	5.1 (0.64)	6.6 (0.64)	6.6 (0.64)	6.2 (0.45)	5.9 (0.45)
95% CI for adjusted mean	(4.6, 7.1)	(3.9, 6.4)	(5.3, 7.8)	(5.3, 7.8)	(5.3, 7.1)	(5.0, 6.7)
Diff in adj means vs afli (SE)	0.7 (0.91)		0.0 (0.91)		0.4 (0.64)	
95% CI for adjusted mean diff	(-1.1, 2.5)		(-1.7, 1.8)		(-0.9, 1.6)	
Average of week 52, 56 and 60						
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI for adjusted mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diff in adj means vs afli (SE)	[redacted]		[redacted]		[redacted]	
95% CI for adjusted mean diff	[redacted]		[redacted]		[redacted]	

Units: letters. BCVA, Best Corrected Visual Acuity; MMRM, Mixed-Model Repeated-Measures; SE, standard error

For the MMRM analysis, the model adjusted for treatment group, visit, visit-by-treatment group interaction, baseline BCVA (continuous), baseline BCVA score (≥74 letters, 73-55 letters, and ≤54 letters), low-luminance deficit (< 33 letters and ≥33 letters), region (U.S. and Canada, Asia, and the rest of the world). The model for pooled also adjusted for study (GR40306 vs GR40844). An unstructured covariance structure is used. For the average over Weeks 40, 44, and 48, the estimate of the difference between the two groups uses a composite contrast over Weeks 40, 44 and 48. For the average over Weeks 52, 56, and 60, the estimate of the difference between the two groups uses a composite contrast over Weeks 52, 56 and 60. 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. 95% CI is reported for pooled. 95.03% CI is reported for the individual studies.

Table 10: Summary of change from baseline in BCVA in the study eye at Week 40/44/48: primary and select supplementary analyses (Pooled TENAYA and LUCERNE)

	Faricimab 6.0 mg Adjusted Mean (SE) (95% CI)	Aflibercept 2.0 mg Adjusted Mean (SE) (95% CI)	Difference in Adjusted Means (SE) (95% CI)
Primary Analysis – MMRM Method			
ITT Population	[redacted]	[redacted]	[redacted]
Supplementary Analyses			
Per Protocol Analysis – MMRM Method			
PP Population	[redacted]	[redacted]	[redacted]
Analysis using Treatment Policy Strategy for All Intercurrent Events – MMRM Method			
ITT Population	[redacted]	[redacted]	[redacted]
Analysis using Hypothetical Strategy for All Intercurrent Events – MMRM Method			
ITT Population	[redacted]	[redacted]	[redacted]
Trimmed Mean Analysis – ANCOVA Method			
ITT Population	[redacted]	[redacted]	[redacted]

ANCOVA, analysis of covariance; CI, confidence interval; ITT, Intent-to-Treat; MMRM, mixed model for repeated measures; PP, per protocol; SE, standard error

Note: ITT population: faricimab (n=6), faricimab PTI (n=632), aflibercept Q8W (n=627); TN population: faricimab Q8W (n=492), faricimab PTI (n=500), aflibercept Q8W =490); PP population: faricimab Q8W (n=509), faricimab PTI (n=546), aflibercept Q8W (n=547)

Table 11: Summary of change from baseline in BCVA in the study eye from the individual and pooled Phase III nAMD studies at Week 52/56/60: ITT population and select supplementary analyses (Pooled TENAYA and LUCERNE)

	TENAYA N=671			LUCERNE N=658			Pooled TENAYA and LUCERNE N=1329		
	Faricimab 6.0 mg Adjusted Mean (SE) (95% CI)	Aflibercept 2.0 mg Adjusted Mean (SE) (95% CI)	Difference in Adjusted Means (SE) (95% CI)	Faricimab 6.0 mg Adjusted Mean (SE) (95% CI)	Aflibercept 2.0 mg Adjusted Mean (SE) (95% CI)	Difference in Adjusted Means (SE) (95% CI)	Faricimab 6.0 mg Adjusted Mean (SE) (95% CI)	Aflibercept 2.0 mg Adjusted Mean (SE) (95% CI)	Difference in Adjusted Means (SE) (95% CI)
Main Analysis – MMRM Method									
ITT Population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Supplementary Analyses									
Per Protocol Analysis – MMRM Method									
PP Population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Analysis using Treatment Policy Strategy for All Intercurrent Events – MMRM Method									
ITT Population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Analysis using Hypothetical Strategy for All Intercurrent Events – MMRM Method									
ITT Population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Multiple Imputation Analysis – ANCOVA Method									
ITT Population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ANCOVA, analysis of covariance; BCVA, best corrected visual acuity; ITT, Intent-to-Treat; LLD, low-luminance deficit; MMRM, mixed model for repeated measures; PP, per protocol

Intercurrent events

Intercurrent events for the primary efficacy endpoint are defined identically in TENAYA and LUCERNE. Through Week 48, the proportion of patients in each treatment arm who experienced at least one intercurrent event was comparable across studies TENAYA and LUCERNE (Table 12). In the pooled ITT population, [redacted] in the faricimab arm and [redacted] in the aflibercept 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 TENAYA and LUCERNE was missed dose (faricimab or aflibercept) with a potentially major impact on efficacy (Weeks 36, 40, 44) due to COVID-19. In the pooled ITT population, this event occurred in [redacted] in each of the faricimab and aflibercept arms.

Through Week 60, the proportion of patients who experienced at least one intercurrent event was comparable between treatment arms in TENAYA and LUCERNE, and was comparable across studies (Table 12). In the pooled ITT population, [redacted] in the faricimab arm and [redacted] in the aflibercept arm experienced at least one intercurrent event.

The type and frequency of intercurrent events were also similar between treatment arms in TENAYA and LUCERNE and were similar across studies. The most common intercurrent event in both TENAYA and LUCERNE was missed dose (faricimab or aflibercept) with a potentially major impact on efficacy (Weeks 48, 52, 56) due to COVID-19. In the pooled ITT population, this event occurred in [redacted] in the faricimab arm and [redacted] in the aflibercept arm.

Table 12: Summary of intercurrent events through Week 48 and Week 60 from pooled phase III nAMD Studies (ITT Population)

n (%)	Fari 6.0 mg n=655	Afli 2.0 mg n=664
Week 48		
Pts with at least one intercurrent event*	[redacted]	[redacted]
Pts who discontinued study treatment due to AEs or lack of efficacy (not COVID-19)**	[redacted]	[redacted]
Pts who received any prohibited systemic treatment or prohibited treatment in the study eye (not due to COVID-19)***	[redacted]	[redacted]
Pts who discontinued study treatment due to COVID-19	[redacted]	[redacted]
Pts who received any prohibited systemic treatment or prohibited treatment in the study eye (not due to COVID-19)***	[redacted]	[redacted]
Pts with missed dose(s) with potentially major impact on efficacy due to COVID-19	[redacted]	[redacted]
COVID-19 death	[redacted]	[redacted]
Week 60		
Pts with at least one intercurrent event****	[redacted]	[redacted]
Pts who discontinued study treatment due to AEs or lack of efficacy (not COVID-19)**	[redacted]	[redacted]
Pts who received any prohibited systemic treatment or prohibited treatment in the study eye (not due to COVID-19)***	[redacted]	[redacted]
Pts who discontinued study treatment due to COVID-19	[redacted]	[redacted]

Pts who received any prohibited systemic treatment or prohibited treatment in the study eye (not due to COVID-19)***	[redacted]	[redacted]
Pts with missed dose(s) with potentially major impact on efficacy due to COVID-19	[redacted]	[redacted]
COVID-19 death	[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 349 (last day of Week 48 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.

**** Includes events occurred on or prior to Day 433 (last day of Week 60 analysis visit window).

B.3.6.2 Secondary endpoints

Change from baseline in BCVA over time

The adjusted mean change from baseline in BCVA over time through Week 60 was comparable between the faricimab and aflibercept arms, and demonstrated consistency in BCVA response between Week 48 and Week 60 in both TENAYA and LUCERNE. In the pooled ITT population, the adjusted mean change from baseline in BCVA over time was is depicted below

Figure 4: Pooled phase III nAMD studies: plot of change from baseline in BCVA in the study eye through Week 60: MMRM Method (primary estimand) (ITT population)

[redacted]

Proportion of patients gaining ≥15 or ≥10 letters in BCVA from baseline at Week 52/56/60

In both TENAYA and LUCERNE, the proportion of patients who gained ≥15 letters from baseline at Week 52/56/60

[redacted]

(Table 13).

In the pooled ITT population, [redacted] of patients in the faricimab and aflibercept arms, respectively, gained ≥15 letters in BCVA score from baseline at Week 52/56/60; the difference between treatment arms was [redacted]

Table 13: Proportion of patients gaining ≥15 letters in the study eye BCVA in the individual and pooled phase III nAMD studies at Week 52/56/60: CMH method (primary estimand) (ITT population)

	TENAYA		LUCERNE		Pooled TENAYA and LUCERNE	
	Fari 6.0 mg n=334	Afli 2.0 mg n=337	Fari 6.0 mg n=331	Afli 2.0 mg n=327	Fari 6.0 mg n=665	Afli 2.0 mg n=664
Average of weeks 40, 44 and 48						
n	292	300	302	291	[redacted]	[redacted]
CMH weighted estimate						
%	20.0	15.7	20.2	22.2	[redacted]	[redacted]
95% CI	(15.6, 24.4)	(11.9, 19.6)	(15.9, 24.6)	(17.7, 26.8)	[redacted]	[redacted]
Difference						
Diff in CMH weighted %	4.3		-2.0		[redacted]	
95% CI for CMH weighted % diff	(-1.6, 10.1)		(-8.3, 4.3)		[redacted]	
Average of weeks 52, 56 and 60						
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CMH weighted estimate						
%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference						
Diff in CMH weighted %	[redacted]		[redacted]		[redacted]	
95% CI for CMH weighted % diff	[redacted]		[redacted]		[redacted]	

Afli, aflibercept; BCVA, Best-corrected visual acuity; CMH, Cochran-Mantel-Haenszel

The weighted estimate is based on CMH test stratified by baseline BCVA (≥74 letters, 73-55 letters, and <=54 letters), baseline LLD (<33 letters and ≥33 letters), region (U.S. and Canada, Asia, and the rest of the world). Pooled is also stratified by study (GR40306 vs GR40844). 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. Invalid BCVA values are excluded from analysis.95% CI is reported for pooled. 95.03% 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 randomisation

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

In both TENAYA and LUCERNE, the proportion of patients who gained ≥ 15 letters from baseline at Week 60 was comparable between the treatment arms.

In the pooled ITT population [redacted] in the faricimab and aflibercept arms gained ≥15 letters or ≥10 letters in BCVA from baseline over time through Week 60.

Figure 5: Pooled phase III nAMD studies: proportion of patients gaining ≥15 letters in BCVA from baseline in the study eye over time through Week 60: CMH method (primary estimand) (ITT population)

[redacted]

Proportion of patients avoiding a loss of ≥15 letters in BCVA from baseline at Week 52/56/60

In both TENAYA and LUCERNE, the proportion of patients who avoided a loss of ≥15 letters in BCVA score from baseline at Week 52/56/60 [redacted] (Table 14).

In the pooled ITT population, [redacted] and [redacted] of patients in the faricimab and aflibercept arms, respectively, avoided a loss of ≥15 letters in BCVA score from baseline at Week 52/56/60; the difference between arms was [redacted]

Table 14: Proportion of patients avoiding a loss of ≥15 letters in the study eye BCVA in the individual and pooled phase III nAMD studies at Week 52/56/60: CMH method (primary estimand) (ITT population)

	TENAYA		LUCERNE		Pooled TENAYA and LUCERNE	
	Fari 6.0 mg n=334	Afli 2.0 mg n=337	Fari 6.0 mg n=331	Afli 2.0 mg n=327	Fari 6.0 mg n=665	Afli 2.0 mg n=664
Average of weeks 40, 44 and 48						
n	292	300	302	291	[redacted]	[redacted]
CMH weighted estimate						
%	95.4	94.1	95.8	97.3	[redacted]	[redacted]
95% CI	(93.0, 97.7)	(91.5, 96.7)	(93.6, 98.0)	(95.5, 99.1)	[redacted]	[redacted]
Difference						
Diff in CMH weighted %	1.3		-1.5		[redacted]	
95% CI for CMH weighted % diff	(-2.2, 4.8)		(-4.4, 1.3)		[redacted]	
Average of weeks 52, 56 and 60						
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CMH weighted estimate						
%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference						
Diff in CMH weighted %	[redacted]		[redacted]		[redacted]	
95% CI for CMH weighted % diff	[redacted]		[redacted]		[redacted]	

Afli, aflibercept; BCVA, Best-corrected visual acuity; CMH, Cochran-Mantel-Haenszel

The weighted estimate is based on CMH test stratified by baseline BCVA (≥74 letters, 73-55 letters, and <=54 letters), baseline LLD (<33 letters and ≥33 letters), region (U.S. and Canada, Asia, and the rest of the world). Pooled is also stratified by study (GR40306 vs GR40844). 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. Invalid BCVA values are excluded from analysis.95% CI is reported for pooled. 95.03% 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 TENAYA and LUCERNE, comparable adjusted proportions of patients treated with faricimab and patients treated with aflibercept avoided a loss of ≥15 letters from baseline over time through Week 60. Results were consistent across studies.

In the pooled ITT population, [redacted] in the faricimab and aflibercept arms avoided a loss of ≥15 letters from baseline over time through Week 60.

Figure 6: Pooled Phase III nAMD studies: proportion of patients avoiding a loss of ≥15 letters in BCVA from baseline in the study eye over time through Week 60: CMH method (primary estimand) (ITT population)

[redacted]

Proportion of patients on different treatment intervals

In TENAYA and LUCERNE at Week 60, [redacted] of patients, respectively, in the faricimab dosing arm were on a dosing regimen of Q12W or Q16W. In TENAYA, the proportions of faricimab-treated patients on a Q8W, Q12W or Q16W treatment interval at Week 60 were [redacted]. In LUCERNE, the proportions of faricimab-treated patients on a Q8W, Q12W, or Q16W treatment interval at Week 60 were [redacted]

In the pooled ITT population at Week 48, 78.7% of patients in the faricimab dosing arm were on a dosing regimen of Q12W or longer. Overall, 21.2%, 33.4%, and 45.3% of patients were on a Q8W, Q12W, and Q16W dosing regimen at Week 48 (Table 15).

At Week 60, [redacted] of patients in the faricimab dosing arm were on a dosing regimen of Q12W or longer. Overall, [redacted] of patients were on a Q8W, Q12W, and Q16W dosing regimen at Week 60 (Table 15). Percentages are based on the number of patients randomised to the faricimab arm who had not discontinued the study at Week 60.

Table 15: Proportion of patients in the faricimab arm from the individual and pooled Phase III nAMD studies on a Q8W, Q12W, or Q16W treatment interval at Week 60

	TENAYA	LUCERNE	Pooled
	Fari 6.0 mg n=334	Fari 6.0 mg n=331	Fari 6.0 mg n=665
Week 48 N	315	316	631
Q8W, n (%) 95% CI	64 (20.3) (15.9, 24.8)	70 (22.2) (17.6, 26.7)	134 (21.2) (18.0, 24.4)
Q12W, n (%) 95% CI	107 (34.0) (28.7, 39.2)	104 (32.9) (27.7, 38.1)	211 (33.4) (29.8, 37.1)
Q16W, n (%) 95% CI	144 (45.7) (40.2, 51.2)	142 (44.9) (39.4, 50.4)	286 (45.3) (41.4, 49.2)
Week 60 N	[redacted]	[redacted]	[redacted]
Q8W, n (%)	[redacted]	[redacted]	[redacted]

95% CI			
Q12W, n (%) 95% CI	[redacted]	[redacted]	[redacted]
Q16W, n (%) 95% CI	[redacted]	[redacted]	[redacted]

Percentages are based on number of patients randomised to the faricimab arm who have not discontinued the study at specified visit. Treatment interval at a given visit is defined as the treatment interval decision followed at that visit.

95% CI is reported for pooled. 95.03% CI is reported for the individual studies

Change in PTI treatment interval

From Week 60 onward, all patients in the faricimab arm are treated according to a PTI dosing regimen (between Q8W and Q16W) up to Week 108. At study drug dosing visits, treatment intervals can be maintained or adjusted (i.e., increased by 4 weeks or decreased by 4 or 8 weeks) based on OCT, BCVA, and clinical assessment.

Table 16 below presents the PTI data for patients in the pooled analysis population at the Week 64 visit, where the adjustments to treatment interval at Week 60 will be captured and first observed at Week 64.

[redacted]

Table 16: Change in PTI treatment interval in Week 60 (first column) to Week 64 (stable, extend, decrease) for the pooled ITT Population

	Stable n	Extend interval n	Decrease interval n	Total n
Week 60 Q16W	[redacted]	-	[redacted]	[redacted]
Week 60 Q12W	[redacted]	[redacted]	[redacted]	[redacted]
Week 60 Q8W	[redacted]	[redacted]	-	[redacted]

Figure 7 presents the PTI data to date from the Week 60 through follow up for individual patients (up to Week 108) and

[redacted]

Figure 7: PTI treatment intervals from Week 60 through follow−up for individual patients(Pooled ITT Population)

(A) Q16W at Week 60

[redacted]

(B) Q12W at Week 60

[redacted]

(C) Q8W at Week 60

[redacted]

Anatomic outcome measures using SD-OCT

Change from baseline in CST at Week 52/56/60

In both TENAYA and LUCERNE, patients in the faricimab and aflibercept arms had comparable reductions in CST from baseline at Week 52/56/60 (Table 17). In the pooled ITT population, the adjusted mean change in CST from baseline at Week 52/56/60 was [redacted] and [redacted] in the faricimab and aflibercept arms, respectively; the difference between treatment arms was [redacted]

Table 17: Change from baseline in CST in the study eye at Week 52/56/60 in individual and pooled Phase III nAMD studies: MMRM method (primary estimand) (ITT population)

	TENAYA		LUCERNE		Pooled TENAYA and LUCERNE	
	Fari 6.0 mg n=334	Afli 2.0 mg n=337	Fari 6.0 mg n=331	Afli 2.0 mg n=327	Fari 6.0 mg n=665	Afli 2.0 mg n=664
Average of weeks 40, 44 and 48						
n	291	297	299	287	590	584
Adjusted mean (SE)	-136.8 (2.97)	-129.4 (2.96)	-137.1 (3.02)	-130.8 (3.05)	-137.0 (2.11)	-130.1 (2.12)
95% CI for adj mean	(-142.6, -131.0)	(-135.2, -123.5)	(-143.1, -131.2)	(-136.8, -124.8)	(-141.2, -132.9)	(-134.2, -125.9)
Diff in adj means vs afli (SE)	-7.4 (4.19)		-6.4 (4.30)		-7.0 (2.99)	
95% CI for adj mean diff	(-15.7, 0.8)		(-14.8, 2.1)		(-12.8, -1.1)	
Average of weeks 52, 56 and 60						
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI for adj mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diff in adj means vs afli (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI for adj mean diff	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Units: microns.

For the MMRM analysis, the model adjusted for treatment group, visit, visit-by-treatment group interaction, baseline CST (continuous), baseline BCVA (≥74 letters, 73–55 letters, and ≤ 54 letters), baseline LLD (<33 letters and ≥33 letters), region (U.S. and Canada, Asia, and the rest of the world). Asia and rest of the world regions are combined due to a small number of enrolled patients. The model for pooled also adjusted for study (GR40306 vs GR40844). An unstructured covariance structure is used. The estimate of the difference between the two groups is using a composite contrast over Weeks 52, 56 and 60. 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. 95.03% CI is reported for the individual studies. CST is defined as the distance between ILM and RPE, as assessed by CRC.

Change from baseline in CST over time

In both TENAYA and LUCERNE, patients in the faricimab and aflibercept arms had comparable reductions in CST from baseline over time through Week 60

In the pooled ITT population, patients treated with faricimab also had [redacted] to patients treated with aflibercept in adjusted mean change from baseline in CST over time through Week 60.

Figure 8: Pooled Phase III nAMD studies: change from baseline in CST in the study eye over time through Week 60: MMRM method (primary estimand) (ITT population)

[redacted]

Change from baseline in total area of CNV lesion at Week 48

In the pooled ITT population, the mean change from baseline (SD) in the total area of CNV lesion at Week 48 was [redacted] with faricimab, compared to [redacted] with aflibercept (Table 18).

Change from baseline in total area of leakage at Week 48

In the pooled ITT population, the mean change from baseline (SD) in the total area of leakage in the study eye at Week 48 was [redacted] with faricimab, compared to [redacted] with aflibercept (Table 19).

Table 18: Change from baseline in total area of CNV lesion at Week 48 in individual and pooled Phase III nAMD studies: MMRM method (primary estimand) (ITT population)

	TENAYA		LUCERNE		Pooled TENAYA and LUCERNE	
	Fari 6.0 mg n=334	Afli 2.0 mg n=337	Fari 6.0 mg n=331	Afli 2.0 mg n=327	Fari 6.0 mg n=665	Afli 2.0 mg n=664
Baseline						
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean lesion size, mm^2 (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median lesion size, mm^2 (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 48						
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean lesion size, mm^2 (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline, mm^2 (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Assessments were censored following COVID-19 related intercurrent events. Baseline is defined as the last available measurement obtained on or prior to randomisation. 95% CI is for pooled. 95.03% is for individual study.

Table 19: Change from baseline in total area of leakage in the study eye at Week 48 in individual and pooled Phase III nAMD studies: MMRM method (primary estimand) (ITT population)

	TENAYA		LUCERNE		Pooled TENAYA and LUCERNE	
	Fari 6.0 mg n=334	Afli 2.0 mg n=337	Fari 6.0 mg n=331	Afli 2.0 mg n=327	Fari 6.0 mg n=665	Afli 2.0 mg n=664
Baseline						
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean area of leakage, mm^2 (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median area of leakage, mm^2 (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 48						
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean area of leakage, mm^2 (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline, mm^2 (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Assessments were censored following COVID-19 related intercurrent events. Baseline is defined as the last available measurement obtained on or prior to randomisation. 95% CI is for pooled. 95.03% is for individual study.

B.3.6.3. Patient-reported outcomes

In both TENAYA and LUCERNE, patients treated with faricimab had a comparable adjusted mean change from baseline in the NEI VFQ-25 composite score at Week 24 and Week 48 compared with patients treated with aflibercept (Table 20). Results were consistent across studies. In the pooled ITT population, the adjusted mean (SE) change from baseline in the NEI VFQ-25 composite score at Week 48 was [redacted] and [redacted] points in the faricimab and aflibercept arms, respectively; the difference between the faricimab and aflibercept arms was [redacted] points. In all but the aflibercept arm of TENAYA, the threshold for clinically meaningful change of 4 points was exceeded (114).

Table 20: Change from baseline in NEI VFQ-25 composite score at Week 48 in individual and pooled Phase III nAMD studies: MMRM method (primary estimand) (ITT population)

	TENAYA		LUCERNE		Pooled TENAYA and LUCERNE	
	Fari 6.0 mg n=334	Afli 2.0 mg n=337	Fari 6.0 mg n=331	Afli 2.0 mg n=327	Fari 6.0 mg n=665	Afli 2.0 mg n=664
Baseline					[redacted]	[redacted]
n	334	336	330	324		
Mean (SE)	78.5 (0.84)	80.3 (0.81)	76.7 (0.89)	77.7 (0.86)		
Week 48					[redacted]	[redacted]
n	272	277	276	273		
Adjusted mean (SE)	4.5 (0.58)	2.8 (0.58)	4.2 (0.57)	5.4 (0.58)		
95% CI for adj mean	(3.4, 5.7)	(1.7, 3.9)	(3.1, 5.3)	(4.2, 6.6)		
Diff in adj means vs afli (SE)	1.7 (0.82)		-1.2 (0.81)			
95% CI for adj mean diff	(0.1, 3.3)		(-2.8, 0.4)			

BCVA, best corrected visual acuity; MMRM, mixed-model repeated-measures; NEI VFQ-25, National Eye Institute Visual Function Questionnaire-25

For the MMRM analysis, the model adjusted for treatment group, visit, visit-by-treatment group interaction, baseline CST (continuous), baseline BCVA (≥74 letters, 73 - 55 letters, and ≤ 54 letters), baseline LLD (<33 letters and ≥33 letters), region (U.S. and Canada, Asia, and the rest of the world). Asia and rest of the world regions are combined due to a small number of enrolled patients. The model for pooled also adjusted for study (GR40306 vs GR40844). An unstructured covariance structure is used. The estimate of the difference between the two groups is using a composite contrast over Weeks 52, 56 and 60. 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. 95.03% CI is reported for the individual studies.

B.3.7 Subgroup analysis

The primary endpoint of the change from baseline in BCVA at Week 40/44/48 was analysed across various baseline demographic subgroups (e.g. by age, gender, race, baseline LLD, baseline CNV lesion subtype and size). In the pooled ITT population, the differences in adjusted mean change in BCVA at Week 40/44/48 between the two treatment groups were consistent across all subgroups and were consistent with the overall population. 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 nAMD were found, no meta-analysis was conducted.

B.3.9 Indirect and mixed treatment comparisons

TENAYA and LUCERNE 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 efficacy 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 (NMA). 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 SLR was conducted to identify relevant randomised controlled trial (RCT) evidence for the efficacy, safety and HRQoL data for respective pharmacological interventions for the treatment of nAMD. In total, 5,431 publications were screened, of which 551 were reviewed at the full text-stage. Following the exclusion of publications not meeting the criteria, a total of 138 publications reporting 67 studies were deemed eligible for inclusion in the SLR, of which 115 were full publications, 16 were conference abstracts and six were clinical study reports (CSRs) for the ARCHWAY, AVENUE (identified via hand searching), LADDER, STAIRWAY, LUCERNE and TENAYA studies (Figure 9).

Following the identification of relevant studies from the clinical SLR, a feasibility assessment for inclusion within a 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 (115). Full details are presented in Appendix D.

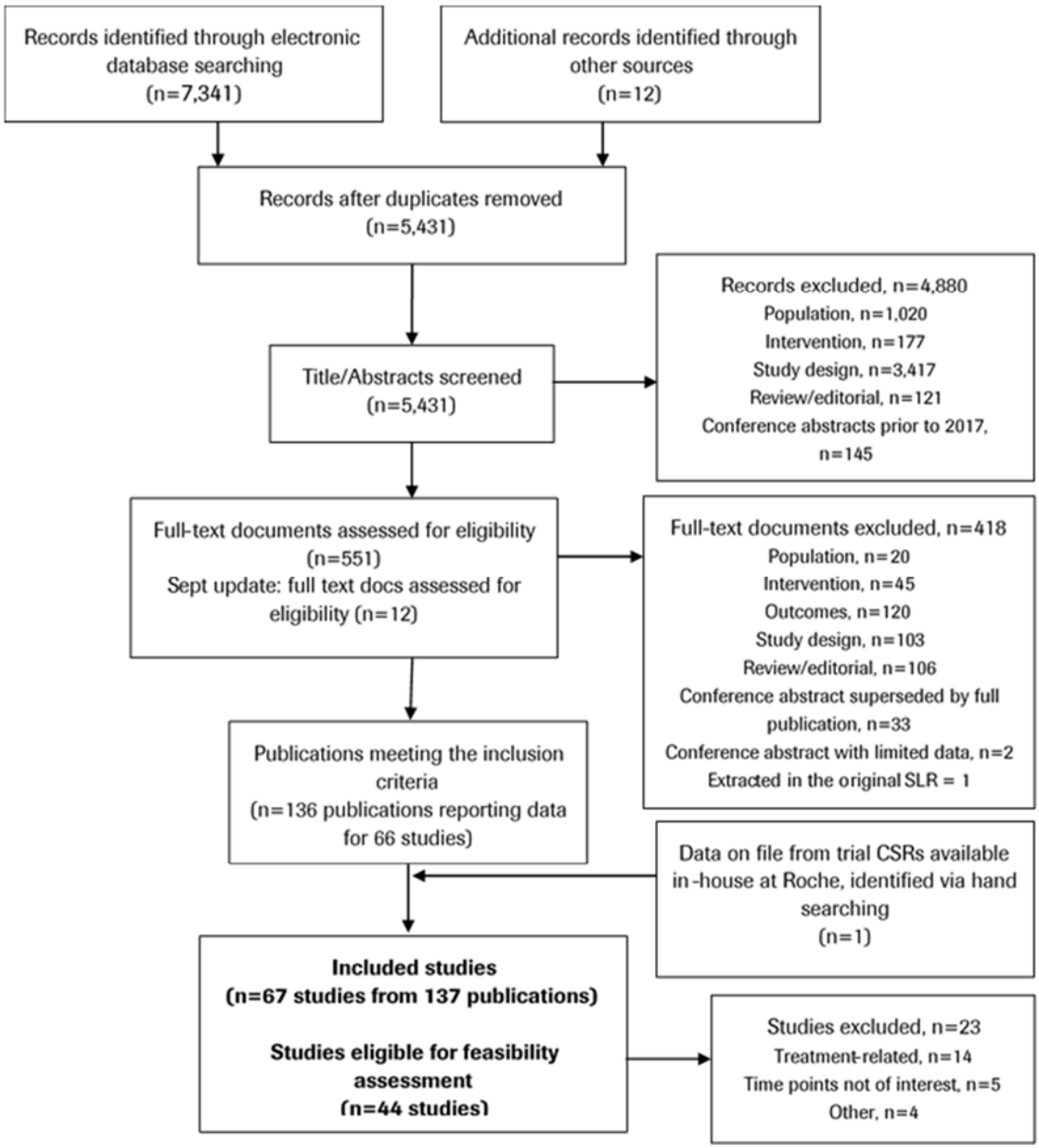
September 2021 update

The primary systematic literature review was completed in October 2020. Cochrane guidance states searches should be re-run 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, 10 studies had been included in the original SLR and twelve new studies were identified. None of the twelve studies were deemed to be eligible for inclusion within the NMA, for the following reasons: reported data is limited to sub-population not matching population of interest, intervention and/or comparator not within scope, cohort not generalizable to the population within the scope, small study population and lack of study design information. Full details are presented in Appendix D. Based on this, the decision was taken not to update the ITC following the re-running of the searches.

Of the 67 studies of interest for the NMA, a total of 44 studies met the feasibility assessment and formed a connected general network.

Figure 9: PRISMA flow chart of included and excluded publications from the original SLR (no new relevant data found in the September 2021 update)



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 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 21.

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 and to ranibizumab are considered relevant to this appraisal.

Table 21: PICO framework for NMA

Criteria	Inclusion
Population	Patients >18 years old with nAMD
Intervention	Faricimab
Comparators	Licensed and / or standard doses only of • Ranibizumab • Aflibercept • Bevacizumab • Brolucizumab • Port delivery system with Ranibizumab (PDS) • Placebo/sham

Outcomes	**Timepoints for all outcomes:** 12 months, additionally 24 months for number of injections
	Vision outcomes:
	• Mean change from baseline in BCVA score
	• Proportion of patients gaining letters:
	  • at least 15 letters
	  • at least 10 letters
	• Proportion of patients avoiding loss of letters:
	  • at least 15 letters
	  • at least 10 letters
	Anatomic outcomes:
	• Mean change in CST (Central Subfield thickness)
	Other:
	• Treatment frequency:
	  • Number of injections
	• Overall treatment discontinuation/withdrawal
	Safety outcomes:
	• Overall ocular AEs rate
	• Overall ocular SAE rate

AE, adverse event; BCVA, best-corrected visual acuity; CST, central subfield thickness; nAMD, neovascular age-related macular degeneration; PICO, population, intervention, control, and outcomes; SAE, serious adverse event.

All potential treatment strategies were included:

- Fixed interval: injections are administered on a fixed schedule every X weeks, for example, Q4W (monthly), Q8W (2-monthly), Q12W (3-monthly), Q16W (4-monthly) treatment
- PRN (pro re nata): injections are administered as needed, following a PRN definition pre-specified in the study protocol
- PRNX (pro re nata and extend): PRN with the potential to extend the assessment interval
- T&E (treat-and-extend): treat with the potential to extend the treatment interval, for example, +2-week adjustment, -2-week adjustment between treatment timings

An overview of the different treatment regimens included in the NMA is presented in Table 22. All regimens could either include or exclude a loading phase.

Table 22: Treatment doses and regimens included in the NMA

Treatment	Dose	Regimen (with or without >1 loading dose)
Aflibercept	• 0.5 mg • 2 mg	• PRN • Q4W / Q8W • T&E
Bevacizumab	• 1.25 mg	• PRN • Q4W / Q6W / Q8W / Q12W • T&E
Brolucizumab	• 3 mg • 6 mg	• Q8W / Q12W
Faricimab	• 1.5 mg • 6 mg	• Q4W / Q8W / Q12W / Q16W
Ranibizumab IVT	• 0.3 mg • 0.5 mg • 2 mg	• PRN • PRNX • Q4W / Q8W / Q12W • T&E
PDS	• 10 mg/mL • 40 mg/mL • 100 mg/mL	• PRN • Q24W
Sham / placebo	N/A	• Treatment schedule to match active treatment

IVT, intravitreal injections; PDS, port delivery system with ranibizumab; PRN, pro re nata (as needed); PRNX, PRN-and-extend regimen; Q4W/Q6W/Q8W/Q12W/Q16W, every 4/6/8/12/16 weeks; T&E, treat and extend.

Results of the feasibility assessment showed that it was possible to develop a connected network of trials which assessed various treatments for nAMD and were similar in design to TENAYA and LUCERNE.

B.3.9.3 Network meta-analysis methodology

General considerations and assumptions

Given the high likelihood of heterogeneity between trials, random effects models were used in the base-case analysis for all endpoints (116). A Bayesian framework was used when developing the network as it captures and characterises uncertainty. Ranibizumab 0.5mg

IVT Q4w was used as the reference treatment for computational efficiency (best connected node).

The following assumptions were made when developing the networks:

- Different approaches were taken to PRN dosing across the studies, with some studies including a loading dose regimen of 3-4 treatment injections before entering the PRN phase of treatment and others using 0-1 treatment injections before entering the PRN stage of dosing. These have been treated as separate nodes in the network. This is a conservative assumption, as this method accounts for any effect that may occur from the loading phase; although the results from the meta-regression shows that there is no effect on the results based on the loading phase. The treatment regimens that have been pooled for PRN, treat and extend (T&E) and sham / placebo treatment nodes are described in full detail in Appendix D (Tables 25–27).
- 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 as well as for a number of injections for two year outcomes. This is comparable to the definition of the primary endpoint in TENAYA and LUCERNE, which was the mean change in BCVA score from baseline through Weeks 40–48. Several trials, including TENAYA and LUCERNE, demonstrate that gains in visual acuity in nAMD are usually achieved within the first months of treatment with anti-VEGF ther-apy. Further therapy beyond that point typically allows preserving these vision gains achieved without further improvement. This suggests that there was no impact on the results because of the equivalence assumption. Clinical experts agreed that these time points could be considered to be equivalent for the purposes of reported one-year and two-year outcomes.
- Full details of the NMA methodology can be seen in the NMA report (116)

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 (CI) using standard methods based on the normal distribution.

If neither the CI nor variance of the change from baseline was reported, but estimates of baseline and follow-up values along with variances were available, it may be appropriate to calculate the required figures. The mean change can be calculated simply as: Value at follow-up – Value at baseline. The variance of the change can be calculated according to Equation 1

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 (117).

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 the treatment schedule and/or patient characteristics, meta-regressions were conducted to determine the best fit for each NMA model.

B.3.9.4 NMA results

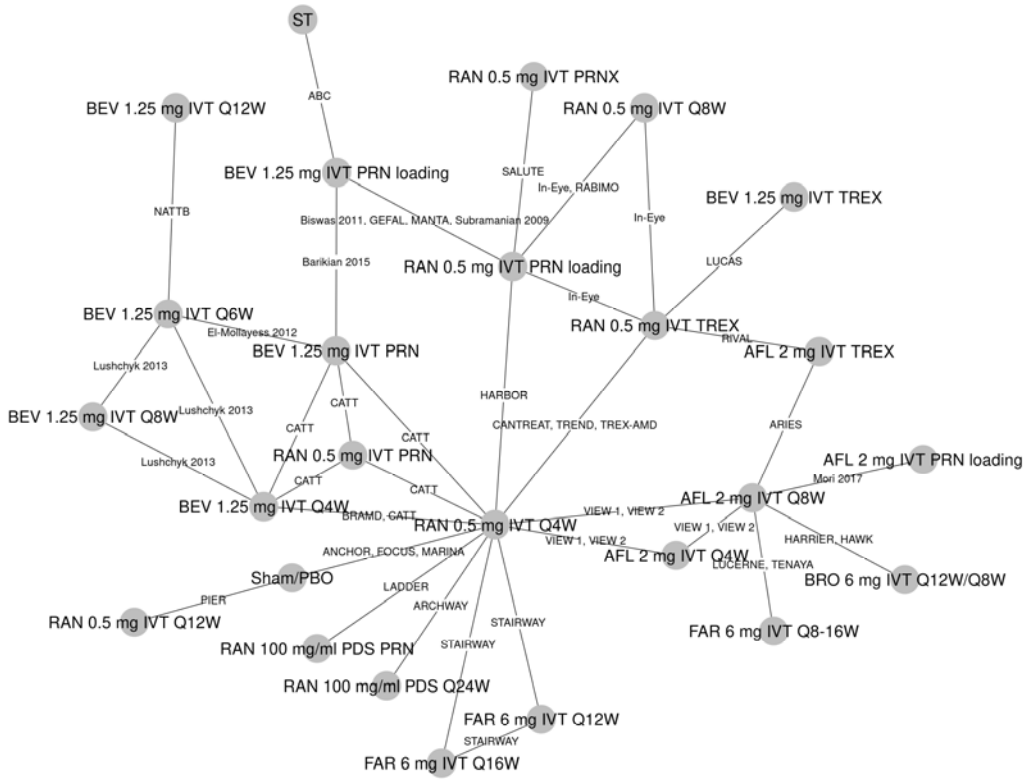
The results of the NMA models are presented in the following sections (full results can be seen within the NMA report (116). For the efficacy outcomes (mean change in BCVA, anatomical changes as well as categorical letter changes), the base case is the meta-regression NMA. The results of the NMA models 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 and ranibizumab regimens are presented below (full detailed results are in the NMA report (116). To strengthen 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.

Mean change in BCVA (Baseline to one year)

The corresponding network is displayed at Figure 10.

Figure 10: Network diagram: BCVA score mean change from baseline at 12m



AFL, aflibercept; BEV, bevacizumab; BRO, brolucizumab; FAR, faricimab; RAN, ranibizumab; IVT, intravitreal; PBO, placebo; PRN, treatment as needed (pro re nata); PRNX, PRN and extend; Q4/6/8/12/16W, every 4/6/8/12/16 weeks; TREX, treat and extend; loading, with loading phase.

The indirect comparisons for mean change in BCVA from baseline to one year obtained through the random effects network meta-regression are reported in Figure 11. The forest plot presents the differences in mean change in BCVA for faricimab (6.0mg Q8-Q16W) versus each comparator; positive differences indicate a larger vision gain for faricimab. 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. In fact, results indicate that all active treatment regimens perform very similarly.

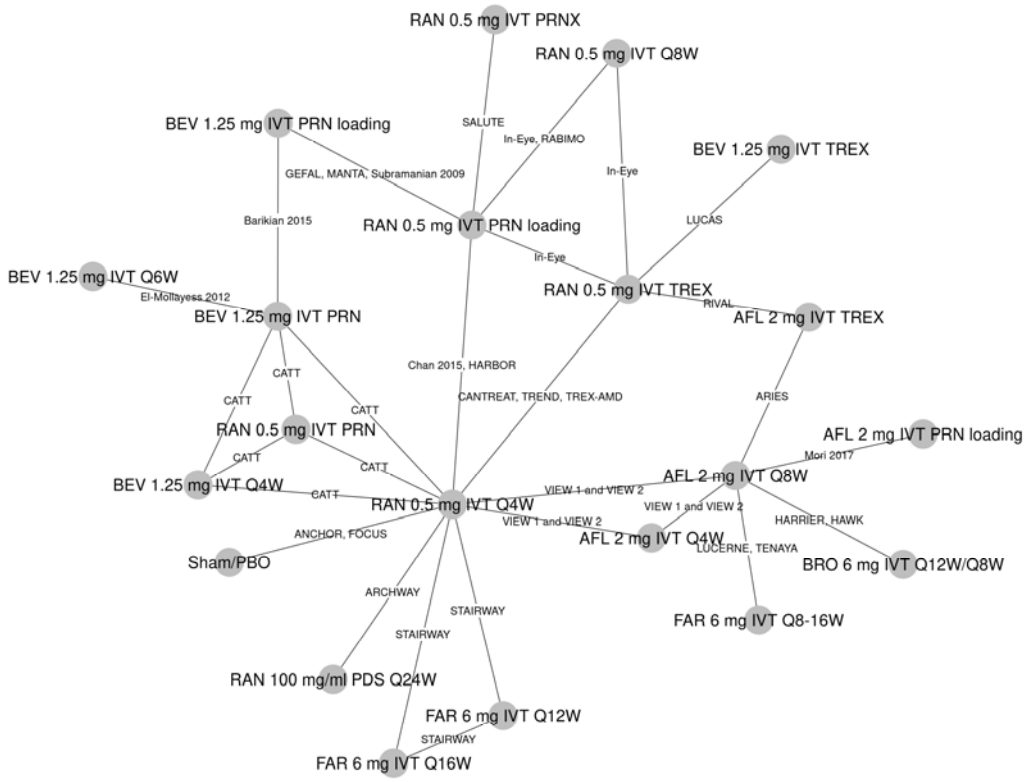
Figure 11: Forest plot of differences and 95% credible intervals of faricimab (6 mg IVT Q8-16W) versus other comparators: BCVA score mean change from baseline at 12m (base case, random-effects model)

Abbreviations: AFL, aflibercept; FAR, faricimab; RAN, ranibizumab; IVT, intravitreal; PBO, placebo; PRN, treatment as needed (pro re nata); Q4/6/8/12/16W, every 4/6/8/12/16 weeks; TREX, treat and extend.

Injection frequency, baseline to 12 months

A large quantity of data are 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. The network for mean number of injections from baseline to one year is displayed at Figure 12.

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



Abbreviations: AFL, aflibercept; BEV, bevacizumab; BRO, brolucizumab; FAR, faricimab; RAN, ranibizumab; IVT, intravitreal; PBO, placebo; PRN, treatment as needed (pro re nata); Q4/6/8/12/16W, every 4/6/8/12/16 weeks; TREX, treat and extend.

The indirect comparisons for injection administration frequency estimates obtained through the NMA are reported in Figure 13. The forest plot presents the differences in injection administration frequency for faricimab (6.0 mg Q8-16W) compared with each comparator; negative differences indicate a smaller number of injections for faricimab. The results demonstrate that faricimab is associated with comparable or less frequent dosing to all comparators in terms of mean number of injections at one year.

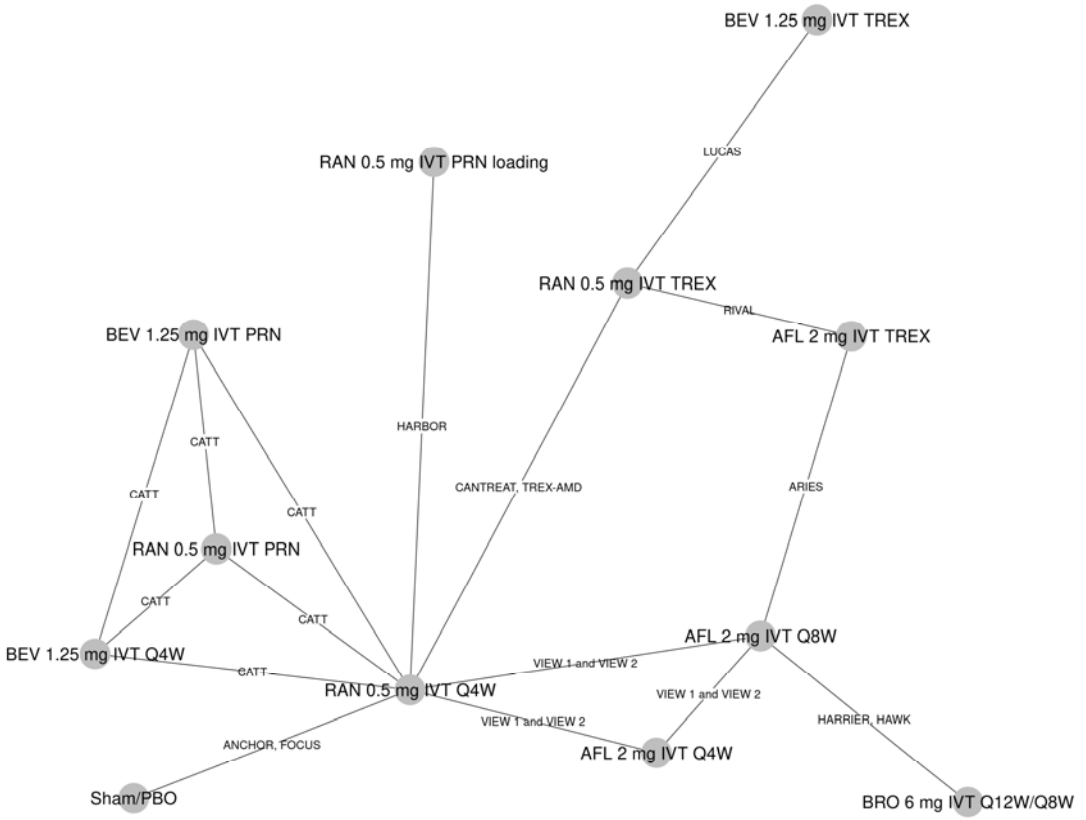
Figure 13: Forest plot of differences and 95% credible intervals of faricimab (6.0 mg Q8-16W) compared with other comparators: Mean number of injections at 12 months (base-case, random-effects model)

Abbreviations: AFL, aflibercept; FAR, faricimab; RAN, ranibizumab; IVT, intravitreal; PBO, placebo; PRN, treatment as needed (pro re nata); Q4/6/8/12/16W, every 4/6/8/12/16 weeks; TREX, treat and extend.

Injection frequency, baseline to 24 months

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

Figure 14: Network diagram: Mean number of administration injections at 24 months



AFL, aflibercept; BEV, bevacizumab; BRO, brolucizumab; FAR, faricimab; RAN, ranibizumab; IVT, intravitreal; PBO, placebo; PRN, treatment as needed (pro re nata); Q4/6/8/12/16W, every 4/6/8/12/16 weeks; TREX, treat and extend.

As there are currently no 2-year data available for faricimab, the TENAYA and LUCERNE comparator arm, aflibercept Q8w has been used as the anchor for the comparison. Additionally, as there is no 2-year RCT evidence investigating aflibercept at a strict Q8w regimen, some assumptions were necessary in order to form a connected network. The ARIES study aflibercept 2mg arm is given at a frequency of Q8w for the first 12 months followed by T&E; similarly, studies VIEW 1&2 have an aflibercept arm with a Q8w dosing regimen from baseline to 12 months, after which PRN is followed. The 12-month data from these studies has been extrapolated to 24 months, based on the adherence observed in

these studies for the first year (see Table 23); this assumption allowed the network to remain connected.

The indirect comparisons for injection administration frequency estimates obtained through the NMA are reported in Figure 15 for aflibercept IVT Q8w versus each comparator; negative differences here indicate a smaller number of injections for aflibercept.
The data derived for comparators from the NMA for the baseline to 24-months injection frequency output, can be used to indirectly compare to the extrapolated faricimab 24-month injection frequency (approach explained at Section B.4.2.8).

Table 23: Trial data used to calculate extrapolated injection frequency at 24 months for aflibercept 2mg, Q8w

Trial	ARIES	VIEW 1&2		
Treatment arm	AFL 2mg, Q8w	AFL 2mg, Q8w	AFL 2mg, Q4w	RAN 0.5mg, Q4w
0-12 months				
Scheduled treatments	8	8	13	13
Observed treatments (mean)	8	7	11.9	11.8
Adherence, %	100	87.5	91.5	90.8
1-year time point, weeks	48	48	48	48
12-24 months				
Scheduled treatments	[redacted]	[redacted]	[redacted]	[redacted]
Extrapolated injection frequency	[redacted]	[redacted]	[redacted]	[redacted]
2-year time point, weeks	[redacted]	[redacted]	[redacted]	[redacted]
Total injections at 24 months	[redacted]	[redacted]	[redacted]	[redacted]

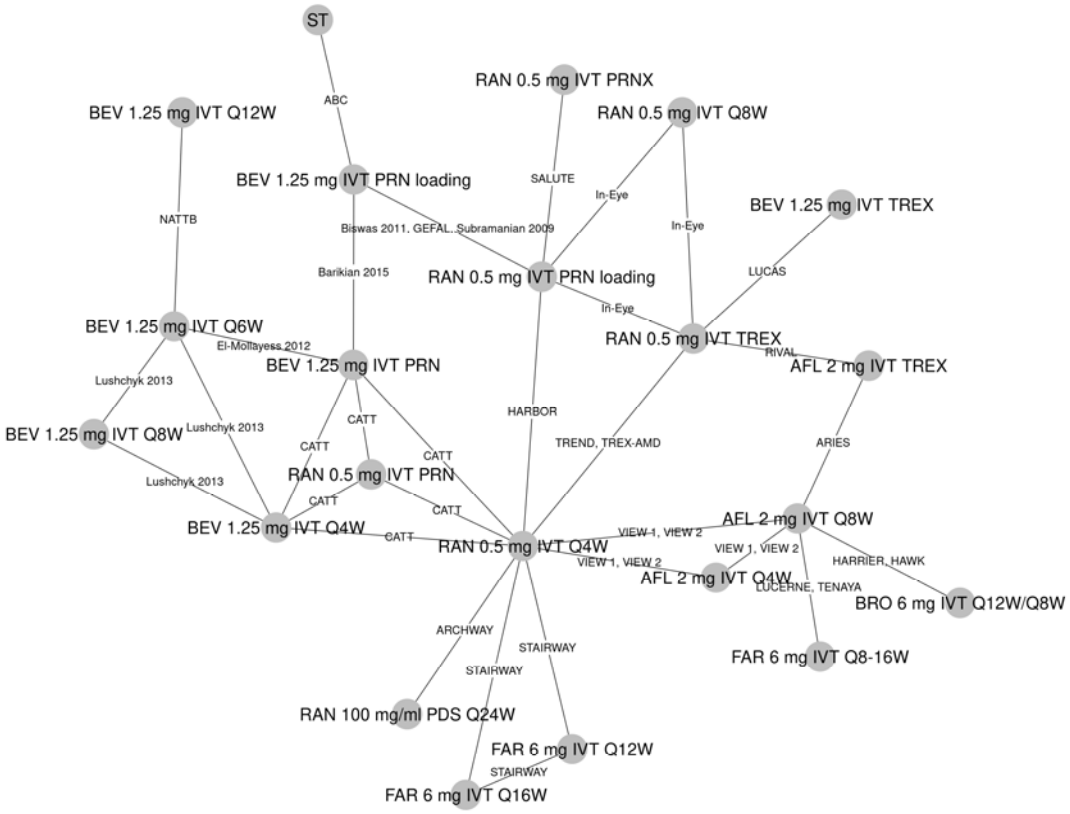
Figure 15: Forest plot of differences and 95% credible intervals of aflibercept (2mg IVT Q8W) compared with other comparators: Mean number of injections at 24 months (base-case, random-effects model)

Abbreviations: AFL, aflibercept; RAN, ranibizumab; IVT, intravitreal; PBO, placebo; PRN, treatment as needed (pro re nata); Q4/6/8/12/16W, every 4/6/8/12/16 weeks; TREX, treat and extend.

Central subfield thickness (CST)

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

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



AFL, aflibercept; BEV, bevacizumab; BRO, brolucizumab; FAR, faricimab; RAN, ranibizumab; IVT, intravitreal; PBO, placebo; PRN, treatment as needed (pro re nata); Q4/6/8/12/16W, every 4/6/8/12/16 weeks; TREX, treat and extend.

The indirect comparisons for mean change in CST from baseline to one year obtained through the random effects network meta-regression are reported in Figure 17. The forest plot presents the differences in CST for faricimab (6.0 mg Q8–16W) compared to each comparator; negative differences indicate a better drying activity for faricimab.

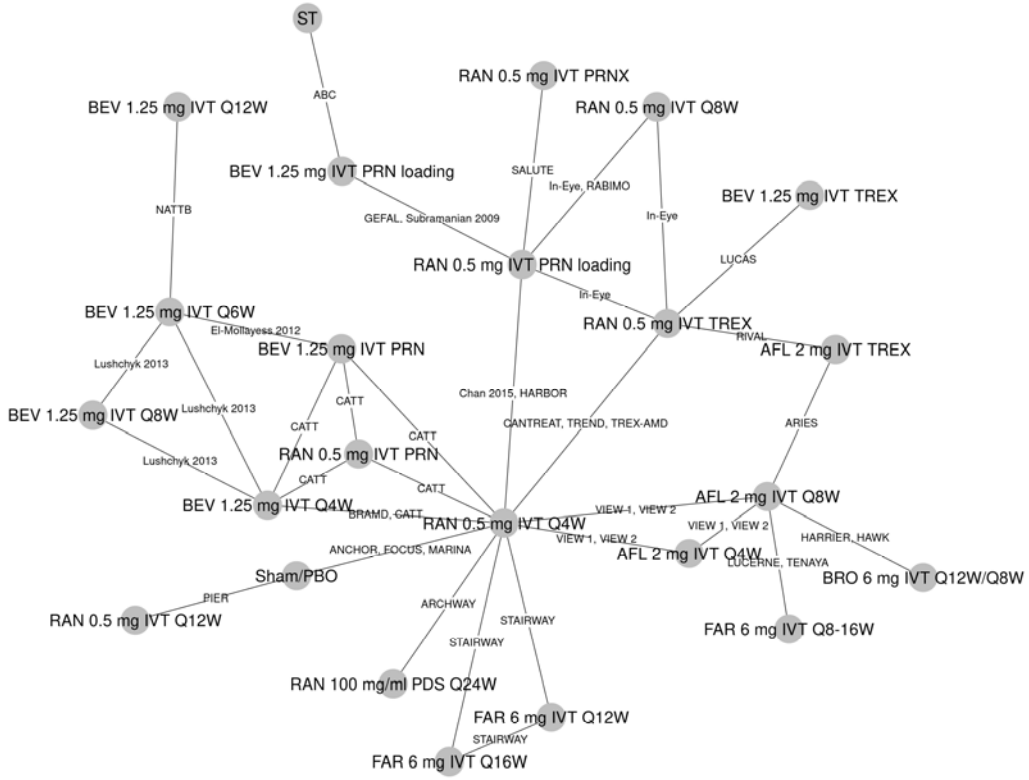
Figure 17: Forest plot of differences and 95% credible intervals of faricimab (6.0 mg Q8-16W) versus other comparators: CST mean change from baseline at 12m (base case, RE model)

AFL, aflibercept; FAR, faricimab; RAN, ranibizumab; IVT, intravitreal; PBO, placebo; PRN, treatment as needed (pro re nata); Q4/6/8/12/16W, every 4/6/8/12/16 weeks; TREX, 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 shown at Figure 18.

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



AFL, aflibercept; BEV, bevacizumab; BRO, brolucizumab; FAR, faricimab; RAN, ranibizumab; IVT, intravitreal; PBO, placebo; PRN, treatment as needed (pro re nata); Q4/6/8/12/16W, every 4/6/8/12/16 weeks; TREX, treat and extend.

The indirect comparisons for the proportion of patients gaining or losing ≥10/15 letters (assessed by ETDRS) from baseline to one year obtained through the network meta-regression are reported in Figure 19. The forest plot presents the differences for faricimab (6.0 mg Q8-16W) versus each comparator; negative differences indicate a larger probability of gaining vision for faricimab. 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, yet the results of the model are consistent with previous NMAs reported in this disease area. However, the results presented in Figure 19 should be interpreted with caution.

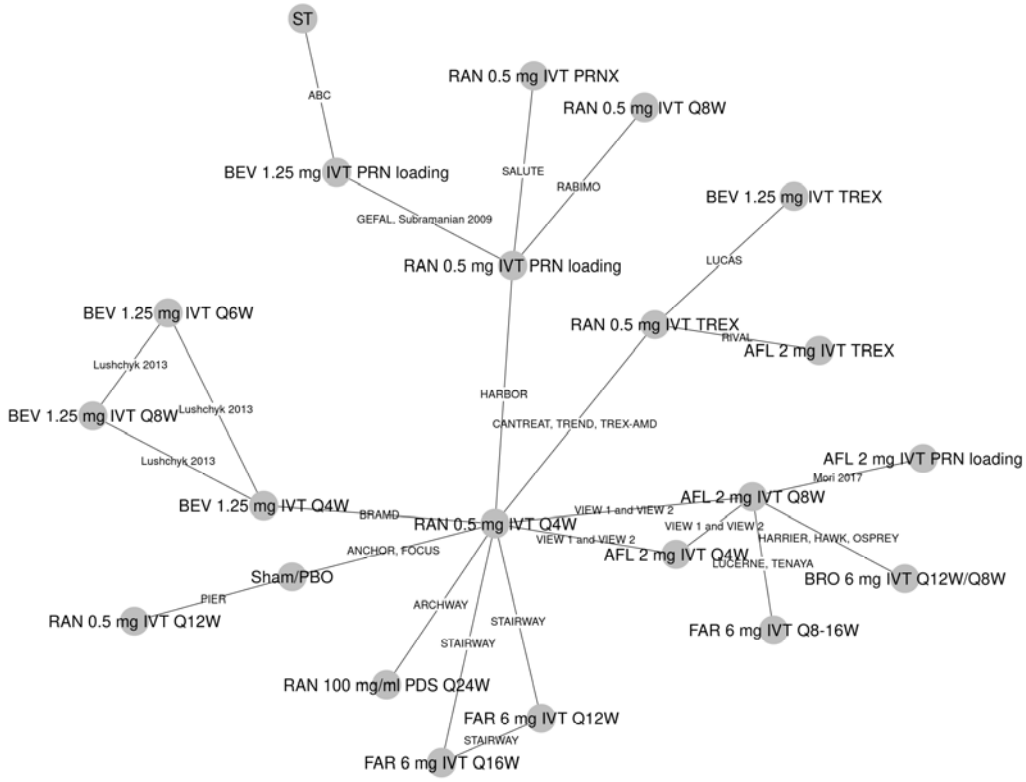
Figure 19: Forest plot of probit scale treatment differences and 95% credible intervals of faricimab (6.0 mg Q8–16W) versus other comparators: ETDRS letters categories at 12m (base case, RE model)

AFL, aflibercept; FAR, faricimab; RAN, ranibizumab; IVT, intravitreal; PBO, placebo; PRN, treatment as needed (pro re nata); Q4/6/8/12/16W, every 4/6/8/12/16 weeks; TREX, treat and extend.

Discontinuation

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

Figure 20: Network diagram - all cause discontinuation at 12 months



AFL, aflibercept; BEV, bevacizumab; BRO, brolucizumab; FAR, faricimab; RAN, ranibizumab; IVT, intravitreal; PBO, placebo; PRN, treatment as needed (pro re nata); Q4/6/8/12/16W, every 4/6/8/12/16 weeks; TREX, treat and extend.

The indirect comparisons for all-cause discontinuation obtained through the NMA is reported at Figure 21 for faricimab (Q8-16W) compared with each comparator. The forest plots show that the probability of discontinuation was comparable for faricimab versus all comparators from baseline to one year; odds ratios smaller than one indicate a smaller chance of discontinuation for faricimab. It is worth noting that a significant share of discontinuation rates in TENAYA and LUCERNE are due to the death of patients (4 events in faricimab arms versus 1 in the aflibercept arm and 2 events in the faricimab arms versus 5 in the aflibercept arm, for TENAYA and LUCERNE, respectively), which are not considered to be treatment-related. Additionally, due to rare events, a normal likelihood model on the odds ratio scale with continuity correction model was applied for the discontinuation analyses. Continuity corrections may introduce bias. Therefore, these results should be interpreted with caution.

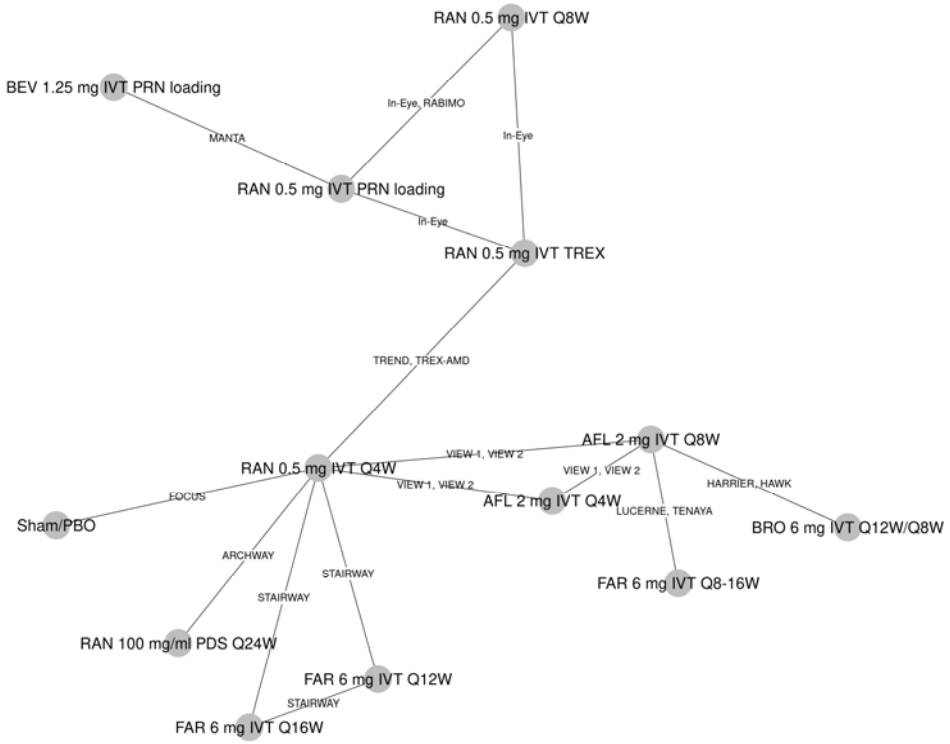
Figure 21: Forest plot of odds ratios and 95% credible intervals of faricimab (6.0 mg Q8-16W) versus other comparators: All cause discontinuation at 12 months (sensitivity, fixed-effects model)

AFL, aflibercept; FAR, faricimab; RAN, ranibizumab; IVT, intravitreal; PBO, placebo; PRN, treatment as needed (pro re nata); Q4/6/8/12/16W, every 4/6/8/12/16 weeks; TREX, treat and extend.

Adverse events

The network for ocular adverse events from baseline to one year is shown at Figure 22.

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



AFL, aflibercept; BEV, bevacizumab; BRO, brolucizumab; FAR, faricimab; RAN, ranibizumab; IVT, intravitreal; PBO, placebo; PRN, treatment as needed (pro re nata); Q4/6/8/12/16W, every 4/6/8/12/16 weeks; TREX, treat and extend.

The indirect comparisons for adverse events obtained through the NMA are reported at Figure 23 for faricimab (6.0 mg Q8–16W) 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; odds ratios smaller than one indicate a better safety profile for faricimab. 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 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 (Q8-16W) versus other comparators: ocular adverse events at 12 months (sensitivity, fixed-effects model)

AFL, aflibercept; FAR, faricimab; RAN, ranibizumab; IVT, intravitreal; PBO, placebo; PRN, treatment as needed (pro re nata); Q4/6/8/12/16W, every 4/6/8/12/16 weeks; TREX, 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 as well as a for number of injections for two year outcomes. This is comparable to the definition of the primary endpoint in TENAYA and LUCERNE, which was the mean change in BCVA score from baseline through Weeks 40 – 48. Several trials, including TENAYA and LUCERNE, demonstrate that gains in visual acuity in nAMD are usually achieved within the first months of treatment with anti-VEGF therapy. Further therapy beyond that point typically allows preserving these vision gains achieved without further improvement. This suggests that there was no impact on the results because of the equivalence assumption (116).

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, CPT, CRT in that order) are used if CST values were not reported. These definitions are often used interchangeably, and previous NMAs have used similar approaches (118).

As more data becomes available for faricimab, it will be possible to consider longer follow-up at 24 months. Within the current NMA, no 24-month data was available for faricimab at the time of submission. The NMA reported within the NICE AMD clinical guidance did consider the network of evidence for 24 month follow-up for change from baseline in BCVA, concluding that ranibizumab 0.5mg Q4w was the node with most evidence at both 12 months and 24 months, supporting the findings and approach of this NMA (12).

A final limitation of the NMA was that in particular for treatment discontinuation and AEs limited evidence was available, making these networks less robust. Additionally, some information for the number of injections over two years relies on assumptions due to the lack of available evidence.

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 comparable visual outcomes in terms of BCVA and superior or comparable anatomical outcomes in terms of decreasing retinal thickness with a lower or similar 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 48 (the timepoint of the primary analysis) (119).

B.3.10.1 Treatment exposure

Week 48

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 48; 1 patient randomised to the faricimab arm and 2 patients randomised to the aflibercept 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 48 was [redacted] in the faricimab arm compared to the aflibercept arm ([redacted] in the faricimab arm and [redacted] in the aflibercept arm), with the total number of injections in the study eye of [redacted] in the faricimab arm and [redacted] in the aflibercept arm. Through Week 48, [redacted] and [redacted] of patients received at least one anti-VEGF administration in the fellow eye in the faricimab and aflibercept arms, respectively, with the most common anti-VEGFs being aflibercept and ranibizumab

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 were also assessed (i.e., the subset of patients with follow-up data beyond Week 48). After Week 48, an additional 7.4 weeks (median) of treatment duration for 509 patients (out of 664 patients) in the faricimab arm and 8.1 weeks (median) of treatment duration for 501 patients (out of 662 patients) in the aflibercept arm are available up to the CCOD. As the study was ongoing at the time of the CCOD, not all patients have the same treatment duration at the time of the CCOD with some patients not having any additional treatment duration beyond Week 48.

After Week 48 to the CCOD, an additional (mean) number of study drug administrations were [redacted] in the faricimab arm and [redacted] in the aflibercept arm. After Week 48 to the CCOD, [redacted] and [redacted] of patients received at least one anti-VEGF administration in the fellow eye in the faricimab and aflibercept arms, respectively, with the most common anti-VEGFs being aflibercept and ranibizumab.

Week 60

As expected through Week 60, the median duration of exposure was the same between both treatment arms (60.1 weeks), and the mean number of study drug administrations through Week 60 was [redacted] ([redacted] in the faricimab arm and [redacted] in the aflibercept arm). The total number of injections in the study eye was [redacted] in the faricimab arm and [redacted] in the aflibercept arm.

Through Week 60, [redacted] and [redacted] of patients received at least one anti-VEGF administration in the fellow eye in the faricimab and aflibercept arms, respectively, with the most common anti-VEGFs being aflibercept and ranibizumab.

Table 24: Summary of study treatment exposure in the study eye through Week 48 from individual and pooled Phase III nAMD studies (pooled safety-evaluable population)

	TENAYA		LUCERNE		Pooled TENAYA and LUCERNE	
	Fari 6.0 mg n=333	Afli 2.0 mg n=336	Fari 6.0 mg n=331	Afli 2.0 mg n=326	Fari 6.0 mg n=664	Afli 2.0 mg n=662
Mean treatment duration, weeks (SD)	46.0 (7.92)	46.3 (7.51)	46.4 (6.78)	46.0 (8.06)	[redacted]	[redacted]
Mean no. of administrations (SD)	6.3 (1.11)	7.4 (1.12)	6.5 (1.05)	7.5 (1.16)	[redacted]	[redacted]
Median no. of administrations (min–max)	6.0 (1–8)	8.0 (1–8)	6.0 (1–8)	8.0 (1–8)	[redacted]	[redacted]
Dose interruptions, n (%)						
n	27	25	26	23	[redacted]	[redacted]
At least one interrupted dose	24 (7.2)	20 (6.0)	16 (4.8)	21 (6.4)	[redacted]	[redacted]
Intraocular inflammation	2 (0.6)	1 (0.3)	6 (1.8)	3 (0.9)	[redacted]	[redacted]
BCVA decrease	1 (0.3)	0	1 (0.3)	0	[redacted]	[redacted]
Elevated intraocular pressure	0	0	3 (0.9)	0	[redacted]	[redacted]
Rhegmatogenous retinal break	1 (0.3)	0	0	0	[redacted]	[redacted]
Active infection	3 (0.9)	6 (1.8)	4 (1.2)	6 (1.8)	[redacted]	[redacted]
Intraocular surgery (study eye)	0	2 (0.6)	1 (0.3)	3 (0.9)	[redacted]	[redacted]
On-study prohibited medications	1 (0.3)	0	0	0	[redacted]	[redacted]
Other	17 (5.1)	11 (3.3)	5 (1.5)	9 (2.8)	[redacted]	[redacted]
Interruptions per patient						
n	24	20	16	21	[redacted]	[redacted]
1	21 (6.3)	19 (5.7)	10 (3.0)	20 (6.1)	[redacted]	[redacted]
2	3 (0.9)	0	5 (1.5)	0	[redacted]	[redacted]
3	0	0	0	1 (0.3)	[redacted]	[redacted]
6	0	1 (0.3)	1 (0.3)	0	[redacted]	[redacted]

BCVA, best-corrected visual acuity

Study drug corresponds to faricimab or aflibercept. Study treatment corresponds to faricimab, aflibercept or sham. Treatment duration is the (maximum of the date of the last dose of study treatment and the date of the last treatment dose hold) minus the date of the first dose plus one day. Includes study treatment received and dose hold on or prior to Day 349 (last day of Week 48 analysis visit window). Percentages are based on N in the column headings. The number of study drug administrations may include any active drug administered including medication errors. The number of injections does not take into account the use of prohibited therapies

B.3.10.2 Overview of safety profile

Overall, based on the pooled safety data from 1326 patients from the TENAYA and LUCERNE studies, the safety data indicate that faricimab has a comparable safety profile to aflibercept, faricimab was generally well tolerated as evidenced by the low incidence of AEs leading to treatment withdrawal, and AEs were generally manageable. No new or unexpected safety signals were identified.

Table 25: Overview of safety through Week 48 and Week 60 in pooled analysis (pooled safety-evaluable patients)

	Week 48		Week 60	
	Fari 6.0 mg n=664	Afli 2.0 mg n=662	Fari 6.0 mg n=664	Afli 2.0 mg n=662
Total no. of patients with at least one AE	[redacted]	[redacted]	[redacted]	[redacted]
Total no. of AEs	[redacted]	[redacted]	[redacted]	[redacted]
Total no. of patients with at least one SAE	[redacted]	[redacted]	[redacted]	[redacted]
Total no. of SAEs	[redacted]	[redacted]	[redacted]	[redacted]
Total no. of deaths	[redacted]	[redacted]	[redacted]	[redacted]
Total no. of patients withdrawn from study due to AE	[redacted]	[redacted]	[redacted]	[redacted]
Total no. of patients withdrawn from study treatment due to AE	[redacted]	[redacted]	[redacted]	[redacted]
Total no. of patients with at least one AESI	[redacted]	[redacted]	[redacted]	[redacted]
Ocular events: study eye				
Total no. of patients with at least one:				
AE	254 (38.3)	246 (37.2)	[redacted]	[redacted]
SAE	[redacted]	[redacted]	[redacted]	[redacted]
AE leading to study treatment withdrawal	[redacted]	[redacted]	[redacted]	[redacted]
Treatment related AE	[redacted]	[redacted]	[redacted]	[redacted]
Treatment related SAE	[redacted]	[redacted]	[redacted]	[redacted]
AE of special interest	[redacted]	[redacted]	[redacted]	[redacted]
Drop in VA score ≥30	[redacted]	[redacted]	[redacted]	[redacted]
Associated with severe IOI	[redacted]	[redacted]	[redacted]	[redacted]
Intervention req to prevent permanent vision loss	[redacted]	[redacted]	[redacted]	[redacted]
Suspected transmission of infectious agent by study drug	[redacted]	[redacted]	[redacted]	[redacted]
Non-ocular events				
Total no. of patients with at least one:				
AE	[redacted]	[redacted]	[redacted]	[redacted]
SAE	[redacted]	[redacted]	[redacted]	[redacted]
AE leading to study treatment withdrawal	[redacted]	[redacted]	[redacted]	[redacted]
AE of special interest	[redacted]	[redacted]	[redacted]	[redacted]

Elevated ALT or AST with either elevated bilirubin or clinical jaundice	[redacted]	[redacted]	[redacted]	[redacted]
Adjudicated APTC events	[redacted]	[redacted]	[redacted]	[redacted]
Non-fatal MI	[redacted]	[redacted]	[redacted]	[redacted]
Non-fatal stroke	[redacted]	[redacted]	[redacted]	[redacted]
Death	[redacted]	[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; 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 349 (last day of Week 48 analysis visit window).

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

AE by frequency

Week 48

Through Week 48, the incidence of ocular AEs in the study eye was comparable between the treatment arms (38.3% in the faricimab arm and 37.2% in the aflibercept arm), with the exception (≥1% difference in any treatment arms: faricimab arm vs. aflibercept arm) of dry eye (13 patients [2.0%] vs. 22 patients [3.3%]), vitreous floaters (20 patients [3.0%] vs. 11 patients [1.7%]), and retinal pigment epithelial tear (19 patients [2.9%] vs. 9 patients [1.4%]). The difference in frequency of these AEs (95% CI) were -1.37 (-3.31, 0.51) for dry eye, 1.35 (-0.43, 3.21) for vitreous floaters, and 1.50 (-0.19, 3.30) for retinal pigment epithelial tear; the differences were not considered to be clinically significant.

The vitreous floaters were all reported as non-serious and mild in severity. The retinal pigment epithelial tear events were mostly reported as either mild or moderate in severity. There were 5 patients in the faricimab arm and 1 patient in the aflibercept arm with a retinal pigment epithelial tear event in the study eye associated with vision loss ≥15 letters (4 patients in the faricimab arm and 1 patient in the aflibercept arm with vision loss ≥15 letters; and 1 patient with vision loss ≥30 letters in the faricimab arm. Sustained vision loss of ≥15 letters or ≥30 letters associated with an AE by Week 48 was measured as the change in vision defined as the highest BCVA recorded after the event onset until Week 48 minus the BCVA closest to and strictly before the first event onset; in the table, events with vision loss ≥30 letters were counted in both the vision loss ≥15 letters and ≥30 letters categories.

The most common ocular AEs in the study eye (≥2% incidence in any treatment arm: faricimab arm vs. aflibercept arm) by PT were conjunctival haemorrhage (6.8% vs. 7.7%), neovascular age-related macular degeneration (verbatim, worsening of nAMD) (5.7% vs. 5.7%), vitreous detachment (3.3% vs. 3.0%), eye pain (2.6% vs. 3.0%), dry eye (2.0% vs. 3.3%), cataract (3.0% vs. 2.1%), intraocular pressure increased (2.6% vs. 2.3%), vitreous floaters (3.0% vs. 1.7%), retinal pigment epithelial tear (2.9% vs. 1.4%), foreign body sensation in eyes (1.5% vs. 2.0%), and punctate keratitis (1.4% vs. 2.0%).

The per-injection rate of ocular AEs in the study eye through Week 48 was 12.24% in the faricimab arm and 9.95% in the aflibercept arm. The per-injection rate of ocular AEs in the study eye with a ≥0.1% higher incidence (in faricimab arm vs. aflibercept arm) by PT were nAMD (verbatim, worsening of nAMD) (1.06% vs. 0.83%), vitreous detachment (0.52% vs. 0.41%), eye irritation (0.75% vs. 0.12%), vitreous floaters (0.50% vs. 0.28%), cataract (0.47% vs. 0.28%), retinal pigment epithelial tear (0.45% vs. 0.18%), ocular discomfort (0.42% vs. 0.16%), ocular hyperaemia (0.38% vs. 0.08%), and eye discharge (0.21% vs. 0).

Ocular AEs in the study eye occurring in ≥1% in any treatment arm through Week 48 are summarised below.

Table 26: Ocular adverse events in the study eye occurring in ≥1% in any treatment arm through Week 48 from pooled Phase III nAMD Studies (pooled safety evaluable population)

n (%)	Fari 6.0 mg n=664	Afli 2.0 mg n=662
Total no. of patients with at least one AE	254 (38.3)	246 (37.2)
Total no. of events, n	519	489
Conjunctival haemorrhage	45 (6.8)	51 (7.7)
Neovascular age-related macular degeneration	38 (5.7)	38 (5.7)
Vitreous detachment	22 (3.3)	20 (3.0)
Eye pain	17 (2.6)	20 (3.0)
Dry eye	13 (2.0)	22 (3.3)
Cataract	20 (3.0)	14 (2.1)
Intraocular pressure increased	17 (2.6)	15 (2.3)
Vitreous floaters	20 (3.0)	11 (1.7)
Retinal pigment epithelial tear	19 (2.9)	9 (1.4)
Sensation of foreign body	10 (1.5)	13 (2.0)
Punctate keratitis	9 (1.4)	13 (2.0)
Blepharitis	9 (1.4)	8 (1.2)
Posterior capsule opacification	10 (1.5)	7 (1.1)
Dry age-related macular degeneration	8 (1.2)	8 (1.2)
Lacrimation increased	6 (0.9)	9 (1.4)
Photopsia	6 (0.9)	8 (1.2
Eye irritation	9 (1.4)	4 (0.6
Corneal abrasion	4 (0.6)	8 (1.2
Ocular discomfort	8 (1.2)	4 (0.6)

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. 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 349 (last day of Week 48 analysis visit window). AE reported as neovascular age-related macular degeneration in the study eye indicates an accelerated worsening of the condition, as judged by the investigator.

Week 60

Through Week 60, the incidence of ocular AEs in the study eye was [redacted] and generally consistent with the Week 48 dataset considering the increase in exposure duration (faricimab: [redacted] [Week 60] and [redacted] [Week 48] vs aflibercept: [redacted] [Week 60] and [redacted] [Week 48]). Through Week 60, the most common ocular AEs (≥2% in any treatment arm) and most common treatment-related ocular AEs (≥0.5% in any treatment arm) in both the faricimab and aflibercept arms were the same as those through Week 48.

Ocular AEs suspected to be related to faricimab by the Investigator

Through Week 48, the incidence of ocular AEs suspected by the investigator to be related to faricimab was [redacted]

The most common treatment-related ocular AEs in the study eye (≥0.5%) were retinal pigment epithelial tear ([redacted] and vitritis ([redacted]

Ocular AEs in study eye by severity

Week 48

The majority of ocular AEs in the study eye through Week 48 were mild or moderate in severity in the faricimab and aflibercept treatment arms. Through Week 48, [redacted] in the faricimab arm and [redacted] in the aflibercept arm experienced at least one severe ocular AE in the study eye. The severe ocular AEs in the study eye in the faricimab arm by PT were retinal pigment epithelial tear, uveitis, intraocular pressure increased ([redacted]), neovascular age-related macular degeneration (verbatim, worsening of nAMD), eye pain, cataract, punctate keratitis, subretinal fibrosis, cataract nuclear, hyalosis asteroid, procedural pain, viral uveitis, chorioretinitis (viral) [redacted]). The severe ocular AEs in the study eye in the aflibercept arm by PT were neovascular age-related macular degeneration (verbatim, worsening of nAMD) ([redacted]), eye pain, subretinal fibrosis, vitreoretinal traction syndrome, uveitis, cataract cortical, diplopia, intraocular pressure increased, and blepharal papilloma [redacted]). The severe ocular AEs in the study eye suspected by the investigator to be related to study treatment by PT were uveitis ([redacted]), hyalosis asteroid, retinal pigment epithelial tear ([redacted]) in the faricimab arm; and uveitis ([redacted]) in the aflibercept arm.

Week 60

Through Week 60, the incidence of mild or moderate ocular AEs in the study eye was generally consistent with the Week 48 dataset considering the increase in exposure duration (faricimab: [redacted] [Week 60] and [redacted] [Week 48] vs aflibercept: [redacted] [Week 60] and [redacted] [Week 48]). Between Week 48 and Week 60, an additional [redacted] in each treatment arm experienced at least one severe ocular AE in the study eye.

Deaths

Week 48

In total, through Week 48, death was reported in 17 patients ([redacted] in the faricimab arm and [redacted] [redacted] in the aflibercept arm). None of the deaths were suspected by the investigator to be related to study treatment.

Week 60

Through Week 60, the incidence of deaths was consistent with the Week 48 dataset (faricimab: [redacted] and [redacted] vs aflibercept: [redacted] and [redacted]). Between Week 48 and Week 60, there were an additional [redacted] in the faricimab arm; the primary causes of death were cardiac failure chronic, pulmonary oedema, and respiratory failure ([redacted] each). None of the deaths were suspected by the investigator to be related to study treatment.

Serious ocular AEs in the study eye

Week 48

Through Week 48, the incidence of serious ocular AEs occurring in the study eye [redacted] ([redacted] in the faricimab arm and [redacted] in the aflibercept arm), with the exception (≥0.5% difference in any treatment arms) of retinal pigment epithelial tear [redacted] in the faricimab arm and [redacted] in the aflibercept

arm). Through Week 48 in the faricimab arm and in the aflibercept arm experienced at least one serious ocular AE suspected by the investigator to be related to study treatment.

Table 27: Serious ocular adverse events in the study eye through Week 48 from pooled Phase III nAMD Studies (pooled safety evaluable population)

n (%)	Fari 6.0 mg n=664	Afli 2.0 mg n=662
Total no. of patients with at least one AE		
Total no. of events, n		
Neovascular age-related macular degeneration		
Retinal pigment epithelial tear		
Uveitis		
Viral uveitis		
Vitritis		
Age-related macular degeneration		
Cataract		
Cataract cortical		
Chorioretinitis		
Corneal abrasion		
Corneal oedema		
Endophthalmitis		
Eye allergy		
Facial bones fracture		
Intraocular pressure increased		
Subretinal fibrosis		
Vitreous haemorrhage		

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. 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 349 (last day of Week 48 analysis visit window). AE reported as neovascular age-related macular degeneration in the study eye indicates an accelerated worsening of the condition, as judged by the investigator.

Week 60

Through Week 60, the incidence of serious ocular AEs in the study eye (faricimab: and vs aflibercept: and Between Week 48 and Week 60, the serious ocular AEs in the study eye by PT were neovascular age-related macular degeneration (verbatim, worsening of nAMD), visual acuity reduced, and rhegmatogenous retinal detachment ( ) in the faricimab arm; and cataract, visual acuity reduced, cataract operation complication, cataract traumatic, non-infectious endophthalmitis, retinal degeneration ( ) in the aflibercept arm. One of these serious ocular AEs in the study eye ( ) was suspected by the investigator to be related to study treatment (non-infectious endophthalmitis); this event resolved by the CCOD.

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

Week 48

Overall through Week 48, the incidence of ocular AEs leading to study treatment discontinuation [redacted]. Through Week 48, [redacted]

Table 28: Ocular adverse events leading to study treatment discontinuation through Week 48 from pooled Phase III nAMD Studies (pooled safety evaluable population)

n (%)	Fari 6.0 mg n=664	Afli 2.0 mg n=662
Total no. of patients with at least one AE	[redacted]	[redacted]
Total no. of events, n	[redacted]	[redacted]
Uveitis	[redacted]	[redacted]
Iridocyclitis	[redacted]	[redacted]
Neovascular age-related macular degeneration	[redacted]	[redacted]
Retinal pigment epithelial tear	[redacted]	[redacted]
Vitreous detachment	[redacted]	[redacted]
Vitritis	[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. 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 349 (last day of Week 48 analysis visit window). AE reported as neovascular age-related macular degeneration in the study eye indicates an accelerated worsening of the condition, as judged by the investigator.

Week 60

Through Week 60, the incidence of AEs leading to study treatment discontinuation [redacted] (faricimab: [redacted] and [redacted] vs aflibercept: [redacted] and [redacted] Through Week 60, the incidence of AEs leading to study discontinuation [redacted] (faricimab: [redacted] and [redacted] vs aflibercept: [redacted] and [redacted]

Adverse events that led to dose interruption

Week 48

Overall through Week 48, the incidence of ocular AEs leading to dose interruption was [redacted] between the treatment arms

Table 29: Ocular adverse events leading to dose interruption through Week 48 from pooled Phase III nAMD Studies (pooled safety evaluable population)

n (%)	Fari 6.0 mg n=664	Afli 2.0 mg n=662
Total no. of patients with at least one AE	[redacted]	[redacted]
Total no. of events, n	[redacted]	[redacted]
Iridocyclitis	[redacted]	[redacted]
Intraocular pressure increased	[redacted]	[redacted]
Blepharitis	[redacted]	[redacted]
Hordeolum	[redacted]	[redacted]
Viral uveitis	[redacted]	[redacted]
Vitritis	[redacted]	[redacted]

Chorioretinitis	[redacted]	[redacted]
Conjunctivitis	[redacted]	[redacted]
Conjunctivitis viral	[redacted]	[redacted]
Iritis	[redacted]	[redacted]
Neovascular age-related macular degeneration	[redacted]	[redacted]
Ophthalmic herpes simplex	[redacted]	[redacted]
Uveitis	[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. 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 349 (last day of Week 48 analysis visit window). AE reported as neovascular age-related macular degeneration in the study eye indicates an accelerated worsening of the condition, as judged by the investigator.

Week 60

Through Week 60, the incidence of ocular AEs leading to dose interruption [redacted] (faricimab: [redacted] and [redacted] vs aflibercept: [redacted] and [redacted]).

Non-ocular adverse events

Week 48

Through Week 48, the incidence of non-ocular AEs was [redacted] with the exception (≥1% difference in any treatment arms: faricimab arm vs aflibercept arm) of hypertension, arthralgia, fall, bronchitis, blood pressure increased, and dyspnoea. The majority of non-ocular AEs were mild or moderate in severity in both the faricimab arm and aflibercept arm.

Table 30: Non-ocular adverse events (≥2%) through Week 48 from pooled Phase III nAMD Studies (pooled safety evaluable population)

n (%)	Fari 6.0 mg n=664	Afli 2.0 mg n=662
Total no. of patients with at least one AE	[redacted]	[redacted]
Total no. of events, n	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]
Fall	[redacted]	[redacted]
Bronchitis	[redacted]	[redacted]
Headache	[redacted]	[redacted]
Sinusitis	[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. 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 349 (last day of Week 48 analysis visit window). AE reported as neovascular age-related macular degeneration in the study eye indicates an accelerated worsening of the condition, as judged by the investigator.

Week 60

Through Week 60, the incidence of non-ocular AEs was [redacted] with the Week 48 dataset considering the increase in exposure duration (faricimab: [redacted] and [redacted] vs aflibercept: [redacted] and [redacted]). Through Week 60, the incidence of serious non-ocular AEs was [redacted] with the Week 48 dataset considering the increase in exposure duration (faricimab: [redacted] and [redacted] vs aflibercept: [redacted] and [redacted]

B.3.11 Conclusions about comparable health benefits and safety

Despite the proven efficacy of anti-VEGF therapies for the treatment of nAMD in controlled clinical trial settings, currently available therapies require frequent injections to maintain efficacy, which is difficult to achieve in the real-world setting, leading to unsustained vision outcomes that decline over time (65, 75, 78, 82, 83). In real-world clinical practice, IVT injection frequency may decline to five or fewer injections per year (75, 81), while optimal responses to anti-VEGF treatment often require 7–12 injections per year (76). The frequent injections place a high treatment burden on patients, their caregivers, and healthcare providers (43, 44, 77). As a result of the burden associated with current anti-VEGF injections, patients desire new treatments to have long-lasting efficacy and less frequent injections, without compromising efficacy and safety (33). Similarly, physicians also see improved treatment durability as one of the greatest unmet needs in the treatment of retinal diseases (85, 86).

Faricimab is a first-in-class dual-pathway inhibitor of Ang-2 and VEGF, two key drivers of nAMD. The unique dual inhibition of two distinct ligands (Ang-2 and VEGF-A) 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. Ang-2 mediated inactivation of the Tie-2 receptor is a crucial and necessary step to initiate the angiogenic switch that sensitises blood vessels for the effects of growth factors from the VEGF family ultimately driving blood vessels towards angiogenesis, permeability, and inflammation. 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 TENAYA and LUCERNE trials for nAMD were designed to primarily show non-inferiority of faricimab compared with aflibercept in treatment-naïve patients. An additional objective was to assess extended durability of faricimab compared with a fixed-interval aflibercept regimen dosed per the prescribing information (120). Clinical experts concurred that the enrolled populations are reflective of patients seen in UK clinical practice (121).

In TENAYA and LUCERNE, the pre-specified primary endpoint was met independently in each trial; faricimab at up to Q16W dosing regimens demonstrated non-inferiority in mean change from baseline in BCVA averaged over Weeks 40, 44, and 48 compared with aflibercept Q8W. Overall, at Week 40/44/48 the adjusted mean change from baseline in BCVA in the pooled ITT population was 6.2 and 5.9 letters in the faricimab up to Q16W arm and aflibercept Q8W arm, respectively; the difference between the faricimab up to Q16W arm and aflibercept Q8W arm was 0.4 letters (95% CI: -0.9, 1.6). Results from key efficacy

and safety analyses based on complete data for all patients through Week 60

[redacted]

In order to reduce the treatment burden associated with monthly dosing, alternative anti-VEGF regimens such as PRN and T&E have been studied. Data from these trials demonstrated suboptimal vision outcomes with PRN regimens compared with a fixed monthly regimen (122, 123). Furthermore, while T&E regimens offer visual acuity benefits with fewer injections over 1 year compared with monthly dosing or PRN regimens (124, 125), the durability of treatment effect may be limited by only targeting the VEGF pathway.

At Week 48, almost 80% of patients in the pooled population were on a faricimab Q12W or longer dosing regimen, with 45% were on Q16W regimen. Patients in the faricimab up to Q16W dosing regimen achieved comparable vision outcomes to those of the more frequently dosed aflibercept Q8W dosing regimen, with almost half of patients on treatment intervals twice as long as the comparator highlighting the increased durability of effect without compromising efficacy and safety, thereby allowing greater patient and caregiver independence. Following the loading phase, 45% of patients required only two injections during Year 1. By comparison, patients receiving aflibercept Q8W required five injections after the loading phase during the same period. Similar results to the aflibercept Q8W treatment regimen were also demonstrated for faricimab up to Q16W via multiple secondary outcomes based on VA and patient-reported quality of life. These results highlight that better disease control as a result of improved vascular stability allows for longer treatment intervals without compromising vision outcomes. Through its unique mechanism of action inhibiting two key disease pathways, faricimab demonstrates unprecedented durability and a clinically meaningful reduction in the treatment burden in patients with nAMD.

Overall, UK clinical experts were encouraged by the efficacy, durability and anatomical benefits associated with faricimab,; in particular, they were impressed that 45% of patients in the faricimab arm reached Q16W dosing at Week 48, with the vast majority remaining on this regimen for the duration of the study (121).

Safety data from TENAYA and LUCERNE 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 programme compared with aflibercept. In totality, faricimab has been investigated across four Phase III trials in more than 3,000 patients with nAMD or DMO.

TENAYA and LUCERNE are large global trials conducted during the COVID-19 pandemic, which had the potential of impacting trial participants, study conduct and data collection. Mitigation measures were implemented to minimise the impact of the pandemic on data collection, while sensitivity and supplemental analyses were performed to test the robustness of the primary results. These measures ensured interpretability of efficacy and safety data, and conclusively established the benefit-risk profile of faricimab.

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 comparable visual outcomes in terms of BCVA and comparable

anatomical outcomes in terms of decreasing retinal thickness with a lower or similar 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 TENAYA and LUCERNE are currently reported, therefore long-term data will be needed to fully understand the durability benefits of dual Ang-2/VEGF-A inhibition and to assess the potential for faricimab to reduce treatment burden and improve quality of life. However, 2-year outcomes are expected in [redacted] while patients who complete week 112 will be eligible to enter a 2-year open-label long-term extension study, AVONELLE-X (NCT04777201) (126). The observed durability of faricimab is also limited by the fact that aflibercept was administered as a fixed Q8W regimen according to its licenced indication, with no possibility to extend treatment interval as in the faricimab arm. A head-to-head comparison of the durability of faricimab versus aflibercept was not possible since extended regimens for aflibercept had not been established, therefore fixed Q8W was the most appropriate regimen to evaluate non-inferiority with faricimab. The aflibercept dose and schedule used in the VIEW studies are well-established and consistent with global recommended dosing posologies.

Conclusion

The results from the TENAYA and LUCERNE phase 3 trials evaluating dual Ang-2 and VEGF-A inhibition with IVT faricimab, administered at up to Q16W, demonstrated vision benefits and anatomic outcomes comparable with VEGF pathway inhibition alone with Q8W aflibercept. The observed extended durability of effect with faricimab, likely driven by the vascular-stabilising effects of dual Ang-2 and VEGF pathway inhibition, has the potential to improve patient outcomes in clinical practice beyond targeting VEGF pathway alone. The disease control afforded by the novel dual pathway inhibition with faricimab could allow extending time between treatments whilst maximising vision gains, addressing a key clinical unmet need for durable therapies in the management of nAMD. Furthermore, faricimab was generally well tolerated, with a safety profile comparable to aflibercept.

Overall, faricimab provides an effective and well-tolerated treatment option for patients with nAMD which can be administered less frequently than current approved treatments, with comparable outcomes. Moreover, with its unique dual mechanism of action, faricimab achieves unprecedented durability of effect (with 80% of patients on an extended treatment interval of Q12W or longer), providing patients and the healthcare system with an opportunity to alleviate the substantial treatment burden associated with current anti-VEGF therapies and reducing overall costs, while improving independence for those living with nAMD and their caregivers.

B.3.12 Ongoing studies

Two-year data for TENAYA and LUCERNE will be available in [redacted]

AVONELLE–X is a 2-year, global, open-label extension study to evaluate the long-term safety and tolerability of faricimab in patients with nAMD who have completed TENAYA or LUCERNE. Timelines for availability of data from AVONELLE-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 outpatient hospital setting, in line with currently licensed anti-VEGF therapies used for nAMD, namely aflibercept and ranibizumab. There are no additional requirements anticipated in terms of service provision or disease management with the inclusion of faricimab in the treatment pathway.

It is anticipated that the majority of patients who receive faricimab will be able to have their treatment intervals extended out to Q16w, following the loading dose. The outputs of our analysis suggest that the number of injections and monitoring visits required with faricimab versus the aflibercept and ranibizumab will be much lower. Details of the resource consumption associated with the use of faricimab are provided in Section B.4.2 below.

B.4.2 Cost-comparison analysis inputs and assumptions

B.4.2.1 Features of the cost-comparison analysis

The aim of this analysis was to evaluate the costs and resource use associated with faricimab, versus aflibercept and ranibizumab for the treatment of nAMD from a UK (England and Wales) healthcare perspective. A cost-comparison model was developed to capture the lifetime costs and resource use associated with the use of faricimab, aflibercept and ranibizumab in the treatment of nAMD patients.

The results from the pre-specified primary endpoint analysis for TENAYA and LUCERNE was met with faricimab demonstrating up to Q16w dosing with non-inferior efficacy in terms of mean change from baseline in best-corrected visual acuity (BCVA) averaged over Weeks 40, 44 and 48, versus aflibercept Q8w in nAMD patients (109, 111). Across both trials, initial BCVA gains were sustained and vision remained consistently high and comparable across both treatment arms, with majority of patients in the faricimab arm on extended fixed regimens up to Q16w. Patients also demonstrated meaningful and comparable reductions in central subfield thickness (CST) across both arms of faricimab up to Q16w and aflibercept Q8w, from baseline through Week 48. Low rates of adverse events were observed in both treatment arms and occurrences of serious ocular adverse events were comparable between both treatments and studies. The results of a network meta-analysis study also confirmed [redacted] 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 TENAYA and LUCERNE were similar for faricimab and aflibercept, [redacted]

Based on this information, a cost-comparison analysis whereby treatment efficacy, treatment safety and treatment discontinuation rates were all set to equal was deemed appropriate and the most reasonable model framework.

An overview of the cost-comparison analysis is presented below.

Table 31: Summary of the cost-comparison analysis.

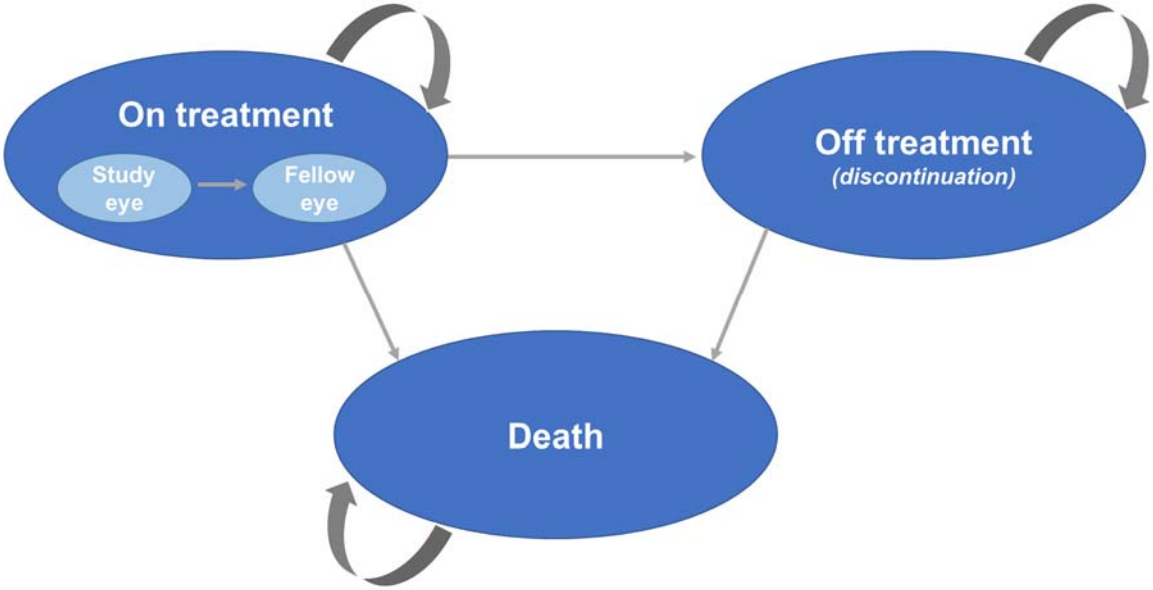
Feature	Chosen approach
Population	Adults (aged ≥18 years) with nAMD to reflect the populations included in the TENAYA and LUCERNE trials.
Intervention	Faricimab (4 LD → Q8/Q12/Q16w [T&E])
Comparator(s)	Aflibercept (3 LD → T&E to Q4/Q8/Q12/Q16w) Ranibizumab (3 LD → T&E to Q4/Q8/Q12w)
Outcomes	Mean incremental per-patient costs and total per-patient costs
Perspective	NHS and personal social services (PSS) in England and Wales
Time horizon	Lifetime – 25 Years (assuming maximum age of 100 Years)
Discounting	Costs discounted at 3.5% per annum
Technology acquisition cost	£857 (list price)

LD: loading dose; NHS: National Health Service; PSS: Personal Social Services; T&E: treat and extend; nAMD: neovascular age-related macular degeneration; QX: one injection every X weeks.

B.4.2.2 Model structure

A cost-comparison model was developed in Microsoft Excel® 2016 using a Markov model 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: Cost-comparison model structure). Patients could enter the model with either unilateral or bilateral disease. Those with unilateral disease could develop bilateral disease over time according to an annual probability of developing fellow eye nAMD involvement. However, once bilateral disease occurs, patients could not transition back to having unilateral disease. A similar model structure was used and accepted in the recent brolucizumab submission to NICE for the treatment of nAMD (69). Furthermore, clinical experts also agreed that the model appropriately reflected the disease pathway for nAMD patients.

Figure 24: Cost-comparison model structure



A lifetime time horizon (25 years) was adopted based on patients entering the model at 75 years old (mean age as per the pooled intent-to-treat (ITT) populations across the TENAYA and LUCERNE studies). The time horizon was considered sufficiently long enough to reflect any significant differences in costs across the technologies being compared. A cycle length of four-weeks was adopted in order to reflect the shortest possible treatment interval (Q4w) that could be applied within the model. A half-cycle correction was also applied. Aligned with the NICE reference case (115), a discount rate of 3.5% was applied to costs in the model.

To assess the plausibility and robustness of the model predictions, the impact of varying assumptions and parameter values that have been identified as drivers of the model, have been explored in sensitivity and scenario analyses (see Section B.4.4).

B.4.2.3 Patient population

The patient population modelled in the analysis was reflective of both the anticipated marketing authorisation for faricimab and of the populations evaluated in the TENAYA and LUCERNE trials:

[redacted]

TENAYA and LUCERNE are identical in design, both were conducted simultaneously, and there are no notable differences in the key baseline characteristics between the two study patient populations (see Section B.3.3). The main data sources used in the model are the pooled data covering the patient populations of TENAYA and LUCERNE (109, 111) and the populations of studies included within the network meta-analysis (see Sections B.3.8 and B.3.9).

[redacted]

[redacted]

Therefore, the ITT population was deemed appropriate to use within this analysis.

In the base case analysis, the key population baseline characteristics, namely age and gender distribution were derived from the pooled ITT populations of the TENAYA and LUCERNE trials (Table 32). Estimates for the proportion of patients with nAMD fellow eye involvement (i.e. bilateral disease) at both baseline and monthly incidence, were informed by the NICE clinical guidelines for AMD (NG82) (12). Feedback from UK clinical experts agreed that the patient demographics incorporated in the model were representative of the UK nAMD population.

Table 32: Population baseline characteristics included in the model.

Characteristic	Value	Source
Age, mean at baseline	75 Years (8.6)	TENAYA and LUCERNE trials
Percentage male	41%	TENAYA and LUCERNE trials
Incidence of nAMD in second eye at baseline	7.3%	NICE nAMD guideline review (NG82)
Monthly incidence of nAMD in second eye	1.39%	NICE nAMD guideline review (NG82)

DMO: diabetic macular degeneration SD: standard deviation; nAMD: wet age-related macular degeneration.

B.4.2.4 Mortality

Mortality was modelled by applying general population all-cause mortality data obtained from 2019 England and Wales National Life Tables published by the Office for National Statistics based on 2017-2019 mortality data (127). To reflect the patient population in the model, age- and gender-specific mortality rates were combined into a single blended rate using the proportion of males and mean age set in the model to reflect the patient population in the TENAYA and LUCERNE trials (109, 111). The rate of mortality is assumed to be equal across all treatment arms to reflect equivalent efficacy between the intervention and all comparators.

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.

B.4.2.5 Intervention and comparators' acquisition costs

Aflibercept and ranibizumab are licensed treatments for patients with nAMD with associated NICE guidance (TA294 and TA155) (1, 2). Both of these technologies are part of the treatment pathway for this patient population and are appropriate to include as comparators to faricimab in this appraisal. A recent assessment of nAMD treatment market share confirms that both aflibercept and ranibizumab are used in over [redacted] of the market (aflibercept: [redacted] injections; ranibizumab: [redacted] injections) (70).

Although brolucizumab has been recently approved for nAMD, clinical expert opinion and low market share ([redacted]) confirms that brolucizumab is not used in routine care for these patients (70). Clinical expert opinion further validated that both aflibercept and ranibizumab are considered to be standard of care treatments for this patient population.

A summary of the acquisition costs for faricimab, aflibercept and ranibizumab in presented in Table 33 below. The drug acquisition costs for aflibercept and ranibizumab were based on the list price stated in the British National Formulary (BNF) (128). The confidential patient access scheme (PAS) discounts for aflibercept and ranibizumab have been agreed with the Department of Health and are unknown to Roche. Therefore, the list price for each treatment has been used in the base case cost-comparison analyses. The dosing and monitoring frequencies listed in the table showcase the figures utilised within the base case analysis. Additional scenarios exploring different injection and monitoring estimations, along with the impact of confidential discounts on the overall results, has been explored in scenario analyses, see Section B.4.4.

If recommended, faricimab will be provided at a simple confidential PAS discount of [redacted], this is the price that has been used to inform the base case cost-comparison analysis.

Table 33 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** £816.00	**NHS list price** £551.00
Method of administration	Intravitreal injection	Intravitreal injection	Intravitreal injection
Dose	6mg	2mg	0.5mg
Dosing regimen	LP→ Q16/Q12/Q8w (T&E)	LP→Q16/Q12/Q8/Q4w (T&E)	LP → Q12/Q8/Q4w (T&E)
Dosing frequency (no. of injections)	Y1: 6.79 [redacted]	[redacted] Y3+: 4.00	[redacted] Y3+: 4.00
Separate monitoring visits (excluding those for injections)	All monitoring visits expected to take place at the same time as treatment administration, under the assumption of T&E dosing regimen		
Data sources used to inform dosing and monitoring assumptions	Y1 and Y2: TENAYA and LUCERNE trials (109, 111) validated by clinical expert opinion Y3+: Adjusted and informed using the NICE preferred and accepted assumption from TA294 and TA672 (2, 69), along with clinical expert opinion	Y1 and Y2: Informed by the NMA estimates (116) for T&E regimens Y3+: Informed by the NICE preferred and accepted scenario from TA294 and TA672 (2, 69)	

*Price listed includes an approved patient access scheme.

LP: loading phase; T&E: treat and extend; QXw: one injection every X weeks.

B.4.2.6 Dosing regimens

In TENAYA and LUCERNE following the loading phase, patients receiving faricimab were assessed for their disease activity at Weeks 20 and 24, which determined their treatment interval up until Week 60. The results demonstrated that almost 80% of patients receiving faricimab were on a Q12w or longer dosing regimen immediately after completion of the loading phase, and 45% were on a Q16w regimen, at Week 48 (109, 111). The base case analysis models the dosing regimen of faricimab with a loading phase of four 6mg injections leading to a treat-and-extend (T&E), up to Q16w. The T&E regimen has been modelled as multiple fixed treatment intervals (i.e. Q8w, Q12w and Q16w); the proportion of faricimab patients on each dosing interval is based on the data from the pivotal trials – there is no switching of patients between dosing intervals (109, 111), see Table 35. This is in line with the rapid extension of treatment intervals, up to Q16w, that occurred immediately after the loading phase within TENAYA and LUCERNE. This method has been validated with clinical experts, who confirmed that this was a plausible method to model T&E regimens for the interventions.

Furthermore, from Week 60 patients in the faricimab arm were treated according to a personalised treatment interval (PTI) dosing regimen, with treatment intervals between Q8w and Q16w (107, 112). During the PTI phase, at drug dosing visits, treatment intervals could be maintained or adjusted (i.e. increased by 4 weeks or decreased by 4 or 8 weeks) based on optical coherence tomography (OCT) scans, BCVA and clinical assessments, as per protocol. The PTI dosing regimen phase is not part of the primary analysis reported within this submission, as the PTI dosing occurred from Week 60 onwards; the analyses presented contains data from the Week 60 data cut. Whilst the PTI data has not been fed into the economic analysis, preliminary PTI data has been presented within Table 16 and Figure 7 shows the PTI pooled TENAYA and LUCERNE data to date.

[redacted]. The extended treatment intervals carried out within both TENAYA and LUCERNE are aligned with the anticipated marketing authorisation for faricimab (3). UK clinical experts agreed that the pooled TENAYA and LUCERNE data to date (Week 60 data cut) does support the use of T&E in clinical practice.

For the comparators, there are a range of dosing schedules that are available for aflibercept and ranibizumab (i.e. fixed dosing intervals, pro-re-nata (PRN) and PRN extend (PRNX)). In the base case analysis, it is assumed that both comparators are administered on a T&E basis (up to Q16w for aflibercept and up to Q12w for ranibizumab) following the loading phase, as this dosing regimen is most reflective of UK clinical practice as confirmed by UK clinical experts. It is assumed that patients receiving either of the comparators, will have 3 injections (Q4w for 3 months) in the loading phase (LP) and then go onto the flexible dosing regimen T&E: aflibercept 2mg LP → T&E; ranibizumab 0.5mg LP → T&E (see Table 33).

The T&E regimen has been modelled using the same approach as was used in the faricimab arm. The proportion of patients on a T&E regimen for ranibizumab has been informed by a post-hoc analysis of VIEW 1 and 2 studies, respectively (129). Although the marketing authorisation for aflibercept allows it to be administered on a Q16w basis, clinical experts confirmed that aflibercept was not frequently used at this interval (as the ARIES study

reported (130)) and more commonly, Q12w or less intervals are utilised in practice. This assumption is further validated with the outputs from a retrospective, observational, real-world data study; data from [redacted] anonymised electronic medical records (EMRs) from five UK sites was analysed using the Medisoft database (patients had an initial diagnosis between 1st January 2014 and 31st December 2018). The aim of the study was to collect data on key healthcare resource utilization (e.g. injection frequency monitoring burden, visits per year), information on treatment patterns and treatment burden over time (see Appendix I). Table 34: Summary of the number of treatment visits in each year from index date (date of first injection) and the summary of length of treatment interval (in days) between consecutive anti-VEGF injections for the study eye in each year of treatment from index date, stratified by initial anti-VEGF received (aflibercept or ranibizumab). [Outputs from the Medisoft EHR real-world data study] shows the mean number of treatment visits and the treatment intervals that were observed for patients, by anti-VEGF received over a 5-year period. Due to the retrospective, observational nature of the study, not all patient records had five-year follow-up data (inclusion criteria: patients with at least 12 months follow-up period following first anti-VEGF injection); the number of patients with full data by year can be seen in Appendix I.

Table 34: Summary of the number of treatment visits in each year from index date (date of first injection) and the summary of length of treatment interval (in days) between consecutive anti-VEGF injections for the study eye in each year of treatment from index date, stratified by initial anti-VEGF received (aflibercept or ranibizumab). [Outputs from the Medisoft EHR real-world data study]

	Aflibercept		Ranibizumab	
Analysis period (months)	Number of treatment visits	Summary of length of treatment interval (in days) between consecutive anti-VEGF injections for study eye, mean (SD)	Number of treatment visits, mean (SD)	Summary of length of treatment interval (in days) between consecutive anti-VEGF injections for study eye, mean (SD)
0-12	[redacted]	[redacted]	[redacted]	[redacted]
13-24	[redacted]	[redacted]	[redacted]	[redacted]
25-36	[redacted]	[redacted]	[redacted]	[redacted]
37-48	[redacted]	[redacted]	[redacted]	[redacted]
49-60	[redacted]	[redacted]	[redacted]	[redacted]

The results from the real-world data study supports the assumption that aflibercept and ranibizumab are, on average, [redacted] As the ARIES study reported treatment interval data that was not thought to be reflective of clinical practice, the data used to inform the proportion of patients expected to be on each treatment interval for aflibercept T&E regimen is based on input from the consulted UK clinical experts, see Table 35. Moreover, 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 further with faricimab than with aflibercept and ranibizumab. This is in line with the [redacted] (Table 16 and Figure 7) clinical expert opinion and the recently published TA672, where it is agreed that majority of patients in clinical practice will follow a T&E regimen (69).

Table 35: Proportion of patients on Q4w-Q16w intervals to inform T&E dosing regimen (base-case assumptions)

Treatment	Proportion of patients on Q4w-Q16w				Source
	Q4w	Q8w	Q12w	Q16w	
Faricimab 6mg	0%	20%	35%	45%	Pooled ITT TENAYA and LUCERNE data ref (109, 111)
Aflibercept 2mg	[redacted]	[redacted]	[redacted]	[redacted]	Informed by UK clinical experts
Ranibizumab 0.5mg	5%	45%	50%	no Q16w evidence	Post-hoc analysis of VIEW 1 and 2 studies (129)

QX: one injection every X weeks.

Injection administration visits

For the base case analysis, the frequency of injection administrations for faricimab in treatment years 1 and 2 has been derived from the pooled TENAYA and LUCERNE ITT study data (see Sections B.3.6, B.4.2.1 and B.4.2.6). The injection administration frequency for faricimab in treatment years 1 and 2 has been derived as the annualised mean number of faricimab injections given that year, as calculated in Equation 2.

Equation 2. Annualised injection frequency calculation for faricimab in Year 1 and 2

$$\frac{365}{\text{Mean time of treatment exposure in Year } 1/2} * \text{mean number of treatments in Year } 1/2$$

Given the lack of long-term data available to derive injection administration frequency for faricimab after Year 2, alternative approaches are used to estimate injection administration frequencies in Year 3 and beyond (see Section B.4.4). Longer-term assumptions for the base case analysis have been based on the committee-preferred assumptions from TA672 and TA294 (2, 69), where it was assumed that all patients would receive 4 injections in Year 3 and beyond, irrespective of which anti-VEGF was administered (see Section B.4.3). This assumption was informed by clinical expert opinion at the time, with no further rationale detailed in published documents [redacted]

The injection frequency for aflibercept and ranibizumab, in treatment years 1 and 2, has been informed by the results of the NMA assuming T&E regimen administration, derived as described at Section B.3.9.4 (116). 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 (116). The frequency of injection administration visits for Year 3 onwards has been informed by the committee-preferred assumptions from TA672 and TA294, assuming that all patients will receive 4 injections from Year 3 and beyond. Table 36 details the injection frequencies applied within the base case.

Table 36: Annual mean number of injection administration visits (base-case assumptions)

Dosing regimen	Injection administration visits		
	Year 1	Year 2	Year 3+
Faricimab 6mg LP → Q16/12w/8w (T&E)	6.79	[redacted]	[redacted]
Aflibercept 2mg LP → Q12w/8w/4w (T&E)	[redacted]	[redacted]	4.0
Ranibizumab 0.5mg LP → Q12w/8w/4w (T&E)	[redacted]	[redacted]	4.0

LP: loading phase; T&E: treat and extend.

Alternative estimates of injection administration frequencies associated with different treatment regimens (pro-re-nata (PRN) [ranibizumab only] and pro-re-nata extend (PRNX) [aflibercept only]) and data sources have been explored as scenario analyses (see Section B.4.4). The data sources utilised to inform the scenario analyses are TENAYA and LUCERNE, real-world data (as mentioned above), the network meta-analyses (Section B.3.9), and the NICE clinical guideline review (NG82) (12).

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.

Treat and extend (T&E) is considered to be a proactive regimen that allows for the extension of treatment intervals in the absence of disease activity. If a sufficient number of injection administration visits are taking place according to disease activity (can range between Q4w and Q12w dosing for current treatment dependent on disease activity), separate monitoring visits are unlikely to be required when following a T&E regimen. This assumption is aligned with the economic assessment conducted in the NICE clinical guidelines for AMD (NG82) (12), where it was assumed that for all continuous regimens, no additional monitoring visits would be required. Thus, in the base case analysis, the total number of injection administration and monitoring visits was considered to be fully captured by the frequency of injections for all continuous regimens (i.e. T&E), assuming no further additional monitoring visits would be required as it would take place during the injection administration visit. 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).

For scenarios where PRN and PRN-extend regimens are used (ranibizumab and aflibercept, respectively), additional monitoring visits are applied in all years of the model as these regimens require regular monitoring. This assumption is informed by the NICE clinical guidelines for AMD (NG82) (12) and TA672 (69), and is supported by the views of clinical experts who said that although the aim is to avoid additional monitoring visits, due to the nature of PRN regimens, further visits can occur for patients on this treatment schedule (see

B.4.2.11). Faricimab is only expected to be used on a T&E basis in clinical practice and so has not been explored as a PRN/X regimen.

B.4.2.7 Treatment discontinuation

Due to the chronic nature of nAMD, no maximum treatment duration is applied, however annual rates of discontinuation have been utilised within the model. The observed discontinuation rates in TENAYA and LUCERNE (109, 111) and the results of the network meta-analysis found that the annual probability of discontinuation for people treated with faricimab, aflibercept and ranibizumab were low and comparable across treatments (see Sections B.3.6 and B.3.9). This finding was reflected in the base-case analysis where the annual probability of treatment discontinuation was assumed equivalent across treatments. This assumption was supported by clinical expert opinion (see Section B.4.2.11).

The discontinuation probabilities for treatment years 1 and 2 are obtained from the following sources: for faricimab, the annualised all cause discontinuation probabilities have been calculated based on the number of events and exposure time in TENAYA and LUCERNE; the comparator data is also based on faricimab T&E following the finding of comparable discontinuation outcomes in the NMA (see Section B.3.9). Discontinuation probabilities for Year 3 onwards are set to at 0.089 as per the finding referenced in NICE guidance (NG82) (12) Treatment discontinuation rates applied to the intervention and comparators can be seen in Table 37. UK clinical experts, consulted by Roche, confirmed their agreement with the treatment discontinuation rates applied to each year of treatment.

Table 37: Annual treatment discontinuation rates applied in the base case analysis

Year of treatment	Mean annual treatment discontinuation probabilities	Source
1	[redacted]	Pooled TENAYA and LUCERNE data for Year 1 and 2 (109, 111)
2	[redacted]	
3	0.089	NG82 (12)

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

The unit costs for diagnosis, monitoring and injection administration visits were obtained from the NHS Reference Schedule 2019/2020 and NG82 (12, 131). In current UK clinical practice, patients are diagnosed with nAMD using fundus fluorescein angiography (FFA). Although optical coherence tomography (OCT) and can also be used to diagnose the condition in practice, the majority of clinicians utilise FFA (according to clinical expert opinion) and NICE guideline review (NG82) (12). In the model the cost of an FFA is applied across all patients at baseline, irrespective of treatment; it is also applied a second time, in the first model cycle for patients that develop nAMD in their second (fellow) eye. The cost of an FFA was not applied at subsequent monitoring visits.

Table 38: Cost of diagnostic testing

Item	Unit cost	Source
FFA	£130.74	Fundus fluorescein angiography (FFA): Weighted average of Total HRG codes for Contrast Fluoroscopy Procedures:

		RD30Z, RD31Z and RD32Z taken from NHS Reference Costs 2019/2020 (131) based on the approach used in the economic evaluation of NG82 (12).

FFA: Fundus Fluorescein Angiography; HRG: Hospital Resource Group; NHS: National Health Service

For the administration of treatment, it was assumed that intravitreal (IVT) injections would be given during consultant-led outpatient appointments (as per the SmPC for the included treatments (3, 120, 132, 133), following an assessment of retinal fluid using optical coherence tomography (OCT) to monitor disease activity. It was also assumed that there would be an additional resource use and cost associated with IVT injections, applicable to every injection administration visit. The additional 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) (134). Furthermore, as the base-case analysis assumes that patients will receive injections on a T&E basis (following the loading phase), all monitoring occurs at the same time as an injection visit; scenario analyses have been explored where some dosing regimens may require additional monitoring visits (see Section B.4.4). A monitoring visit (without treatment) would comprise of a consultant led outpatient visit and an OCT.

The base case analysis assumes that, in addition to drug acquisition costs, the cost of an injection administration visit comprises of an outpatient consultant-led visit (£101.80), an injection administration cost (£54.54) and an OCT procedure (£125.88) – see Table 39: Resource unit costs 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) were explored in scenario analyses (see Section B.4.4). Day case visits are said to occur in very rare circumstances, according to clinical expert opinion, and so have not been analysed as part of the scenario analyses.

Table 39: Resource 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 (131)
OCT	£125.88	NHSE reference schedule 19/20. Outpatient procedure code for Retinal Tomography: BZ88A (ophthalmology) (131)
IVT injection	£54.54	Estimated from aflibercept for DMO ERG report (TA346) (134)
Scenario analysis only		
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 (131)

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

Bilateral treatment multipliers

In the base case analysis, multipliers have been utilised to illustrate the additional costs incurred through treating two eyes compared to just one. In order to account for the additional drug required for bilateral treatment, it is assumed that drug acquisition costs would double (cost multiplier of 2); this assumption is aligned with the approach adopted in

the NICE clinical guidelines for AMD (NG82) (12) and has been considered to be reflective of UK clinical practice by clinical experts.

With respect to the administration and monitoring costs for bilateral disease, it is assumed that all treatments are administered at a "1-stop" appointment (i.e. the cost of administration and monitoring is shared between eyes). However, in 50% of cases higher (i.e. double) treatment administration and monitoring costs would apply due to the additional time spent preparing the patient and reviewing images, (Table 40). This is aligned with the approach adopted in the NICE clinical guideline for AMD NG82 (12).

Table 40: Cost multipliers for bilateral treatment

Cost multiplier	Value	Assumption	Source
Drug cost multiplier	2.0	Assumed drug costs will double	NICE clinical guideline for AMD NG82 (12).
Administration and monitoring cost multiplier	1.5	Assumed that administration and monitoring costs would double in 50% of the cases and are shared (no extra cost) in other cases	

AMD: age-related macular degeneration; NG: NICE guideline.

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 the TENAYA and LUCERNE trials (109, 111). The safety results found that the incidence of at least one adverse event (AE) across the pooled populations was comparable across treatment arms (76.5% and 77% in the faricimab and aflibercept arms respectively) through to Week 60. The incidence of ocular AEs in the study eye were also comparable between the treatment arms (38.3% of patients in the faricimab arm and 37.2% of patients in the aflibercept arm), with the exception (≥1% difference in any treatment arms: faricimab arm vs. aflibercept arm) of dry eye (13 patients [2.0%] vs. 22 patients [3.3%]), vitreous floaters (20 patients [3.0%] vs. 11 patients [1.7%]), and retinal pigment epithelial tear (19 patients [2.9%] vs. 9 patients [1.4%]). The number of patients experiencing serious ocular AEs in the study eye were similarly low, 2.1% and 2.6% in the faricimab and aflibercept arms, through Week 60. The number of deaths reported during the study were also low, and of the 20 deaths reported (1.8% for faricimab and 1.2% for aflibercept) by Week 60, none were suspected by the investigator to be related to study treatment.

In line with the safety results from TENAYA and LUCERNE, the results of the network meta-analysis, presented in B.3.9, 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. 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.

The vision loss associated with nAMD has a detrimental impact on HRQoL through its negative impact on independence and vision-related activities, as well as medical and psychosocial consequences. Many patients also require the assistance of a caregiver and support when attending treatment visits (44), contributing to absenteeism in the workplace for caregivers. Clinical experts also agreed that patients require the assistance of caregivers when attending clinic appointments, causing disruption to daily lives. These costs will not be taken into consideration in the cost-comparison base case analysis, so the wider societal benefits of faricimab will not be fully considered. To explore the wider societal impact of visual impairment, the impact on caregivers has been explored in scenario analyses (see Section B.4.4), where it is assumed that carers taking patients to nAMD appointments, miss one day of work costed at the average UK wage (£82.00) (135).

As many patients with nAMD are of a retirement age, (UK state pension age 66 years (135)), the workplace productivity of patients has not been taken into account.

B.4.2.11 Clinical expert validation

As TA155, TA294 and TA672 provide information on accepted precedents, the majority of assumptions adopted in the base case analysis have been informed by existing appraisals (1, 2, 69).

Clinical data has been incorporated into the model from pooled ITT TENAYA and LUCERNE data in addition to other published clinical trial data (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 4 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)
- Carer productivity losses (see Section B.4.2.10)

B.4.2.12 Uncertainties in the inputs and assumptions

A summary of the assumptions (along with any related uncertainty) adopted in the base case cost-comparison analysis is presented below.

Table 41: Assumptions adopted in the base case analysis

Assumption	Description
Equivalent efficacy	The 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.

across treatments and regimens	TENAYA and LUCERNE demonstrate that faricimab is non-inferior to aflibercept in terms of BCVA outcomes and safety (B.3.6). Results from the NMA (B.3.9) 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 (127). To reflect the patient population in the model, age- and gender-specific mortality rates were combined into a single blended rate using the proportion of males and mean age set in the model to reflect the patient population in the TENAYA and LUCERNE trials (109, 111). No increase in mortality from bilateral disease or adverse events was assumed, and mortality rates were the same regardless of nAMD treatment.
Discontinuation probability	No maximum treatment duration was applied within the model due to the chronic nature of nAMD. Instead, annual rates of discontinuation have been applied; the NMA showed that that annual probability of discontinuation for those treated with faricimab versus aflibercept or ranibizumab is similarly low and comparable. Therefore, the annual probabilities have been assumed as equivalent across treatments. Treatment discontinuation probabilities for years 1 and 2 have been obtained from TENAYA and LUCERNE (109, 111); year 3 onwards has been set to 0.089, as per NG82 (12)
Treatment switching	Patients were either on or off treatment and did not switch treatments; routinely, patients do not typically switch treatments in clinical practice.
Injection administration visits	Treatment frequency for faricimab in the first two years is derived from data pooled across the TENAYA and LUCERNE studies (see B.3.6 and B.4.2.6). Year 1 frequency is derived as the annualised mean number of faricimab treatments for patients at Week 52 in the faricimab arms of TENAYA and LUCERNE. Year 2 frequency is derived using the same approach but annualising the injection frequency of patients' part way through the second year of the studies (see Section B.4.2.6). The modelled frequency of injection administration visits for aflibercept and ranibizumab in Year 1 and 2 is informed by the results of the NMA assuming T&E regimen administration, derived as described at Section B.3.9) The frequency of injection administration visits for Year 3 onwards has been informed by the committee-preferred assumptions from TA672 and TA294 (2, 69), assuming that all patients will receive 4 injections from Year 3 and beyond for aflibercept and ranibizumab. [redacted]
Monitoring visits	As it is assumed that all treatments will be administered on a T&E basis, no additional monitoring visits are applied as monitoring is expected to take place during the treatment visits, as per NG82 (12).
Adverse event probability	The 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	Estimates for the proportion of patients with nAMD fellow eye involvement (i.e. bilateral disease) at both baseline and monthly incidence, were informed by the NICE clinical guidelines for AMD (NG82) (12).
Cost for bi-	In the base case analysis, patients with bilateral disease incurred twice the treatment costs, and 1.5 times the administration and monitoring cost of people with unilateral

lateral disease	disease. This is aligned with the approach adopted in the NICE clinical guideline for AMD NG82 (12).
FFA	FFA is performed at the incidence of nAMD to confirm diagnosis, and will be reapplied for the second eye if bilateral disease occurs. FFA is not performed in subsequent monitoring visits. The unit cost was calculated as £130.74; a weighted average of Total HRG codes for Contrast Fluoroscopy Procedures: RD30Z, RD31Z and RD32Z taken from NHS Reference Costs 2019/2020 (131) based on the approach used in the economic evaluation of NG82 (12).
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. The unit cost was £125.88, taken from NHSE reference schedule 19/20; Outpatient procedure code for Retinal Tomography: BZ88A (ophthalmology).
Consultant led appointments	It is assumed that all injection administration and monitoring visits are led by a consultant in an outpatient setting.

BCVA: best-corrected visual acuity; nAMD: neovascular age-related macular degeneration; NHSE: National Health Service England; NG: NICE guidance; NMA: network meta-analysis; OCT: Optical coherence tomography; TA: technology appraisal.

B.4.3 Base-case results

The results of the base case cost-comparison analysis are presented below (Table 42). The results presented to 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 below assume aflibercept and ranibizumab are provided at list price (128), 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] versus ranibizumab over a lifetime time horizon (see Section B.4.2.1).

Table 42: Base case results (faricimab at net price; aflibercept and ranibizumab at list price)

Cost	Faricimab 6mg LP→ Q16/Q12/Q8w (T&E)	Aflibercept 2mg LP → Q16/Q12/Q8/Q4w (T&E)	Ranibizumab 0.5mg LP → Q12/Q8/Q4w (T&E)
Drug cost	[redacted]	£36,982	£27,175
Administration cost	[redacted]	£11,207	£12,162
Additional monitoring cost	[redacted]	£0	£0
Diagnostic cost	£225	£225	£225
Costs of visual impairment	£11,133	£11,133	£11,133
Mean total cost	[redacted]	£59,547	£50,695
Incremental cost vs faricimab	N/A	[redacted]	[redacted]

LP: loading phase; T&E: treat and extend; QXw: one injection every X weeks.

With similar results in BCVA outcomes, comparable safety and improved treatment durability to aflibercept and ranibizumab, faricimab represents a cost-effective alternative to currently licensed and NICE recommended anti-VEGF therapies (Table 42).

Acknowledging that aflibercept and ranibizumab are available to the NHS at a confidential 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 43. When adopting the base case cost-comparison assumption, this analysis demonstrates that at the net price, faricimab remains [redacted] compared with aflibercept and ranibizumab up to a discount level of [redacted] and [redacted] respectively.

Table 43: 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. Whenever available, values were varied using confidence intervals obtained directly from the same data source that informed the mean value. In the absence of data on the variability around a particular value, it was varied by ±20% or another realistic alternative (i.e. for age and bilateral cost multiplier). The parameter values used in the deterministic sensitivity analyses are presented in Table 44. Results of the DSA are displayed in Figure 25 and Figure 26, where the 9 parameters that had the greatest impact on the incremental costs are presented.

The results of the DSA show that drug costs and model starting age had the greatest impact on the incremental costs.

Table 44: Parameter values used for Deterministic sensitivity analysis

Parameter	Base-case value	Lower value	Higher value	Variation
Drug cost for aflibercept (£)	816	653	979	± 20%
Drug cost for ranibizumab (£)	551	441	661	± 20%
Drug cost for faricimab (£)	[redacted]	[redacted]	[redacted]	± 20%
Starting age of cohort (years)	75	70	80	± 6.67%
Administration cost multiplier for second eye treatment (%)	1.50	1.00	2.00	± 33%
Administration cost for IVT injections	282.22	225.78	338.67	± 20%
Time horizon (years)	25	20	30	± 20%
Discount rate costs (%)	3.5	2.8	4.2	± 20%
Incidence of nAMD in second eye at baseline (%)	0.073	0.058	0.088	± 20%
Monthly incidence of nAMD in second eye (%)	0.014	0.011	0.017	± 20%

Abbreviations: DSA: deterministic sensitivity analysis; IVT: intravitreal injection; nAMD: neovascular age-related macular degeneration

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

IVT: intravitreal injection; nAMD: neovascular age-related macular degeneration

Figure 26. Tornado plot (faricimab net price compared with ranbizumab list price)

IVT: intravitreal injection; nAMD: neovascular age-related macular degeneration

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 45: Parameters varied in the scenario analysis

Parameter	Description
Age	Varying base-line age of the model population
Bi-lateral cost multiplier	Two scenarios: Assuming all bilateral patients will need double administration and monitoring resource, and that bilateral require the same resource use as unilateral (no additional resource)
Faricimab dosing regimen	Applying different dosing regimens for faricimab (see Table 45)
Aflibercept dosing regimen	Applying different dosing regimens for aflibercept (see Table 45)
Ranibizumab dosing regimen	Applying different dosing regimens for ranibizumab (see Table 45)
Injection setting costs	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) (131)
Carer costs at injection and monitoring visits	Assuming carers take patients to nAMD 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) (135)

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 46.

The base case analysis assumes that the injection frequency at Year 3 is an indicator for long-term treatment visit assumptions, as per the TA294 and TA672 precedent. An alternative assumption to predicting long-term injection frequencies for faricimab, aflibercept and ranibizumab is to use the mean number of injections from Year 2 for all future years of treatment; this is aligned with the base case model used in NG82 (12) and also supported by the findings from the retrospective, observational, real-world data study conducted by Roche Products Ltd (see Section B.4.2.6), where consistent intervals (mean days) can be seen between treatment visits and the number of injections from Year 2 onwards for aflibercept and ranibizumab.

The injection frequency scenarios presented in Table 46 illustrate the base case scenario applied in the cost-minimisation analysis (labelled F1, A1 and R1); this has been informed by the TENAYA and LUCERNE data (109, 111), along with the NMA for the comparators, and long term injection frequency assumptions informed by TA294 and TA672 precedent (2, 69), see Section B.4.2.6. The additional scenarios listed have also been explored:

- F2, A2 and R2: Similar to the base case, the product injection frequencies have been informed by their respective sources (TENAYA/LUCERNE and the NMA T&E outputs), but the assumption that year 2 injection frequencies is a predictor for long-

term resource use levels has been applied, as per the finding in the real-world data study (see Section B.4.2.6 and Appendix I).

- A3 and R3: Applying the data captured from the real-world data study for Y1-3. With respect to faricimab, both the F1 and F2 inputs have been explored in conjunction with this scenario.
- A4 and R4: Utilises the PRN and PRNX data outputs from the NMA (see Section B.3.9.4; With respect to faricimab, the F1 inputs have been explored in conjunction with this scenario.

Table 46: **Annual mean number of injections and total visits per dosing regimen**

Scenario #	Dosing regimen	Data source informing assumption	Injection visits*			Separate monitoring visits		
			Year 1	Year 2	Year 3+	Year 1	Year 2	Year 3+
Base-case								
F1	Faricimab (6mg LP → Q16w/Q12w/Q8w [T&E])	TENAYA/LUCERNE , and TA294/TA672(109, 111) (2, 69)	6.79	[redacted]	[redacted]	0	0	0
A1	Aflibercept (2mg LP → Q16w/Q12w/Q8w/Q4w [T&E])	NMA and TA294/TA672 (supporting Y3+ assumption) (2, 69)	[redacted]	[redacted]	4.00	0	0	0
R1	Ranibizumab (0.5mg LP → Q12w/Q8w/Q4w [T&E])	NMA and TA294/TA672 (supporting Y3+ assumption) (2, 69)	[redacted]	[redacted]	4.00	0	0	0
Scenario analyses								
F2	Faricimab (6mg LP → Q16w/Q12w/Q8w [T&E]) equivalent visits in year 2+	TENAYA/LUCERNE (109, 111), and RWD	6.79	[redacted]	[redacted]	0	0	0
A2	Aflibercept (2mg LP → Q16w/Q12w/Q8w/Q4w [T&E]) equivalent visits in year 2+	NMA and RWD (supporting Y2+ assumption)	[redacted]	[redacted]	[redacted]	0	0	0
A3	Aflibercept (2mg LP → Q16w/Q12w/Q8w/Q4w [T&E])	RWD	[redacted]	[redacted]	[redacted]	0	0	0
A4	Aflibercept (2mg LP → PRNX)	NMA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
R2	Ranibizumab (0.5mg LP → Q12w/Q8w/Q4w [T&E]) equivalent visits in year 2+	NMA and RWD (supporting Y2+ assumption)	[redacted]	[redacted]	[redacted]	0	0	0
R3	Ranibizumab (0.5mg LP → Q12w/Q8w/Q4w [T&E])	RWD	[redacted]	[redacted]	[redacted]	0	0	0
R4	Ranibizumab (0.5mg LP → PRN)	NMA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

LP; loading phase; NMA: network meta-analysis; PRN; pro re nata; PRNX: pro re nata extend; RWD: real-world data; T&E, treat and extend; QXW; one injection every X weeks. *Under T&E regimens, assumed that monitoring takes place at the same time as injection visits.

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

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 are limited, as for the purposes of the cost-comparison analysis, the scenarios analyses are illustrative. The most plausible assumptions, reflecting current UK practice, have been adopted in the base-case.

Of the scenario analyses conducted, assuming different treatment regimens and injection frequencies for the comparators as well as the starting age of the patient cohort had the greatest impact on the incremental costs.

Table 47: 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	75 years	70 years	[redacted]	[redacted]	[redacted]	[redacted]
		80 years	[redacted]	[redacted]	[redacted]	[redacted]
Discount rate	3.5%	0%	[redacted]	[redacted]	[redacted]	[redacted]
Bi-lateral cost multiplier	1.5	1.0	[redacted]	[redacted]	[redacted]	[redacted]
		2.0	[redacted]	[redacted]	[redacted]	[redacted]
F2 / A2 / R2	F1 / A1 / R1	Assuming Y2 is the predictor of long-term resource use	[redacted]	[redacted]	[redacted]	[redacted]
F1 / A3 / R3		Applying RWD for comparators with base case for faricimab	[redacted]	[redacted]	[redacted]	[redacted]
F2 / A3 / R3		Applying RWD for comparators with Y2 as the long term predictor for faricimab	[redacted]	[redacted]	[redacted]	[redacted]
F1 / A4 / R4		Applying PRN/X data obtained from NMA with base case for faricimab	[redacted]	[redacted]	[redacted]	[redacted]
Injection setting costs	£282.22	£269.55	[redacted]	[redacted]	[redacted]	[redacted]
Carer costs at injection and monitoring visits	£0	£82	[redacted]	[redacted]	[redacted]	[redacted]

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 nAMD, from a UK health system perspective.

The model draws upon clinical data from the TENAYA and YOSEMITE studies: ongoing, Phase III, randomised, placebo-controlled studies in patients with nAMD. The baseline characteristics of the patients in TENAYA and LUCERNE 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 (136) evidence was presented to demonstrate that faricimab provides similar or greater health benefits to NICE recommended technologies (ranibizumab and aflibercept) (1, 2). As demonstrated in the results from TENAYA and LUCERNE [redacted] 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 (115).

The base case results from the cost-comparison show that faricimab is [redacted] compared to aflibercept ([redacted]) and ranibizumab ([redacted]) – see Table 44. 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 should be interpreted with caution, as we provide a comparison of the faricimab PAS price, to aflibercept and ranibizumab at list price. 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 cohort starting age and the discount rate have the greatest impact on the incremental costs for faricimab versus the listed comparators.

COVID-19 has brought the requirement for more efficient use of healthcare resources into urgent focus. One study found that patients requiring IVT injections (i.e. patients with diabetic macular oedema, proliferative diabetic retinopathy, or both, nAMD, or retinal vein

occlusion) had a delay in treatment of 5.34 weeks during the initial lockdown period (March–May 2020). These patients experienced vision loss by their next scheduled visit to ophthalmologic services (93). A separate study also found that patients with nAMD experienced the greatest loss of vision with treatment delay, and these patients were also less likely to return to baseline upon restarting treatment (94). The need for longer-acting treatments for patients with nAMD 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. Finally, more durable treatments offer a reduction in the risk of missed appointments that may occur due to service disruption, such as COVID-19, and other unforeseen circumstances.

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 (TENAYA and LUCERNE) 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.
- [redacted]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, superior treatment durability and less frequent injections, the results of the economic analysis indicate that faricimab is the most cost-effective treatment option for nAMD 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 nAMD.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Fast track appraisal: cost-comparison case

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

Clarification questions

January 2022

File name	Version	Contains confidential information	Date
Clarification Questions ERG	**1**	**Yes**	**24.01.2022**

Section A: Clarification on effectiveness data

Document B

A1. Please update the brolucizumab market share data for the quarters Apr-Jun 2021, Jul-Sep 2021 and Oct-Dec 2021 as available. Please provide more detail as to what this market share data covers: e.g. all patients treated for AMD in NHS England, and its source?

The data source that we are using is commissioned by Wilmington Healthcare specifically for ophthalmology, who generate reports through Freedom of Information requests, the data collects injection/implant volume data for nAMD and DMO at a Trust level, across the UK. The report covers 100% of the UK; approximately 155 secondary care institutions are contacted, including all provider institutions for England, Scotland, Wales and Northern Ireland. All collected data is collated at an institutional level via direct written contact (and in some cases telephone contact) with the information officer at the Trust. The data is requested from the Trusts by Wilmington Healthcare anonymously, with no reference to any pharmaceutical company and without incentive payments to the Trusts.

The most recent data cut is from Jan-April 2021, however we will be receiving the Sep-Dec 2021 market share data in March. We are happy to provide the more recent data once it arrives in-house.

A2 PRIORITY. Was the improvement in BVCA in the occult subgroup clinically and statistically significant?

Please see the word document with the title “A2 Occult subgroup tables”.

These tables show the BCVA gains from baseline observed between treatment arms and across studies for patients with different lesion compositions and locations; the data show that the BCVA gains in each lesion subtype were similar across arms and between studies, with considerable overlap of confidence intervals. The gains achieved in the different CNV subtypes are also in line with the pivotal ANCHOR (classic CNV composition[1]) and MARINA (occult/minimally classic CNV composition[2]) studies of ranibizumab in nAMD.

While the BCVA improvement in the occult subgroup is clinically meaningful, statistical significance was not formally tested as this was not a pre-specified endpoint. Therefore, the Company is of the opinion that the differences between treatment arms in CNV lesion composition do not impact the interpretability of the key efficacy results.

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A3 PRIORITY. Please present the faricinib arm data of Document B Table 6 split by those who were allocated to (1) Q8W, (2) Q12W and (3) Q16W during week 20 to week 60. If it is possible to also split the aflibercept arm by those who were assessed as having / not having active disease at week 20 (or week 16 if week 20 is not available) this would also be much appreciated:

The faricimab data has been presented as requested. Please see the word document with the title “A3 baseline characteristics tabulated by treatment interval”. It was not possible to provide the aflibercept data by those who were assessed as having / not having active disease. Patients in the aflibercept arm had 3 x Q4W doses in the loading phase followed by a fixed Q8W regimen. The scheduled treatment intervals were therefore unable to be influenced by disease activity assessments.

Overall, the faricimab data suggest that patients assigned to Q12W and Q8W dosing showed meaningful visual gains and CST reductions, despite having a worse nAMD disease status at baseline, and that those assigned the extended Q16W intervals achieved and maintained robust improvements in vision and retinal thickness through the fixed dosing interval period. These faricimab treatment interval subgroup analyses provide further evidence of the sustained efficacy benefit of faricimab, and support the overall results from the faricimab arm presented in the original submission.

A4. Please provide subgroup analyses results for TENAYA and LUCERNE separately

Please see the word document with the title “A4 subgroup analyses for TENAYA and LUCERNE”. The differences in mean change in BCVA at Week 40/44/48 between the two treatment arms across subgroups were consistent with those of the overall population.

A5 PRIORITY. Please provide the Kaplan Meier time on treatment curves to day 784 (week 112), separately by arm, with the faricimab arm being presented separately for those who were allocated to (1) Q8W, (2) Q12W and (3) Q16W during week 20 to week 60, separately for TENAYA and LUCERNE in the following format (8 tables), where N events is the number of discontinuation events and N censored is the number of censoring events. If felt pertinent and if available, this may also be augmented by additional tables treating COVID related discontinuation events as censoring events. The data of the table below is hypothetical and purely for illustrative purposes.

The Kaplan Meier time on treatment data can be found in the PDF document “A5 - KM time on treatment data_CIC”. The tabulated data within the document provides data for TENAYA, LUCERNE and pooled patients. It was not possible to provide

aflibercept and faricimab arms split by treatment interval in one table/figure, however the aflibercept time on treatment data and the faricimab time on treatment data (split by intervals and grouped together) is available in two separate tables.

As there have been limited discontinuations, it is difficult to draw insightful conclusions from the presented data. Overall the number of discontinuations was low, and no discontinuations due to lack of efficacy through to Week 48 were observed. The data after the Week 48 time point is still immature, additional sources of evidence would be required to make further assumptions.

With regards to patients who discontinued study treatment related to COVID19, this was overall low through to Week 60, and so these have not been separated. Table 12 in Document B of the submission contains a summary of intercurrent events through week 48 and week 60 from pooled Phase III nAMD studies; at Week 60, 3 patients from the pooled faricimab arms and 1 from the pooled aflibercept arms had discontinued study treatment related to COVID19.

The data is based on Week 60 data cut (the last patient in each study reached Week 60), some patients have been on the study for longer at this time point (up to Week 92/Week 96 for LUCERNE and TENAYA, respectively) - longer-term data was not accessible at this point in time. Since the study is still ongoing and a substantial proportion of patients have not completed the study yet, the results should be interpreted with caution beyond Week 60.

A6 PRIORITY. Please present the equivalent of Document B Figure 4 and Figure 8 for the faricimab arm separately for the subgroups of those allocated to (1) Q8W, (2) Q12W and (3) Q16W during week 20 to week 60 of the trials (6 figures). Please also tabulated the mean and 95% CI values for Figure 4 and Figure 8, and also for the additional 6 requested figures.

Please see the equivalent of Figure 4 and Figure 8 in Document B for the faricimab arms by treatment interval and the tabulated mean and 95%CI values for the same figures. Please note that for the faricimab arm, the subgroups of those allocated to the different intervals are presented within the same figure instead of separate figures. The figures are provided for the individual TENAYA and LUCERNE studies.

Please see the PDF with the title “A6 TENAYA_figure_change in baseline from BCVA by faricimab treatment interval up to week 60 ACIC”.

Please see the PDF with the title “A6 TENAYA_figure_change in baseline from CST by faricimab treatment interval at week 60 ACIC”.

Please see the PDF with the title, “A6 LUCERNE_figure_ change in baseline from BCVA by faricimab treatment interval up to week 60 ACIC”.

Please see the PDF with the title, “A6 LUCERNE (figure) change in CST from baseline ACIC”.

Please see the PDF with the title, “A6 Table corresponding to Figure 4 Doc B with mean change in baseline BCVA and 95%CI ACIC”.

Please see the PDF with the title, “A6 Table corresponding to Figure 8 Doc B with mean change in baseline CST and 95%CI ACIC”.

Please see the PDF with the title, “A6 TENAYA tabulated change in mean BCVA from baseline and 95% CI values ACIC”.

Please see the PDF with the title. “A6 TENAYA tabulated change in mean CST from baseline and 95% CI values ACIC”.

Please see the PDF with the title, “A6 LUCERNE tabulated change in mean BCVA from baseline and 95% CI values ACIC”.

Please see the PDF with the title, “A6 LUCERNE tabulated change in mean CST from baseline and 95% CI values ACIC”.

The Company has presented data on the outcomes by faricimab treatment interval up to the Week 60 time point. The data show that patients on extended faricimab treatment intervals maintained visual gains and showed anatomical improvement with 3 cycles of Q16W treatment.

A7-A9 PRIORITY. For the faricimab arm please provide the number of patients remaining on treatment at the start of the period (N pat.) and the number of injections (N inj.) received by 4 weekly period during the loading phase, separately for TENYA and LUCERNE (2 tables). For the faricimab arm please provide the number of patients remaining on treatment at the start of the period (N pat.) and the number of injections (N inj.) received by 4 weekly period after the loading phase of weeks 0-15 to end of week 111/start of week 112 split by those allocated to Q8W, Q12W and Q16W during the week 24 to week 60 period of the trial, separately for TENYA and LUCERNE (2 tables). For the aflibercept arm please provide the number of patients remaining on treatment at the start of the period (N pat.) and the number of injections (N inj.) received by 4 weekly period to end of week 111/start of week 112.

The data requested for questions A7-A9, can be found in PDF documents
“A7-A9 [TENAYA] number of injections received in study eye over time_ACIC”, “A7-A9 [TENAYA] summary of patients who have not discontinued study treatment over time_ACIC”,
“A7-A9 [LUCERNE] summary of patients who have not discontinued study treatment over time_ACIC” and
“A7-A9 [LUCERNE] number of injections received in study eye over time_ACIC”.

The tables have not been provided in the requested format, however the documents labelled “number of injections received in study eye over time” provide the number of injections received by 4 weekly intervals from loading to the latest time point in each study. The documents labelled “summary of patients who have not discontinued study treatment over time” provide the number of patients at each time point (every 4 weeks) who are remaining on study treatment. All data is provided with the faricimab arm being split according to the treatment interval at Week20/24.

As the data provided is based on the Week 60 data cut (when the last patient reached Week 60), the data is somewhat misleading after Week 60. Therefore, in addition to the tables providing “summary of patients who have not discontinued study treatment over time” we have also created another output which displays the number of discontinuations per visit, which can be found in documents labelled “A7-A9 [TENAYA] summary discontinuations of study treatment over time_ACIC” and “A7-A9 [LUCERNE] summary discontinuations of study treatment over time_ACIC”. Please note that there may be minor differences between this table and previously submitted discontinuation tables as this table excludes patients who discontinued study treatment prior to the disease activity assessments as they were therefore not assigned to any of the interval subgroups. Also, this table is based on the Week 60 dataset and so there may be some minor updates to the previously reported Week 48 information.

When comparing the number of patients eligible for treatment versus the number of injections received, the patient numbers are not always equal at each 4-weekly interval. This is due to patients either having a missed visit at that week, or having a missed visit/dose hold at a prior visit. Furthermore, within the “number of injections” document, a small number of patients are documented as having active doses at visits that are not within the original cycle - the reason for this is, if a patient missed a dosing visit (or there was a dose hold at a treatment visit), that dose would then be administered at the next visit, as per protocol.

For the documents providing the “number of injections”, the “n” denotes the total number of active treatment injections received by the end of the visit specified; since one patient gets one injection, the “n” is equal to the number of patients. The mean is the average number of injections a patient has received by that time point.

The tables detailing the number of injections show the Q4W loading phase through to Week 12, with the first loading dose taking place at day 1. At week 20, the first disease activity assessment takes place and patients with active disease will be placed on a fixed Q8W regimen. Following the next disease activity assessment at week 24, patients with active disease will be placed on a fixed Q12W regimen. No further disease activity assessments were scheduled and patients without active disease at weeks 20 and 24 will be placed on a Q16W regimen starting at week 28. No supplementary therapy was allowed.

An algorithm-driven flexible dosing regimen (Personalized Treatment Interval, PTI) was implemented from week 60. This allows tailoring of the treatment interval by extending, reducing or maintaining the interval according to assessments made at study drug dosing visits, with extensions allowed in a Q4W increment up to a maximum of Q16W, and reductions to a minimum of Q8W, with no capping at Q4W reductions. If the extension and reduction criteria have not been met, the interval can be maintained. The data outputs provided include all data currently available to the latest time point in each study; the data is based on the Week 60 data cut (when the last patient reached Week 60), with some data available for patients with longer follow-up at that point (up to Week 92/Week 96 for LUCERNE and TENAYA, respectively) - longer term data was not accessible at this point in time. Since the study is still ongoing and a substantial proportion of patients have not completed the study yet, the results should be interpreted with caution beyond Week 60.

A10. Please tabulate the data presented in Document B Figure 7A, Figure 7B and Figure 7C. If possible, please present this separately for TENAYA and LUCERNE.

The data presented in document B Figure 7A, Figure 7B and Figure 7C has been tabulated as pooled and individual data for TENAYA and LUCERNE. Please see the word document with the title “A10 tabulated PTI data_CIC”. [redacted]

A11 PRIORITY. Please tabulate by 4 weekly period to end of week 111/start of week 112 (A) the number of patients remaining on treatment at the start of the period (N pat.), (B) the number of patients assessed for disease activity during this period (N Assess.) and (C) the number of patients assessed as having disease activity (N Active) for (1) aflibercept patients, and for (2) faricinib patients, with the faricinib patient data being presented separately for the three subgroups by their allocation during the week 20 to week 60 period: Q8W, Q12W and Q16W. Please present this separately by trial (8 tables). The ERG appreciates that not all 4 week periods may have disease activity assessments scheduled, but unfortunately cannot determine these from the CSRs due to the absence of Appendix 1.

Please see the protocol for the LUCERNE study for appendix 1 with the full schedule of assessments. Appendix 1 can be found on pages 112 - 121 of the protocol (A11 Protocol_ph3_LUCERNE_V3).

Study design

In TENAYA and LUCERNE, patients randomised to Arm A received 6 mg of intravitreal faricimab every 4 weeks (Q4W) up to Week 12 (four injections). At Week 20, following a protocol-defined assessment of disease activity, patients in Arm A with active disease received faricimab at that visit and continued on a Q8W dosing regimen. At Week 24, following a second protocol-defined assessment of disease activity, patients in Arm A with active disease received faricimab at that visit, and continued on a Q12W dosing regimen. Patients in Arm A who did not have active disease at Week 20 and Week 24 according to the protocol-defined criteria were treated with a fixed- Q16W dosing regimen of faricimab. These faricimab dosing regimens continued until Week 60, and no supplementary therapy was allowed.

From Week 60 (when all patients in Arm A are scheduled to receive faricimab) onward, all patients in Arm A are treated according to a personalised treatment interval (PTI) dosing regimen up to Week 108.

Patients randomised to Arm B received 2 mg of intravitreal aflibercept Q4W up to Week 8 (three injections), followed by 2 mg of intravitreal aflibercept Q8W up to Week 108.

Disease Activity Criteria

For patients randomised to receive faricimab (Arm A), determination of active disease at Weeks 20 and 24 were made if any of the following criteria were met:

- Increase > 50 mm in central subfield thickness (CST) compared with the average CST value over the previous two scheduled visits (Weeks 12 and 16 for the Week 20 assessment and Weeks 16 and 20 for the Week 24 assessment)

Or

- Increase ε 75 mm in CST compared with the lowest CST value recorded at either of the previous two scheduled visits

Or

- Decrease ε 5 letters in BCVA compared with average BCVA value over the previous two scheduled visits, owing to nAMD disease activity (as determined by the investigator)

Or

- Decrease ε 10 letters in BCVA compared with the highest BCVA value recorded at either of the previous two scheduled visits, owing to nAMD disease activity (as determined by the investigator)

Or

- Presence of new macular haemorrhage (as determined by the investigator), owing to nAMD activity

Additional considerations at Week 24: If there was significant nAMD disease activity at Week 24 that did not meet the above criteria, but which, in the opinion of the investigator, warranted treatment, then these patients received treatment at Week 24 and continued with a faricimab Q12W dosing regimen until Week 60.

Patients randomised to faricimab (Arm A) who met the disease activity criteria at Week 20 remained on their Q8W dosing schedule and did not receive treatment at Week 24. Patients randomised to faricimab who met the disease activity criteria at Week 24 were treated at this visit and continued with a Q12W dosing regimen of faricimab until Week 60. The remaining patients randomised to faricimab who did not have active disease at Week 20 or Week 24 were treated with a Q16W dosing regimen of faricimab until Week 60.

Worsening of nAMD in the study eye would be reported as an adverse event and patients in Arm A were not able to move between treatment intervals between weeks 20 and 60, they would have to discontinue study treatment. Rescue injections were also not permitted.

Disease Activity results

We can provide the disease criteria met at weeks 20 and 24 in patients randomised to faricimab. Please see the word document with the title “A11 Faricimab disease activity criteria at weeks 20 and 24 ACIC”.

We will be unable to provide the outcomes of the disease activity assessments for the aflibercept arm, as this could only have been performed at one single time point after the end of the monthly initiation period at week 16 because patients were dosed on a fixed Q8W regimen. It is also important to acknowledge that the loading doses were different between the treatment arms (faricimab (4 x Q4W doses) and aflibercept (3 x Q4W doses) and the performance of the respective drugs during the loading phases are not the same.

A12. Please split Document B Table 12 discontinuations due to AE or lack of efficacy into (1) discontinuations due to AE and (2) discontinuations due to lack of efficacy.

Please see the word document with the title “A12 Discontinuations due to AE and due to lack of efficacy ACIC”.

Table 12 in Document B of the submission is showing the intercurrent events which were measured on the last day of Week 48 and the Week 60 analysis windows. The information presented here are measured on the first day of the analysis windows

and as a result, there are a few numerical differences between these tables and the numbers reported in Table 12 of the submission.

A13 PRIORITY. Please present the faricinib arm data of Document B Table 24 split by those who were allocated to (1) Q8W, (2) Q12W and (3) Q16W during week 20 to week 60. Please also present the equivalent of Table 24 for weeks 48-108 to the extent possible, also split by those who were allocated to (1) Q8W, (2) Q12W and (3) Q16W during week 20 to week 60 if possible

The faricimab data has been tabulated as requested. The data outputs provided include all data currently available to the latest time point in each study; the data is based on the Week 60 data cut, with some data available for patients with longer follow-up at that point). Since the study is still ongoing and a substantial proportion of patients have not completed the study yet, the results should be interpreted with caution beyond week 60.

Please see the word documents with the title "A13 Summary of study treatment exposure in the study eye through to week 60 ACIC" and "A13 Summary of treatment exposure in the study eye through to CCOD ACIC"

A14 PRIORITY. Please provide the ERG with the code and data required to replicate the NMA.

The code and data required to replicate the NMA can be found in the zip folder "NICE model codes and data A14 ACIC".

A15. Table 4 of the 'F.Hoffman-La Roche Ltd - NMA report' presents the extracted data from the studies included in the NMA. Please clarify the dosing schedule for each treatment in detail.

Table 4 of the NMA report was updated to include detailed information on the dosing schedule for each treatment included in the NMA and can be found in Word document "A15 Dosing schedule for each treatment in the NMA".

A16. Please provide the results for all the treatments in all of the NMAs presented in the company submission.

The full results for all treatments included in each NMA can be found in Word document labelled "A16 NMA results for all treatments". The full results from the NMA have been provided on request of the ERG, however the outputs contain data from dosing regimens and treatments that are not relevant comparators to this submission (i.e. bevacizumab and brolucizumab). Bevacizumab is not a relevant comparator for this appraisal because: it is not licensed for neovascular AMD (nAMD) in the UK; it is used infrequently in clinical practice to treat nAMD in the population which will be the focus of the appraisal. [redacted] as per the cost-comparison methods guide, it will be

excluded from the appraisal on the basis of having no associated or published NICE guidance in nAMD. Brolucizumab has been excluded as clinical experts have confirmed to Roche it is not routinely used in clinical practice, [redacted]

The key data to be considered from this NMA are related to aflibercept, ranibizumab and faricimab.

A17. Please re-run the NMA with only trials that include either aflibercept or faricimab.

As discussed during the Company-ERG call on 28.01.22, a streamlined NMA (aflibercept and faricimab studies only) was conducted for the primary endpoint mean change in BCVA from baseline for all patients and it can be found in Word document labelled "A17_nma_bcvachg_aflfaronly_mr_sched_all_ACIC". Company did reiterate to the ERG that this is not our preferred methodology to compare these two interventions, the simplified network is not as robust as the data provided within the original submission documents. The Company does not support the use of this data to base decisions on.

A18. Please outline why there is no estimate for 24 month dosing for Aflibercept PRN loading within Figure 15. If it is not possible to estimate this from the NMA, the ERG would be grateful if the company could supply an estimate for this, what assumptions need to be made for this estimate and why these are the most reasonable assumptions to apply, together with an outline of the underlying arithmetic.

For the NMA mean number of administration injections at 12 months, the data for aflibercept PRN loading at 1-year is informed by the Mori 2017 study; no 2-year data was reported by this study. Whilst Schmidt-Erfurth 2014 publication does report aflibercept PRN data at the 2-year timepoint (VIEW 1/VIEW 2 pooled analysis), the protocol controlled switch from fixed dosing to capped-quarterly PRN regimen, did not start until Week 52 and lasted until Week 96 and so, due to the mixed regimen approach within the study and no other study with such regimen, it was not possible to connect the study to the network. Therefore, an assumption was taken that as ranibizumab Q8w is thought to be equivalent to aflibercept Q8w, data for aflibercept PRN loading was imputed from the closest reference (i.e. the 2-year data for ranibizumab PRN loading) and used to calculate the mean number of injections for aflibercept PRN loading at Year 2. Please find the accompanying Excel spreadsheet attached, labelled "A18, B3, B5 - Faricimab nAMD Injections NMA for CE Model_ACIC".

A19. Please provide p-values for the central estimates of Document B Figures 11, 13, 15, 17, 19 and 21 and for the discontinuation due to AE or lack of efficacy at week 48 and at week 60 of Document B Table 12

As discussed during the Company-ERG call on 28.01.22: For a Bayesian analysis, p-values are not applicable. However, posterior values (as provided for the BCVA outcome in the NMA report) are relevant to the non-inferiority margins of this data. For the other outputs (excluding BCVA), we would not be able to test non-inferiority as no margins have been defined for this threshold. Credible intervals are available for the data to highlight where there is a difference, alongside the forest plot figures, within the NMA report provided as part of the reference pack, supporting the original submission.

A20 i. For the studies within the NMA please tabulate by arm, or if not available by arm by trial, the baseline characteristics in the same format the Document B Table 6, to the extent that this data is available.

The baseline characteristics for each study arm included in each NMA can be found in Word document labelled “A20 - Baseline Characteristics NMA studies”.

A20 ii. Please also tabulate the inputs by trial and by arm of the NMAs of Document B Figures 10, 12, 14, 16, 18, 20 and 22.

As discussed during the Company-ERG call on 28.01.22: this data is available within the NMA report, provided as part of the reference pack, supporting the original submission. In the referenced NMA report, Table 4 from the NMA report provides the original extracted data for Figure 10 (Doc B), Table 7 (NMA report) provides the data for Figure 12 (Doc B), Table 8 (NMA report) provides data for Figure 14 (Doc B), Table 6 (NMA report) provides data for Figure 16, Table 10 (NMA report) provides data for Figure 18 (Doc B), Table 12 (NMA report) provides data for Figure 20 and Table 11 (NMA report) provides data for Figure 22.

A21 PRIORITY. How many patients in the aflibercept arm had inactive disease at each time point after the loading doses? Why were they not allowed to extend intervals between injections if disease was inactive?

We will be unable to provide the outcomes of the disease inactivity for the aflibercept arm after the loading doses. Although standard of care has moved towards a treat-and-extend (T&E) dosing regimen, there would be a challenge in testing non-inferiority in a registrational trial setting using this treatment approach. Registrational, non-inferiority studies require comparison against the proven efficacious dose of the comparator in order to fulfill hypothesis testing.

It is important to acknowledge that the loading doses were different between the treatment arms (faricimab (4 x Q4W doses) and aflibercept (3 x Q4W doses)) and the performance of the respective drugs during the loading phases are not the same. As per the study design the aflibercept arm has a Q8W maintenance regimen. The rationale for this is because the aflibercept dose and schedule used in this study

were consistent with global recommended dosing posologies (e.g., in the United States, the European Union, and Japan) for nAMD product labeling for aflibercept at the time of study design. Aflibercept is a globally approved anti-VEGF therapy with a Q8W maintenance regimen, facilitating a comparison with the longer regimens of faricimab that are being investigated in Arm A. Aflibercept is a standard of care globally, and the fixed 2 mg Q8W dose following 3 monthly initiating doses is consistent with the label, and, furthermore, was agreed during previous EMA and FDA scientific advice regarding Phase III development in nAMD.

The design of the first year of the TENAYA and LUCERNE studies is based on the Phase II STAIRWAY (CR39521) study, in which nAMD patients were randomized in a 2:2:1 fashion to faricimab Q12W, faricimab Q16W or ranibizumab Q4W. In STAIRWAY, patients treated with both Q12W and Q16W faricimab maintained initial improvements in vision through to the primary endpoint, and the data from the study showed a strong durability signal for faricimab. The Phase III studies TENAYA and LUCERNE were designed to replicate the results of Phase II STAIRWAY.
The VIEW 1 and VIEW 2 pivotal aflibercept studies found that fixed Q8W aflibercept dosing was clinically equivalent to monthly ranibizumab. In contrast, the T&E posology listed in the aflibercept SmPC1 was added following the two open-label, non-comparator controlled ALTAIR (Ohji et al. 20202) and ARIES (Mitchell et al. 20213) studies, which compared 2 different aflibercept T&E approaches to manage treatment naive nAMD in a small cohort of patients (254 and 271 patients in each study, respectively). In the ALTAIR study, the decision to extend or reduce the treatment intervals was based on investigator judgement. In the ARIES study, only anatomical criteria were used to guide extension of aflibercept treatment intervals. Thus, there was no standardized T&E regimen studied in these trials. Furthermore, neither of these studies had a comparator control arm. As such, because of the lack of Level 1b (randomized controlled trial) evidence with respect to the efficacy of aflibercept with a T&E regimen, the Company found it necessary to study the proven, most efficacious dosing regimen (i.e., the fixed Q8W dosing interval) in the TENAYA and LUCERNE registrational trials.
The introduction of the T&E approach to nAMD disease management was made out of a clinical need to reduce the healthcare burden, and not through scientific methodology. While there are a number of studies comparing T&E to fixed anti-VEGF dosing intervals, (e.g., Wykoff et al. 20154; Silva et al. 20185; Kertes et al. 20196; Guymer et al. 20197) there is no consensus as to which anatomical and visual changes should be considered when determining the change in treatment interval, and often “investigator judgement” is the main criterion for making treatment extension or reduction decisions (Kodjikian et al. 20218). Thus, while the T&E approach in managing nAMD appears to be favored by clinicians, a recent systematic literature review of real-world data showed that, on average, patients treated with aflibercept received an average of 7.1 injections and 8.65 visits (injections and/or monitoring) per year, which is consistent with Q8W dosing

(Carrasco et al. 20209). Furthermore, even though T&E approaches may result in similar BCVA gains with fewer injections, there is evidence that in the real world, in nAMD eyes, more anti-VEGF injections are required for “good” vision (Khanna et al. 201910).

The results of the TENAYA and LUCERNE studies - where ~34% patients achieved a Q12W interval and ~45% patients achieved a Q16W interval in the faricimab arm- offer Level 1b evidence that a fixed, extended faricimab dosing has comparable efficacy as fixed aflibercept Q8W dosing. Based on the above discussion, the Company is of the opinion that the durability offered by faricimab through fixed, extended dosing intervals will provide a significant reduction in nAMD treatment burden compared with currently available anti-VEGF therapies. The durability of faricimab will be further evaluated after Week 60, when patients are moved to the personalized treatment interval.

References

[1]Eylea (aflibercept injection) Summary of Product Characteristics. European Medicines Agency. https://www.ema.europa.eu/en/documents/product-information/eylea-epar-product-information_en.pdf. eylea-2019-02

[2]Ohji M, Takahashi K, Okada AA, et al. Efficacy and Safety of Intravitreal Aflibercept Treat-and-Extend Regimens in Exudative Age-Related Macular Degeneration: 52- and 96-Week Findings from ALTAIR : A Randomized Controlled Trial. Adv Ther. 2020 Mar;37(3):1173-1187. ohaji-2020-01

[3]Mitchell P, Holz FG, Hykin P, et al. EFFICACY AND SAFETY OF INTRAVITREAL AFLIBERCEPT USING A TREAT-AND-EXTEND REGIMEN FOR NEOVASCULAR AGE-RELATED MACULAR DEGENERATION: The ARIES Study: A Randomized Clinical Trial. Retina. 2021 Sep 1;41(9):1911-1920. mitchell-2021-01

[4]Wykoff CC, Croft DE, Brown DM, et al. Prospective Trial of Treat-and-Extend versus Monthly Dosing for Neovascular Age-Related Macular Degeneration: TREX-AMD 1-Year Results. Ophthalmology. 2015 Dec;122(12):2514-22. wykoff-2015-01

[5]Silva R, Berta A, Larsen M, et al. Treat-and-Extend versus Monthly Regimen in Neovascular Age-Related Macular Degeneration: Results with Ranibizumab from the TREND Study. Ophthalmology. 2018 Jan;125(1):57-65. silva-2018-01

[6]Kertes PJ, Galic IJ, Greve M, et al. Canadian Treat-and-Extend Analysis Trial with Ranibizumab in Patients with Neovascular Age-Related Macular Disease: One-Year Results of the Randomized Canadian Treat-and-Extend Analysis Trial with Ranibizumab Study. Ophthalmology. 2019 Jun;126(6):841-848. kertes-2019-01

[7]Guymer RH, Markey CM, McAllister IL, et al. Tolerating Subretinal Fluid in Neovascular Age-Related Macular Degeneration Treated with Ranibizumab Using a Treat-and-Extend Regimen: FLUID Study 24-Month Results. Ophthalmology. 2019 May;126(5):723-734. guymer-2019-01

[8]Kodjikian L, Parravano M, Clemens A, et al. Fluid as a critical biomarker in neovascular age-related macular degeneration management: literature review and consensus recommendations. Eye (Lond). 2021 Aug;35(8):2119-2135. kodjikian-2021-01

[9]Carrasco J, Pietsch GA, Nicolas MP, et al. Real-World Effectiveness and Real-World Cost-Effectiveness of Intravitreal Aflibercept and Intravitreal Ranibizumab in Neovascular Age-Related Macular Degeneration: Systematic Review and Meta-Analysis of Real-World Studies. Adv Ther. 2020 Jan;37(1):300-315. doi: 10.1007/s12325-019-01147-6. carrasco-2020-01

[10]Khanna S, Komati R, Eichenbaum DA, et al. Current and upcoming anti-VEGF therapies and dosing strategies for the treatment of neovascular AMD: a comparative review. BMJ Open Ophthalmol. 2019 Dec 15;4(1):e000398. khanna-2019-01

Section B: Clarification on cost-effectiveness data

Document B

B1. Please provide the input data to the calculation of Equation 2 for faricimab, separately for TENYA and LUCERNE, together with full referencing to these inputs within Document B or the CSRs. Please provide the corresponding data restricted to year 1: i.e. up to but not including week 52.

Please find attached Word document "B1_Equation 2 calculation_CIC", providing a detailed account of the calculations.

Upon examination of the calculations, a slight difference to the previously shared results for Year 2 was identified for both faricimab [redacted] and aflibercept [redacted]. The NMA figures used can be seen in the "A18, B3, B5 - Faricimab nAMD Injections NMA for CE Model_ACIC" sheet, where the original submission aflibercept Y2 value and the updated aflibercept Y2 value can be found and incorporated. This is due to the previous Year 2 analysis calculating the mean number of treatments in Year 2 using the same N as for Year 1 and including those patients in the Year 2 analysis with 0 treatments. This led to an underestimate in the mean number of treatments (meanTrt) in the earlier analysis. As a result, the relevant analyses have been updated within the submission; please refer to the Word document labelled "B1 - updated base case_CIC".

B2. Is the [redacted] year 3+ injection frequency for faricimab pure assumption? If not, please provide the source data and underlying arithmetic for this estimate. The arithmetic can be presented within an Excel worksheet if this is easier.

Due to a lack of long-term injection frequency data for faricimab, alternative methods were used to estimate injection administration data for Year 3+. The [redacted] figure applied for faricimab has been calculated based on the committee preferred assumptions from TA294 and TA672, where the committee and clinical expert assumed 4 injections would be administered from Year 3 onwards. No further rationale was provided for this figure, therefore an assumption was made that this has been derived assuming a Q12w dosing regimen for anti-VEGFs across a 52 week period. Using this as a basis, and taking into account that >40% of patients received faricimab on a Q16w interval during TENAYA and LUCERNE, it was deemed reasonable to assume patients would receive faricimab at a rate of [redacted] in the real world. The preliminary PTI data taken at the Week 60 snapshot also supports this assumption, with the data demonstrating that faricimab can be maintained longer term with lower injection frequencies. This Year

3+ assumption for faricimab was also validated with clinical experts, who also stated they would expect faricimab to be administered at least one injection less over the longer term versus currently available comparators.

B3. The central estimates for RAN 0.5mg IVT TREX and AFL 2mg IVT TREX of Document B Figure 13 are [redacted] and [redacted], which compare to [redacted] and [redacted] in Table 36. The difference between the central estimates for RAN 0.5mg IVT TREX and AFL 2mg IVT TREX in Figure 15 is [redacted]. The difference between the year 1 + year 2 dosing of the base case in Table 36 is [redacted]. Please provide an account of this difference. Please provide the arithmetic of the calculation of both the year 1 and year 2 dosing for aflibercept and ranibizumab, with reference to the values of Figure 13 and Figure 15, outlining how these are bridged from the numeraire of aflibercept Q8W of Figure 15 to be relative to faricimab, the values for faricimab in Table 36 and if appropriate the values of Table 34 and Table 35. The arithmetic can be presented within an Excel worksheet if this is easier. If the real world study data has been preferred to the NMA estimates please provide a rationale for this, particularly in the light of the faricimab dosing being based upon trial data.

Please find the attached Word document "B3 calculation source explanation_ACIC", providing a detailed account of the calculations and sources. Excel document labelled "A18, B3, B5 - Faricimab nAMD Injections NMA for CE Model_ACIC" also details the calculations. In summary, Table 36 is using the forest plot of results relative to RAN 0.5mg IVT Q4w, leading to the [redacted] and [redacted] differences, the original submission presented the outputs compared to faricimab and so the NMA results slightly differ when changing the reference treatment. The Year 1 and 2 data for aflibercept and ranibizumab is informed using the NMA outputs (relative to ranibizumab Q4w) and faricimab has been informed using data from TENAYA and LUCERNE.

B.4 Please present the arithmetic of the Document B Table 35 ranibizumab estimates, with full referencing to the input data.

The proportion of patients receiving ranibizumab on Q4w-Q12w intervals informing the T&E dosing regimen within the model, has been informed by the post-hoc analysis of VIEW 1 and 2 studies providing the Q12w[1], the Q4w proportion is informed by the results from VIEW 1 and 2 96 week data[2]. Furthermore, this data was validated by clinical expert opinion and informed the Q8w proportion.

References:

1. Khurana RN, Rahimy E, Joseph WA, Saroj N, Gibson A, Vitti R, et al. Extended (Every 12 Weeks or Longer) Dosing Interval With Intravitreal Aflibercept and Ranibizumab in Neovascular Age-Related Macular Degeneration: Post Hoc Analysis of VIEW Trials. Am J Ophthalmol. 2019;200:161-8.

2. Schmidt-Erfurth U, Kaiser PK, Korobelnik, JF, Brown D, Chong V, et al. Intravitreal Aflibercept Injection for Neovascular Age-related Macular Degeneration: Ninety-Six–Week Results of the VIEW Studies. Ophthalmology. 2014;121(1): p193-201.

B5. For the PRN dosing of aflibercept and ranibizumab, please present the arithmetic underlying the calculation of the year 1, year 2 and years 3+ dosing. Please also tabulate the assumed number of monitoring visits, and the resulting number of monitoring visits where there is no treatment administered separately for aflibercept and for ranibizumab, separately for year 1, year 2 and years 3+. Please present an account of the arithmetic of this, together with full referencing to the relevant figures and tables of Document B together with any necessary additional referencing and assumptions. The arithmetic can be presented within an Excel worksheet if this is easier.

Please find Excel document labelled "A18, B3, B5 - Faricimab nAMD Injections NMA for CE Model_ACIC" explaining the calculations for Year 1-2 aflibercept and ranibizumab PRN dosing. As mentioned in the response to B3, the NMA figures used are relative to ranibizumab IVT Q4w (see Word document "B3 source/notes" for the forest plots). As there are no NMA results for the Year 3+ injection frequency, the PRN values were informed using the NICE guideline (NG82) model, where the only long term data source identified for reporting ranibizumab used on a PRN basis, provided a value of 3.7 injections. The Year 2 injection frequency of ranibizumab PRN and aflibercept PRN was divided by the injection frequency of the NICE guideline reported Year 2 ranibizumab PRN value, and factor 3.7 was applied to the equation. This can be found within the original submitted model, sheet 'Administration frequency' under cells DE27 and DI27.

The monitoring visits are calculated using "Total number of monitoring visits - total number of treatment visits". Please see sheet "Monitoring frequency" within the model provided within the original submission, labelled "Tenaya_Lucerne_Faricimab_nAMD_CMM_ACIC_CIC 17.11.21". The implemented number of monitoring visits is based on the brolucizumab appraisal (slide 18)[1].

References:

1. National Institute for Health and Care Excellence. TA672: Brolucizumab for treating wet age-related macular degeneration. 2021.

B6. It appears that the PRN analysis retains the base case dosing assumptions of Document B Table 36 for faricimab. Please outline why this assumption is reasonable for units which dose aflibercept and/or ranibizumab PRN. How might PRN dosing affect faricimab dosing for year 1, year 2 and years 3+.

Faricimab currently does not have any data to support its use on a PRN basis. Clinical expert opinion also validates the assumption that T&E is the most commonly utilised method of treating patients in nAMD (also referenced in TA672). Even within units who dose aflibercept and/or ranibizumab on a PRN basis, it is not expected that they will also dose faricimab in this way due to a paucity of data to support this treatment regimen.

B7. The submission stated that bilateral involvement doubles the drug cost. For newly incident bilateral disease in, say, year 5 please outline how this takes into account the loading phase, the year 1 dosing and the year 2 dosing for the fellow eye given that the study eye will be receiving year 3+ dosing. It would be appreciated if an intuitive account of this could be given, coupled with a worked example referencing cells in the company electronic model.

Bilateral eyes enter over the time horizon in the model. A proportion of bilateral eye patients enter at baseline and then a monthly incidence is applied beyond that. (Columns EO-ET in model markov). There are tunnel states beyond that for each month of treatment - this can be most easily seen in columns ARD:ASE in the markov trace where proportion in each week of treatment is tracked. This is then linked to different costs by year of treatment in ASK:ASM - where the costs are pulled from sheet "Administration frequency" columns C:J by week (split between drug and admin cost).

B8 PRIORITY. To the extent possible please present the baseline characteristics of the real world study cohort in the same format as Document B Table 6. Has any matching analysis been undertaken to align the real world study cohort with the baseline characteristics of TENYA and LUCERNE, and if so what effect does this have upon the results presented in Document B Table 34?

Table A and B within the Excel document labelled “B8_B9_SG42798 - Additional NICE Analysis_ACIC” presents the patient demographics and the baseline study eye characteristics. No matching was conducted between the real-world data study and TENAYA and LUCERNE.

B9 PRIORITY.

i. Please expand Document B Table 34 to report the start of year number of patients and the total number of treatment visits by year

Table C within the Excel document labelled “B8_B9_ACIC” expands on Doc B Table 34. Table C1 provides the summary of the number of treatment visits in each year from the index date stratified by the initial anti-VEGF received, it provides the mean number of treatment visits (where an injection took place) along with the number of patients under treatment and the total number of treatment visits for all of these patients. Table C2 provides a summary of the length of treatment interval (in days) between consecutive anti-VEGF injections for the study eye in each year of treatment from the index date, stratified by the anti-VEGF received, also providing the number of patients under treatment. The number of patients differs between the two outcomes as, due to the observational and retrospective nature of the study, not all patient records reported the same data points.

ii. and also present this table restricted to aflibercept injections for those initially receiving aflibercept and to ranibizumab injections for those initially receiving ranibizumab.

Within the Excel document labelled “B8_B9_ACIC”, Table 4.1 provides a summary of the treatment visits in each year from the index date until the end of index treatment, stratified by index anti-VEGF received. Tables 4.2a and 4.2b provide the length of the treatment interval in days, for those patients who started on the index anti-VEGF until the end of their respective index treatment.

iii. Please present the Kaplan Meier TTD data in the same format as requested under A4 above separately for those initially receiving aflibercept and ranibizumab, and restricted to aflibercept injections for those initially receiving aflibercept and to ranibizumab injections for those initially receiving ranibizumab (4 tables).

Within the Excel document labelled “B8_B9_ACIC”, Tables 4.3a-d provide the time to treatment discontinuation data: Tables 4.3a and 4.3b provide the time from index date to treatment discontinuation in the study eye; Tables 4.3c and 4.3d provide the time from index date to discontinuing index anti-VEGF treatment. It is important to note that this data is from real-world patients, the data is similar between both treatment cohorts.

iv. Please present the equivalent of Document B Table 34, expanded to include the start of year number of patients and the number of patients still only being treated in one eye, for the subset of patients only being treated in one eye at baseline.

Within the Excel document labelled “B8_B9_ACIC”, Table 4.4 provides a summary of the treatment visits in each year from the index date for patients receiving treatment for one eye (unilateral), stratified by index anti-VEGF received. Tables 4.5a and 4.5b provide the length of the treatment interval in days, for those patients who were still only receiving unilateral treatment.

v. Please also present the equivalent of Document B Table 34, expanded to include the start of year number of patients, for the proportion of patients with separate treatment appointments per eye.

As mentioned during the call on 28.01.21 and in communication to NICE, the additional data analyses requested for the real-world data study are coming from a third-party, as we are not able to access the raw data for this study. Whilst we have tried to get all requested analyses on time, we are facing some difficulties to obtain data within a meaningful timeframe. Due to resource constraints on the third-party's side (maternity leave), they are not able to complete this request in a timely manner according to our appraisal timelines and key milestones and so we will not be able to provide this data.

Section C: Textual clarification and additional points

C1. Please provide the following Document B references which could not be found in the reference pack:

- **70. Roche Products Ltd. Market Share Assumptions [Data on File]. 2021.** Please find the Excel document labelled "C1 - Roche Ophthalmology market share data April 2021 11.08.21_CIC" providing the market share data from January-April 2021. [redacted]
- **121. Roche Products Ltd. Data on file: Clinical Expert Validations. 2021.** Please find the Word document labelled "C1 - Summary minutes from clinical expert meetings_Oct Nov_RPL_CIC" providing the summary minutes from the clinical expert meetings.

C2. Please provide a list of the studies excluded from the SLR at the full text screen stage, with reasons for exclusion (148 studies in July 2020 and 134 in September 2021; see Appendix D .1.1 pages 19 and 28.

Please find the Excel documents labelled: "C2 - 8595_Roche_nAMD_Final list of excluded studies_Primary SLR Report_July2020" and "C2 - SLR Search Date Update_Sept 2021"

C3. For the real world data of Document B Table 34 please confirm that the aflibercept number of treatment visits is the mean number of treatment visits. Please also confirm that the number of treatment visits is synonymous with the number of treatment injections, and if it is not augment the table with the number of treatment injections.

This is correct; the number of treatment visits provided in Table 34 is the mean number of treatment visits and is synonymous with the number of treatment injections.

C4. Please provide a copy of the full report of the real world data study that is summarised in Appendix I.

The PDF labelled "C4 Real World Data Study Final Results v2.0. ACIC.pdf" is the full study report for the real world data study. As mentioned during the call on 28.01.21, the study is multi-objective and contains a vast number of results. The data of importance to this study sits within the first and second primary objectives, namely Tables A-C, Tables 1.1a-b and Tables 1.8a-b.

Furthermore, as mentioned in the responses for B9, the results from the real-world data study are supportive to our base case assumptions and validate clinical expert opinion; the data from the study has not been directly imputed into the analysis. The base case analysis is informed by the values from pooled TENAYA and LUCERNE data and the NMA.

C5. Why was the IVAN trial not included in the NMA?

The IVAN trial was a randomised controlled trial with a 2×2 factorial design comparing ranibizumab with bevacizumab and monthly (continuous) with as needed (discontinuous) treatment strategies.Patients in the IVAN trial were randomized to 4 treatment arms; however, results are only available for combined arms (RAN continuous and PRN arm / BEV continuous and PRN arm / continuous BEV and RAN / PRN BEV and RAN)*. It would not be appropriate to pool these arms as patients in the continuous arms will have received up to additional 9 monthly injections compared with the PRN groups and the patient split is 1:1. For this reason, the study was identified as not being suitable for inclusion in the NMA.

Excluding this trial doesn't have an impact on the connectivity of the networks, as other trials comparing RAN with BEV were included in the NMA, such as the BRAMD trial and the large CATT trial.

*The NICE NMA included separate data for all 4 arms from this study, however, the data reported is not consistent with what is reported in Chakravarthy 2013.

C6. Were patients asked if they could distinguish between sham and real injections?

This information was not collected as part of the study. TENAYA and LUCERNE were designed as phase III, multicentre, randomised, double-masked, active comparator-controlled studies to evaluate the efficacy and safety of faricimab in patients with neovascular age-related macular degeneration. All patients were therefore masked to which study arm they were assigned to. Asking whether they could distinguish between sham and real injections was not included in the study protocol, as this could risk potentially unmasking participants. Masking of participants to the study arm they are assigned to occurred in other registrational studies for anti-VEGF treatments.

C7. The ERG has replicated the direct drug costs of the company model, but is having difficulty replicating its administration costs and finds this aspect of the company model particularly difficult to follow. The ERG would be extremely grateful if the company modellers could cast an eye over the ERG amended model and outline the intuition behind the administration cost workings within the model and why these do not accord with the workings of the ERG, the latter being somewhat simpler in execution. The ERG is happy to provide an account of the logic of its calculations if this would help.

The discrepancy appears to be down to how the administration costs for the fellow (second) eye are being accounted for. Within the ERG calculations, the costs are attributed always at only 50% for the second eye (e.g. in cell H31 of ERG tab). In the Roche model, the administration costs are reduced to 50% if the first eye is being treated at the same time as the second eye. In general the two models would align,

unless for example a patient had discontinued treatment for the first eye but is still being treated for the second eye, in which 100% of the administration cost should then fall onto the second eye. If this scenario was to occur, the simpler logic within the ERG model is not appropriate. In the Roche model, the relevant section of the Markov trace would be columns AQZ:ARC, where cases of the first eye no longer being treated and the second eye treatment can be seen over time.

The two models can be aligned if either: the second eye modelling is disabled, the time horizon is reduced so that minimal cases of first eye treatment discontinuation occur, or if the administration costs for the second eye are set to 100%.

NICE National Institute for Health and Care Excellence

Patient organisation submission

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

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

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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	• Bayer (aflibercept) - £8,100 (contribution to support activities around information, support and education) • Novartis (brolucizumab, ranibizumab) - NA • Organon Pharma (bevacizumab) • Pfizer (bevacizumab) • Roche (bevacizumab) - £30,000 (contribution to support activities around information, support and education) • Thornton & Ross (bevacizumab) - NA • Zentiva (bevacizumab) - NA

manufacturers are listed in the appraisal matrix.] 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?	**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?	Age-related macular degeneration (AMD) usually affects people over 50 but can happen earlier. Macular disease is the biggest cause of sight loss in the UK, with AMD affecting around 600,000 people, around half of whom are registered as visually impaired. Wet age-related macular degeneration (AMD) develops when abnormal blood vessels grow into the macula. These leak blood or fluid which leads to scarring of the macula and rapid loss of central vision. Wet AMD can develop very suddenly, but it can now be treated if caught quickly. Fast referral to a hospital specialist is essential. In 2020 estimate is 46,000 new cases per year. Owen et al Wet AMD can be treated if caught early. Drugs are injected into the eye to stop the growth of the abnormal blood vessels. Following diagnosis people will usually have a loading dose of three injections, once a month for three months. A patient will then be assessed to see if more injections are required. Some people do not respond to the injections and may be offered a form of laser treatment instead. There are a range of treatments and options, although not all are available on the NHS.

	Loss of central vision through AMD can be very frustrating and can greatly affect everyday life as well as financial impact due to changes in employment and ability to drive. People affected by AMD told us: **"My poor vision means we are likely to need to sell our house in the country and move to one closer to public transport and other amenities. I also struggle to continue to play competitive golf which is my main pastime. My husband who works full time in his own business takes me to my clinic appointments which means he loses a morning or afternoon's work regularly."** **"As I am a carer for an adult son with Down's syndrome, with no other family, I rely on friends to take me to appointments & take/collect him from day centres whilst I have treatment. Living in a rural area without public transport means the worry of deterioration of my sight & being unable to drive is constant."** **"I feel incredibly fortunate. I have had a total of 66 injections in my left eye (initially Lucentis and now Eylea) and am still having them. This has improved and maintained the level of sight. Because of having both eyes monitored on each visit wet AMD was spotted in my right eye and treatment began very early."** **"It has been difficult to come to terms with the need to rely on others to get routine things done. The injections are horrible but the alternative is worse!"** Vision loss can make daily tasks more difficult, including tasks needed to monitor and manage multi morbidities. Some people with AMD experience visual hallucinations called Charles Bonnet syndrome which adds another level of impact on health and mental well being.

	Family and carers There is a significant burden on family and carers supporting a patient with AMD. A patient with AMD 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. It can be hard attending appointments, as people with diabetes have to attend multiple check-ups for their condition and other complications.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Responses from callers to the Advice & Information Service overwhelmingly report how wonderful the NHS is. Many agree their treatment maintains their sight and can be anxious when treatment intervals are extended or stopped. However, personal experiences of cancelled appointments, frustration over communication with clinics, many hours spent waiting around in clinic, are all common themes. 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. Quotes from people who took part in our wet AMD survey: **"My daughters both live a distance from me so a whole day is needed plus an overnight stay for every appointment. So this impacts considerably on family life for them as well as me."** **"Have had to travel by public transport over a fair distance to the hospital over the last 5 years. Especially after the injection, which can be over a two hour journey, when all you want to do is get home."**

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.
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 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	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.

considering this condition and the technology?	
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 AMD 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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NICE National Institute for Health and Care Excellence

Professional organisation submission

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

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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.

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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	**Specialist Optometrist and College of Optometrists' Council member**
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.**
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant	**No**

manufacturers are listed in the appraisal matrix.] 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 wet age-related macular degeneration in order to stabilise vision.
7. What do you consider a clinically significant treatment response? (For example, a	This is considered an improvement in visual acuity by more than 2 lines on EDTRS or Snellen Chart. Other outcomes include a reduction in central retinal thickness of greater than 20%.

reduction in tumour size by 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, Ranibizumab, Brolucizumab or Bevacizumab but this is used outside its marketing authorisation in some NHS trusts. Photodynamic therapy can also be considered in appropriate patients but is rarely used in NHS Trusts.
• 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 NICE Technology Appraisal Guidance 155 • Aflibercept NICE Technology Appraisal Guidance 294
• 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.
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?	
• 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 private providers of NHS care.

• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Existing infrastructure and models of care currently in place can be utilised. Training of how this treatment is different to other options available would be needed.
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?	
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 should last longer than the current treatment options. This will help to reduce the overall number of treatments given and help to reduce the overall burden of treatment. This would be beneficial to both clinicians and patients. 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.
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?	
• 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/more effective than current treatment options in treating wet age-related macular degeneration? – 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 TA155, TA294 and TA672?	
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?	
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 should last longer than the current treatment options. This will help to reduce the overall number of treatments given and help to reduce the overall burden of treatment. This would be beneficial to both clinicians and patients. • No new safety signals have been identified with this treatment compared to the existing treatment options already available based on current trials • Training of how this treatment is different to other options available is required. Other than this the existing infrastructure and models of care in place are more than sufficient and capable of use this treatment option immediately. • 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.

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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	**Moorfields Eye Hospital**

3. Job title or position	**Consultant Ophthalmologist**
4. Are you (please tick all that apply):	**x**☐ 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):
5a. Brief description of the organisation (including who funds it).	**Royal College of Ophthalmologists (charitable organisation)**

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	To stabilise disease progression and improve vision in wet age related macular degeneration

mobility, to cure the condition, or prevent progression or disability.)	
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.)	Visual acuity improvement
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	There are short acting agents but treatment burden is high and the data from this agents shows more durability.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Intravitreal anti-VEGF injections given regularly for years.
• Are any clinical guidelines used in the	AMD Commissioning Guidance

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.)	Mostly uniform and variations occur due to lack of capacity to deliver current treatment.
• What impact would the technology have on the current pathway of care?	Reduce treatment burden
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?	None, except less treatment visit

• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	None
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes , reduce treatment burden
• 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

12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No
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.)	Same

14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No (follow RCOphth AMD guidance)
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?	Reduced hospital visits
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	Yes to reduce treatment burden

improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	No
• Does the use of the technology address any particular unmet need of the patient population?	Especially those who cant keep up with current treatment regimen
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?	No
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?	Yes , durability extension from 8 weekly injections to 12 or 16 weekly injections.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	No
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
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	No

treatments since the publication of NICE technology appraisal guidance TA155, TA294 and TA672?	
21. How do data on real-world experience compare with the trial data?	Most real world data show suboptimal delivery of the current intense regimen of the anti-VEGF agents.
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
22b. Consider whether these issues are different from issues with current care and why.	None
Key messages	

23. In up to 5 bullet points, please summarise the key messages of your submission.

- Wet AMD results in sudden decrease in central vision
- Anti-VEGF therapies are available for AMD but require 4- 8 weekly injections into the eye.
- Treatment burden is high.
- This trial shows that this intervention may be delivered less frequently
- Treatment with this drug is likely to improve hospital capacity

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 wet age-related macular degeneration [ID3898]

Thank you for agreeing to comment on the evidence review group (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.

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

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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, and all information submitted under 'depersonalised data' in pink. 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.

Deadline for comments by **5pm** on **<<insert deadline>>**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

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NICE National Institute for Health and Care Excellence

Part 1: Treating age-related (wet) macular degeneration and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Clare Bailey
2. Name of organisation	Royal College of Ophthalmologists
3. Job title or position	Consultant Ophthalmologist
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 age-related macular degeneration ? ☐ A specialist in the clinical evidence base for age-related macular degeneration or faricimab? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not 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.	None
8. What is the main aim of treatment for age-related macular degeneration?	To improve and /or maintain vision in patients with wet AMD.

(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)	A reduction in the rate of visual loss compared to the natural history of untreated wet AMD by at least 5 letters at 1 year.
10. In your view, is there an unmet need for patients and healthcare professionals in age-related macular degeneration ?	Yes. There is a need for longer acting treatments and there is also a group of patients for whom the disease is not well controlled with existing treatments and who may lose vision as a result.
11. How is age-related macular degeneration 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?	• In the UK, treatment for wet AMD is with long-term repeated intravitreal injections usually with Aflibercept or Ranibizumab. Brolucizumab is occasionally used in a small number of patients who have poorly responded to these treatments. In a small number of units, Bevacizumab may be used particularly if there are local commissioning arrangements to allow Bevacizumab to be used where the vision is better than the NICE-approved 6/12 threshold for Aflibercept or Ranibizumab. • NICE guidance for AMD as well as RCOphth AMD guidance for commissioners (on RCOphth website). NICE TAGs for Ranibizumab, Aflibercept and Brolucizumab • The need for long term repeat injections is well established. There are different treatment regimes in use, such as Treat and Extend, Fixed dosing or 'as required' (PRN) although PRN is used less more recently. Which regime a particular unit uses may depend on local factors, such as specific capacity constraints. • Criteria for stopping treatment are less well defined and duration of follow-up after treatment stops may vary between different units. • The technology would not significantly impact on the current pathway. There may be a reduction in the number of injections/visits but the overall treatment pathway would be similar.

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 clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	• The treatment would be delivered as part of an existing anti-VEGF treatment pathway. • There may be a reduction in visits/injections compared to current care, and that may vary depending on the current treatment protocols used in a particular unit. (eg Treat and Extend vs fixed dosing). We don't have RCT evidence yet comparing Faricimab to Treat and Extend regimes with existing therapies. • The treatment is delivered in a secondary care specialist setting. • No new investment needed
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?	• There could be a reduction in clinical visits/treatments to achieve similar visual outcomes. • I do not expect the technology to increase length of life more than current care • The treatment is unlikely to significantly increase health-related quality of life more than current care. A potential reduction in treatment visits would be welcome.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	
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	No different.

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?	Current NICE guidance (and NICE TAGs) for treatment of wet AMD with Aflibercept or Ranibizumab states that we need to wait for the vision to drop to 6/12 before Aflibercept or Ranibizumab can be used. There are advantages to starting treatment before vision is lost as it may not be regained on treatment. Current stopping rules for Aflibercept and Ranibizumab may vary somewhat between units and similar rules would be expected to apply to Faricimab.
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? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	If it could be used before vision drops below the driving standard (6/12) that could have a significant impact on quality of life and affect whether they could, for instance, help to support a spouse or other family member. Any possible reduction in injection frequency/visits could also affect care-giver burden as well which may not be reflected in the 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?	• We don't yet have RCT data comparing Faricimab vs Treat and Extend Aflibercept or Ranibizumab treatment. • Not a major 'step change' in the management of the condition • The technology may well help with service capacity issues.
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?	Similar to existing treatments
20. Do the clinical trials on the technology reflect current UK clinical practice?	Many units do not now use fixed dosing with Aflbercept (which was used in the Tenaya and Lucerne studies). Most units now use Treat and extend regimes

• 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? None that I am aware of	with existing therapies and we do not have RCT data comparing Faricimab vs Alflibercept using a Treat and Extend regime. Visual acuity (yes), injection frequency (yes), complications (yes) None that I am aware of
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 treatments aflibercept or ranibizumab since the publication of NICE technology appraisal guidance TA294?	Altair and Aries studies describing the use of Aflibercept with Treat and Extend regimes.
23. How do data on real-world experience compare with the trial data?	Real world outcomes are generally worse than the trial data.
24. NICE considers whether there are any equalities issues at each stage of an appraisal. 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	No

belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this appraisal could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Faricimab was non-inferior to Aflibercept using the treatment schedules in the Tenaya and Lucerne studies.
Currently there is a large burden of clinical visits and treatments for patients and their carers, as well as capacity challenges within the ophthalmic services, and Faricimab may help to reduce this.

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Clinical expert statement

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

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Deadline for comments by **5pm** on **Thursday 10 February** 2022. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

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NICE National Institute for Health and Care Excellence

Part 1: Treating age-related (wet) macular degeneration and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Professor Ian A Pearce
2. Name of organisation	Clinical Expert nominated by Roche
3. Job title or position	Consultant Ophthalmologist, Honorary Clinical Professor of Ophthalmology, Director of Clinical Eye Research Centre, St Paul's Eye Unit, Royal Liverpool University Hospital
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 age-related macular degeneration ? ☒ A specialist in the clinical evidence base for age-related macular degeneration or faricimab? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not 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.	None

8. What is the main aim of treatment for age-related macular degeneration? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	The principal aim of treatment of age-related macular degeneration (AMD) is to prevent visual loss, improve visual acuity when possible and allow the patient to maintain as much normal visual functioning as possible for everyday activities.
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)	Maintaining visual acuity within 15 letters of baseline ETDRS visual acuity and improving visual acuity on average by 5-10 ETDRS letters
10. In your view, is there an unmet need for patients and healthcare professionals in age-related macular degeneration ?	Survey results of EURetina specialists in 2021 have highlighted reducing the frequency of intravitreal injection of agents used to treat AMD as one of the key unmet needs to reduce the burden on patient attendances and reduce the healthcare direct and indirect healthcare demands.
11. How is age-related macular degeneration 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?	Neovascular “Wet” AMD (the subject of this appraisal) is presently managed with regular and repeated intravitreal injections of an anti-vascular endothelial growth factor antibody (Anti-VEGF) with either Ranibizumab (as per NICE TA 155) or Aflibercept (as per NICE TA 294). A further intravitreal agent, Brolucizumab, has recently been NICE approved (NICE TA 672) but it’s general acceptance in UK and global AMD care has been less than expected due to post marketing concerns regarding intraocular inflammation (IOI) and the need for additional monitoring for IOI. In general, once neovascular “Wet” AMD is diagnosed patients will start on treatment within 2 weeks with a loading/initiation phase of 3 intravitreal injection 4 weeks apart. Assuming there is evidence of anatomical and functional improvement after this initial phase then patients will continue with intravitreal repeated injections on either a PRN, fixed dosing (generally 8 weekly in case of aflibercept) or a treat and extend (T+E) regime. The treat and extend regime has grown in popularity particularly for AMD as a strategy to identify the ideal individualised fixed dosing schedule for any particularly patient. It involves gradually increasing the injection interval (by 1-2weeks each time) until a compromise is reached where the injection interval is at its longest period without a significant recurrence of intraretinal or subretinal fluid or a reduction in

	visual acuity. This has become the most common treatment regime for AMD patients both globally and within the UK particularly after the first year of treatment. In my experience the typical AMD pt is on a interval injection of between 4 and 10 weeks in the first year with some extension in the 2nd year and beyond up to a maximum of 12 or 16 weeks. In our unit, utilizing a fairly typical T+E treatment approach, a recent audit of 201 consecutive AMD pts had 20% on a Q12w interval and only 2% extended to Q16w at the end of 2 years of treatment. The Aries and Altair studies using specified retreatment criteria for T+E regimes have managed to extend treatment intervals of Q12w or longer in approx. 50% and 60% of patients receiving intravitreal aflibercept and Q16w in approx. 30% and 40% at then end of 2 years. The introduction of Faricimab would be expected to be a fairly straightforward introduction of a novel intravitreal agent within existing units and regimes for the management of AMD. It would be hoped that the study results of nearly 80% of patients receiving a Q12w dosing with a T+E regime would have a significant positive effect on capacity for units managing AMD and reducing the frequency of injections for patients.
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 clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	Faricimab would be expected to be introduced relatively easily. The intravtitreal injection is the same volume as we already use although I understand It will be drawn up from a vial as there is no pre-filled syringe at present – this will not be a significant barrier. The assessment, monitoring and delivery are almost identical to existing Ranibizumab and Aflibercept treatments in a secondary care setting. There will be minimal extra investment required save for some teaching regards the drug preparation as with any new drug
13. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Although the pivotal TENAYA and LUCERNE trials did not have an arm of Aflibercept that could be extended beyond Q8w the increased durability of

• 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?	Faricimab upto approx. 80% Q12w dosing and approx. 45% on Q16w dosing without compromising visual acuity gains is the longest intervals that we have seen in Phase III pivotal anti-VEGF studies. It remains to be seen if these very encouraging extensions to the treatment intervals are repeated in real world settings. However, it is expected that the use of Faricimab has the potential to make a real difference to patients through extending dosing intervals which will have the effect of freeing up capacity within busy AMD clinics.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	AMD is predominantly a condition affecting older members of our society with average age of patients receiving treatment being approx. 80yrs of age. Reducing treatment visits for this age group will have positive effects.
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)	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
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Existing NICE approved antiVEGF agents are recommended as an option for treating wet age-related macular degeneration in adults, only if, in the eye to be treated: • the best-corrected visual acuity is between 6/12 and 6/96 • there is no permanent structural damage to the central fovea

	• the lesion size is less than or equal to 12 disc areas in greatest linear dimension and • there is recent presumed disease progression (for example, blood vessel growth, as shown by fluorescein angiography, or recent visual acuity changes). It would be acceptable for Faricimab to be approved with similar guidance although this may be more restrictive than it's license. One significant area of contention is that some patients present with vision better than 6/12 (particularly if they are already receiving treatment to their 1st eye and are picked up at routine monitoring visits). Many real word studies including several UK Electronic Medical Record studies of Ranibizumab and Aflibercept have demonstrated the clear benefit of treating eyes with vision better than 6/12 with the final acuity being much better when treated at later stages of the disease. This issue is addressed in current NICE AMD Guidance (NG82) in which it is stated : *1.5.4 Be aware that anti-VEGF treatment for eyes with late AMD (wet active) and visual acuity better than 6/12 is clinically effective and may be cost effective depending on the regimen used* It would be helpful, if considered cost effective, that the TA for Faricimab rather than resorting to precedent and limiting use to visual acuities of less than 6/12

	that the TA acknowledged the advice given in NG82 that patients with better starting vision than 6/12 could be considered for treatment. The advice regards stopping treatments for AMD in NG82 are acceptable and practised by many ophthalmologists globally ie : *1.5.16 Consider observation without giving anti-VEGF treatment if the disease appears stable* *1.5.17 Consider stopping anti-VEGF treatment if the eye develops severe, progressive loss of visual acuity despite treatment* *1.5.18 Stop anti-VEGF treatment if the eye develops late AMD (wet inactive) with no prospect of functional improvement.*
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? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	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.
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?	The innovative nature of this technology in terms of using Ang-2 blockade in partnership with the well established anti VEGF effect in AMD 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 AMD patients.

• Does the use of the technology address any particular unmet need of the patient population?	The technology has potential for an incremental step change in improving care of patients with AMD in terms of increased durability in particular. Improved durability and increased injection intervals as seen in the Pivotal Faricimab Phase III studies are very encouraging and the longest intervals that we have seen in Phase III trials adopting this strategy. The repeated injection burden for patients is directly positively influenced by the introduction of the new technology
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 side effect profile of the novel Faricimab technology is equivalent to the side effect profiles of commonly used anti VEGF drugs used in current practice. No novel side effects have been identified. The most feared complication of antiVEGF injections is infective endophthalmtis whch can severely reduce 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 the over all life time risk for the patient of this complication.
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?	The TENAYA and LUCERNE clinical trials compare Faricimab to the most commonly used antiVEGF for AMD in the UK namely Aflibercept. The Aflibercept bimonthly comparator arm of these trials reflect current UK use of licensed and NICE approved Aflibercept. However, as stated above many units now use aflibercept and ranibizumab in a T+E regime similar to that used in the Faricimab arms of the clinical trials when Faricimab could be extended at weeks 20 and 24 from a 8 week interval to Q12w or Q16w interval. In practice ophthalmologists may introduce the T+E regime at any stage either earlier or later in the course of treatment than the predefined visit schedule of the clinical trial. In addition, T+E regimes generally use either the absence or presence of intraretinal fluid or subretinal fluid to determine whether to shorten or extend the treatment interval rather than using a prespecified threshold of central retinal thickness to make this treatment decision. However, that said, the retreatment criteria used in the study are reasonably acceptable and it is reassuring that with these thresholds the 12mth

	acuity and percentage of patients losing vision was non inferior to the fixed dosing Aflibercept patients in the studies. The ability to extend the treatment intervals with intravitreal Faricimab upto 12 weeks in >75 % in trial participants and 16 weeks in >45% 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. Anatomical gains and stability in OCT thickness of central retina thickness are commonly used in clinical practice as signs of effective treatment response. These secondary outcome measures in the Faricimab trials compared well to the Aflibercept treated patients. No novel side effects have come to light since the 12mth trial data published.
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 treatments aflibercept or ranibizumab since the publication of NICE technology appraisal guidance TA294?	ARIES and ALTAIR studies of Aflibercept show some increased injection interval as stated above but not to the same percentage at Q12w and Q16w as seen in the Faricimab trials – different treatment criteria affecting the extension or shortening of the injection intervals were used in all these studies.
23. How do data on real-world experience compare with the trial data?	The Aflibercept arms of the TENAYA and LUCERNE studies are typical of the results for Aflibercept use in the real world – I am unawre of any real word data for Faricimab as it has only just received FDA license on 31st Jan 2022.
24. NICE considers whether there are any equalities issues at each stage of an appraisal. Are there any potential equality issues that should be taken into	No

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. Please state if you think this appraisal could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- AMD 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 AMD patients by improving vision, maintaining this sustained improvement.

- The burden of repeated intravitreal injections for AMD of approximately 6-8 times per year affects patients and healthcare providers significantly

- Robust 1 year data from TENAYA/LUCERNE AMD trials of Faricimab versus the most commonly used comparator treatment in UK AMD care (Aflibercept) has shown encouraging functional and anatomical results with no new safety signals

- The ability to extend the treatment intervals with intravitreal Faricimab upto 12 weeks in >75% of trial participants and upto16 weeks in >45% 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.

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Patient expert statement

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

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments and feedback on the key issues below are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources. The evidence review group (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 about living with age-related macular degeneration or caring for a patient with age-related macular degeneration. 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.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

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.

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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. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

Deadline for comments by **5pm** on **Thursday 10 February 2022**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Part 1: Living with this condition or caring for a patient with age-related (wet) macular degeneration

Table 1 About you, age-related macular degeneration, current treatments and equality

1. Your name	Bryan Naylor
2. Are you (please tick all that apply)	☐ A patient with age-related macular degeneration ? ☒ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with age-related macular degeneration ? ☒ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	The Macular Society
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when 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 or experience (for example, I am drawing on others' experiences). Please specify what other experience:

6. What is your experience of living with age-related macular degeneration? **If you are a carer (for someone with macular degeneration) please share your experience of caring for them**	
7a. What do you think of the current treatments and care available for age-related macular degeneration 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 age-related macular degeneration (for example, how aflibercept or ranibizumab is given or taken, side effects of treatment, and any others) please describe these	
9a. If there are advantages of faricimab over current treatments on the NHS please describe these. For example, the effect 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 faricimab help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	
10. If there are disadvantages of faricimab over current treatments on the NHS please describe these.	

For example, are there any risks with faricimab? If you are concerned about any potential side effects you have heard about, please describe them and explain why	
11. Are there any groups of patients who might benefit more from faricimab 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	
12. Are there any potential equality issues that should be taken into account when considering age-related macular degeneration and faricimab? 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 Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	

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Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.

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Patient expert statement

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Part 1: Living with this condition or caring for a patient with age-related (wet) macular degeneration

Table 1 About you, age-related macular degeneration, current treatments and equality

1. Your name	Stephen Scowcroft
2. Are you (please tick all that apply)	☐ A patient with age-related macular degeneration ? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with age-related macular degeneration ? ☒ 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 and provide answers when 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 or experience (for example, I am drawing on others' experiences). Please specify what other experience:

6. What is your experience of living with age-related macular degeneration? **If you are a carer (for someone with macular degeneration) please share your experience of caring for them**	
7a. What do you think of the current treatments and care available for age-related macular degeneration 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 age-related macular degeneration (for example, how aflibercept or ranibizumab is given or taken, side effects of treatment, and any others) please describe these	
9a. If there are advantages of faricimab over current treatments on the NHS please describe these. For example, the effect 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 faricimab help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	
10. If there are disadvantages of faricimab over current treatments on the NHS please describe these.	

For example, are there any risks with faricimab? If you are concerned about any potential side effects you have heard about, please describe them and explain why	
11. Are there any groups of patients who might benefit more from faricimab 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	
12. Are there any potential equality issues that should be taken into account when considering age-related macular degeneration and faricimab? 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 Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	

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Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
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Evidence Review Group's Report

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

Produced by	Warwick Evidence
Authors	Lena Al-Khudairy, Associate Professor, Warwick Evidence
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Date completed	*04/04/2022*

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Declared competing interests of the authors
None.

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Dr Samer El-Sherbiny, Consultant Ophthalmic Surgeon, Machen Eye Unit, Warwick Hospital for providing clinical input.

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.

This report should be referenced as follows:
Al-Khudairy, L, Patel, N., Cummins, E, Waugh, N. Faricimab for treating wet age-related macular degeneration*: A Fast Track Appraisal. Warwick Evidence, 2022.*

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

Table of Contents

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

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

Table 1. FTA cost-comparison

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

2 Executive summary

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

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

2.1 Overview of the ERG's key issues

Table 2: Summary of key issues

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

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

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

Additional issues are:

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

2.2 Overview of cost comparison outcomes

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

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

Table 3: Cost per dose

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

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

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

[redacted]

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

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

Table 4: Base case annual dosing frequencies

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

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

Table 5: Company base case cost comparison

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

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

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

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

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

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

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

Issue 1: Appropriateness of brolucizumab as a comparator

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

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

Issue 2: Aflibercept dosing frequency

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

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

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

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

Issue 4: What is the administration cost?

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

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

2.6 Summary of ERG's preferred assumptions and resulting ICER

The ERG revises the company base case as follows:

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

Table 6: ERG preferred assumptions and resulting ICER

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

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

3.1 Population

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

3.2 Intervention

The intervention matches the NICE final scope "Faricimab"

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

3.3 Comparator

NICE final scope included the following comparators:

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

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

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

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

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

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

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

3.4 Outcome

NICE final scope included the following outcomes:

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

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

3.5 Marketing authorization

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

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

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

4.1 Literature search

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

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

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

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

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

4.2 Clinical evidence

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

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

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

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

4.2.1 Study design

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

4.2.2 Study sites

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

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

4.2.3 Population

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

4.2.4 Procedure

Participants were randomised into 1:1 ratio to either:

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

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

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

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

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

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

Table 7. Alfibercept regimens – injections by year

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

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

4.2.5 Outcomes

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

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

Table 8. Pooled efficacy outcomes of TENAYA and LUCERNE trials

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

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

4.2.6 Adverse events

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

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

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

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

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

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

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

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

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

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

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

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

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

Table 9. Mean numbers of injections

Year	Mean injections
1	5.3

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

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

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

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

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

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

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

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

4.2.9 Other developments

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

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

4.3 Network meta-analysis

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

	ERG's results – focussed

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

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

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

5.1 Summary of the company's submitted cost comparison

5.1.1 Model structure summary

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

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

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

The resulting cohort flow can then be coupled with:

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

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

5.1.2 Population

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

5.1.3 Interventions and comparators

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

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

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

5.1.4 Perspective, time horizon and discounting

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

5.1.5 Treatment effectiveness and extrapolation

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

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

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

Figure 1Modelled OS and proportion initial eyes remaining on treatment

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

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

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

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

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

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

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

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

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

Table 14: Company base case annual dosing

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

5.1.7 Fellow eye involvement

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

5.2 Model validation

5.2.1 Cross check model rebuild

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

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

5.2.2 Modelled number of doses vs NMA

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

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

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

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

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

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

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

5.3 Correspondence between model inputs and cited sources

5.3.1 Aflibercept injections: Mori et al

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

Table 16: Aflibercept Q8W dosing vs bi-monthly dosing

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

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

5.3.2 Administration and monitoring costs: TA346

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

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

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

5.4 ERG critique: Main Issues

5.4.1 Year 3+ dosing estimates

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

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

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

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

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

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

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

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

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

5.4.3 TTD curves and discontinuation rates

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

Table 17: Real world discontinuation data compared to model

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

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

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

5.4.4 Aflibercept and ranibizumab PRN dosing

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

5.4.5 Comparator choice and brolucizumab

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

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

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

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

5.5 [redacted] ERG critique: Other Issues

5.5.1 Faricimab trial dosing adjustments and draft SmPC

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

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

[redacted]

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

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

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

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

5.5.2 NMA dosing and discontinuation rate interactions

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

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

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

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

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

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

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

5.5.3 Fellow eye involvement

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

5.5.4 Faricimab wastage

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

5.5.5 PRN dosing and monitoring

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

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

5.5.6 Aflibercept PRN [loading] Year 2 dosing estimate

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

6 COST EFFECTIVENESS RESULTS

6.1 Company's cost comparison results

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

Table 19: Company base case cost comparison

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

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

6.2 Company sensitivity analyses

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

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

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

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

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

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

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

7 EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

7.1 ERG's preferred assumptions

The ERG revises the company base case as follows:

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

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

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

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

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

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

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

Table 23: ERG preferred cost comparison assumptions

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

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

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

Table 24: ERG revised base case cost comparison

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

7.2 ERG sensitivity analyses

The ERG presents the following sensitivity analyses:

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

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

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

Table 25: ERG sensitivity analyses

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

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

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

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

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

8.1 Strengths

8.2 Weaknesses and areas of uncertainty

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

8.2.1 Research needs

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

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

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

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

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Appendix 1.

Subtypes of CNV

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Table 27. Differences in response to treatment by CVN subtype

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

Treatment regimens

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

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

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

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

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

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

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

Faricimab: Real world study TTD KM data appendix

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

Table 1: Real world discontinuation data compared to model

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

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

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

The ERG provides the following additional scenario analyses:

- SA01a: Year 1 and Year 2 discontinuation rates of [redacted], with 8.9% for Years 3+.
- SA01b: Year 1 and Year 2 discontinuation rates of [redacted], with 13% for Years 3+.

Table 2: Additional ERG sensitivity analyses

	Faricimab net cost versus	
Sensitivity analysis	**Ranibizumab**	**Aflibercept**
ERG preferred base-case	[redacted]	[redacted]
SA01a: Discontinuation Year 1+2 [redacted] Years 3+ 8.9%	[redacted]	[redacted]

	Faricimab net cost versus	
Sensitivity analysis	**Ranibizumab**	**Aflibercept**
SA01b: Discontinuation Year 1+2 [redacted] Years 3+ 13%	[redacted]	[redacted]

The above also raises the possibility that approval of faricimab will not only displace other anti-VEGF use. It may also add to the treatment sequences that are possible, changing treatment patterns and increasing the time patients spend on anti-VEGF treatment. This might argue for an STA. But assuming that aflibercept is the main comparator it can be noted that the discontinuation rates from aflibercept are little different from the anti-VEGF discontinuation rate among those starting with aflibercept. This suggests little switching from aflibercept to ranibizumab.

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check and confidential information check

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

'*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 Wednesday 13 April 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 '[redacted]' in turquoise, all information submitted as '[redacted]' in yellow, and all information submitted as '[redacted]' in pink.

Issue 1

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ID3898 faricimab Final ERG report v1.0 04042022 LJ [ACIC]: Section 2.2, Page 7 footnote, states "The company did not submit a revised electronic model at clarification." this was provided on the 11th Feb through NICE docs.	The company provided the revised electronic model on the 11th Feb – this statement should be removed as it is incorrect.	It appears as though the company did not provide the relevant requested and supporting documents during clarification stage.	Amended

Issue 2

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ID3898 faricimab Final ERG report v1.0 04042022 LJ [ACIC]: Throughout the document, the ERG report has spelled "faricinib" when the molecular name is faricimab	Correction of typo throughout the document	Incorrect molecular name currently listed sporadically throughout the document.	Amended

Issue 3

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ID3898 faricimab Final ERG report v1.0 04042022 LJ [ACIC]: Section 2.3, Page 8, states that an amended version of the report will be shared based on the recent market share data	Will the company see this updated version of the report? Can the text be amended accordingly.	Clarification as to which report will be made publically available	This is provided in the updated ERG report.

provided by the company			

Issue 4

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ID3898 faricimab Final ERG report v1.0 04042022 LJ [ACIC]: Section 4.2.9, Page 22, "The ranibizumab prolonged delivery system, the port delivery system Susvimo, is not included by NICE as a comparator. It is produced by Genentech a Roche subsidiary. It has been approved by the FDA. It lasts for six months so injections (or implantations?) could be reduced to two a year."	The ranibizumab prolonged delivery system, the port delivery system (PDS), Susvimo, is not included by NICE as a comparator. The PDS is a surgically implanted long-acting treatment solution for nAMD that uses a customised formulation of ranibizumab to provide a continuous drug delivery profile, and is refilled every 24 weeks (approximately every 6 months). It is produced by Genentech a Roche subsidiary. It has been approved by the FDA.	Correction of the PDS description	Not a factual error. No change.

Issue 5

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ID3898 faricimab Final ERG report v1.0 04042022 LJ [ACIC]: Section 4.2.4 Page 16: "Intervention (faricimab up to Q16W) TENYA n=334 and LUCERNE n=331: patients received 6 mg of intravitreal faricimab every 4 weeks (Q4W) up to Week 12 (four injections).	Intervention (faricimab up to Q16W) TENYA n=334 and LUCERNE n=331: Patients received 6 mg of intravitreal faricimab every 4 weeks (Q4W) up to Week 12 (four injections). Patients then went onto receive faricimab at either a Q8w, Q12w or Q16w interval until Week 60, depending on the outcome of their disease activity assessment. From Week 60-108, patients were treated according to a	Correction of the faricimab dosing regimen within the trials	Not a factual error. "Depending on the outcome of their disease activity assessment" is equivalent to personalised.

All patients received a personalised treatment interval dosing regimen up to week 108.”	personalised treatment interval-dosing regimen.		

Issue 6

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ID3898 faricimab Final ERG report v1.0 04042022 LJ [ACIC]: Section 5.1.5, Page 26, Only the discontinuation rates affect the cost comparison, since the faricimab cost per dose is not equal to the comparators’ costs per dose. Annual discontinuation rates of [redacted] for Year1 and Year 2 are estimated from the faricimab trials’ pooled arms, while the estimate of 8.90% for Year 3+ is taken from NG82.	Only the discontinuation rates affect the cost comparison, since the faricimab cost per dose is not equal to the comparators’ costs per dose. Annual discontinuation rates of [redacted] for Year1 and Year 2 are estimated from the faricimab trials’ pooled arms, while the estimate of 8.90% for Year 3+ is	Incorrect rates had been listed	Amended

Issue 7

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ID3898 faricimab Final ERG report v1.0 04042022 LJ [ACIC]: Section 4.2.9, Page 22, Further trials are underway in various countries using 36-week intervals for the ranibizumab PDS - NCT03683251 (Velodrome), NCT04108156 (Pagoda) and NCT04657289. NCT04853251 (Belvedere) is looking at the effectiveness of the port delivery system in patients previously treated with. and who responded to, other anti-VEGF drugs. NCT05126966 (Diagrid) is comparing the ranibizumab PDS with aflibercept TREX in Dubai.	Further trials are ongoing and investigating (1) 24 week vs 36-week treatment intervals for the ranibizumab PDS in the treatment of nAMD NCT03683251 (Velodrome); (2) the efficacy of ranibizumab PDS in patients with DMO NCT04108156 (Pagoda); (3) the efficacy of ranibizumab PDS in patients with diabetic retinopathy without centre-involving DMO NCT04503551 (Pavilion); (4) the efficacy of ranibizumab PDS in patients who have previously been treated with and responded to other anti-VEGF drugs (Belvedere) and (5) ranibizumab PDS compared to aflibercept TREX (Diagrid). These studies are taking place in multiple countries, including the UK.	Incorrect trial description and NCT numbers listed	Amended the misplaced NCT number NCT04657289