CONFIDENTIAL REPORT

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Bevacizumab gamma for wet age-related macular degeneration

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Professor Andrew Lotery, Professor of Ophthalmology, University Hospital Southampton NHS Foundation Trust.

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Declared competing interests of the authors and advisors

The authors declare no competing interests.

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Dr Chhabra is the Principal investigator of VOYAGER, a real-world, non-interventional multinational, multicentre study assessing the safety and effectiveness of faricimab and the Port Delivery System with ranibizumab (PDS) for neovascular age-related macular degeneration (nAMD) or diabetic macular oedema in clinical practice. The trial is supported by F. Hoffmann-La Roche Ltd.

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Professor Lotery is Chairman of the Macular Society research committee and is also one of two clinical representatives contributing to The Royal College of Ophthalmologists professional organisation submission to NICE for this appraisal.

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Contributions of authors

Jonathan Shepherd critically appraised the clinical effectiveness evidence, drafted the report and is the project co-ordinator and guarantor. Emma Maund critically appraised the clinical effectiveness evidence and drafted the report. Fay Chinnery critically appraised the cost comparison analysis and analysis drafted the report. David Scott critically appraised the NMA and MAIC and drafted the report. Joanne Lord critically appraised the cost comparison analysis and drafted the report.

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LIST OF ABBREVIATIONS

AE	Adverse event
AIC	Academic in confidence
BNF	British National Formulary
CI	Confidence interval
CIC	Commercial in confidence
CRD	Centre for Reviews and Dissemination
CS	Company submission
CSR	Clinical study report
DSU	Decision Support Unit
EAG	External Assessment Group
EMC	Electronic Medicines Compendium
EPAR	European Public Assessment Report
EQ-5D-3L	European Quality of Life Working Group Health Status Measure 3 Dimensions, 3 Levels
EQ-5D-5L	European Quality of Life Working Group Health Status Measure 5 Dimensions, 5 Levels
EQ-VAS	EuroQol Visual Analogue Scale
HRG	Healthcare Resource Group
HRQoL	Health-related quality of life
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
IPD	Individual patient level data
ITT	Intent to treat
mITT	Modified intent to treat
MAIC	Matching-adjusted indirect comparison
MPSC	Medicines Procurement Supply Chain
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NR	Not reported
PAS	Patient Access Scheme
PRN	Pro-re-nata dosing regimen
PSS	Personal Social Services
Q4W	One injection every 4 weeks

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Q8W	One injection every 8 weeks
Q12W	One injection every 12 weeks
Q16W	One injection every 16 weeks
QALY	Quality-adjusted life year
QoL	Quality of life
RAN	Ranibizumab
RCT	Randomised controlled trial
RR	Relative risk/risk ratio
SAE	Serious adverse event
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
SmPC	Summary of product characteristics
TA	Technology appraisal
TEAE	Treatment-emergent adverse event
TREX	Treat-and extend dosing regimen
TSD	Technical Support Document
UK	United Kingdom
US	United States
VAS	Visual analogue scale
VEGF	Vascular endothelial growth factor

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1 EXECUTIVE SUMMARY

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

Table 1 Suitability for cost-comparison

Criteria	Criteria met?	EAG considerations
The technology's expected licensed indication is the same as the chosen comparators	Yes	Bevacizumab gamma is licensed for use in adults for treatment of neovascular (wet) age-related macular degeneration (nAMD). This is identical to the licensed indications for the three chosen comparators aflibercept, faricimab and ranibizumab.
The chosen comparators meet NICE's criteria for cost-comparison	Yes No	Of the three chosen comparators: • Aflibercept and faricimab are the most commonly used first line treatments for wet AMD in clinical practice. • Ranibizumab is now rarely used for patients eligible for NICE recommended anti-VEGF treatments
It is plausible that the technology may incur similar or lower costs compared with the comparators.	Unclear	Requires consideration of the results of the cost comparison model using discounts available in the NHS for comparator drugs reported in a confidential addendum to this report.

1.2 The decision problem: summary of the EAG's critique

The company's decision problem adheres to the NICE scope, with a couple of exceptions: exclusion of brolucizumab as a comparator and omission of health-related quality of life outcome data. The company's justification for the former is acceptable, whilst no justification is given for the latter. However, this does not appear to undermine the case for a cost-comparison evaluation.

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1.3 The clinical effectiveness evidence: summary of the EAG's critique

NORSE TWO is a well conducted trial and considered relevant to clinical practice. However, the disparity in dose regimens likely over estimates the clinical efficacy of bevacizumab gamma versus ranibizumab.

The company's network meta-analysis uses standard statistical approaches and is transparently reported. However, there is some clinical heterogeneity and the effects of this is unclear. There are also uncertainties regarding the robustness of certain nodes in the network, including two trials which used sham injections in the comparison group, and there is heavy reliance on imputation of missing data. The company and the EAG urge caution in the interpretation of the results of the NMA. The company's alternative approach to indirect comparison, using a MAIC, also has some methodological uncertainties.

1.4 The cost-effectiveness evidence: summary of the EAG's critique

The key issue in the company's base case with which we disagree is the injection frequency for bevacizumab gamma: the [redacted], but expert advice to the EAG is that the frequency would be similar to ranibizumab. See section 5.1.5.1 below for further detail.

In addition to a change to the injection frequency for bevacizumab gamma, the EAG preferred analysis includes the lowest available cost for ranibizumab (section 5.1.6) and a correction to the annual incidence of bilateral disease (section 5.1.3.2). The cumulative effects of applying these changes to the company's revised base case analysis are shown in Table 2. Both the company's and EAG's analyses suggest that bevacizumab gamma is associated with lifetime cost savings relative to the included comparators when the PAS discount for bevacizumab gamma is applied and comparators are costed at list price. Results with price discounts for all comparators are reported in a separate addendum. See sections 5.3.3 and 6 for additional scenario analysis.

Table 2 Cumulative change from company's revised base case to the EAG's preferred analysis (PAS discounted price for bevacizumab gamma, other drugs at list price)

Scenario	Drug	Total cost	Incr. cost [a]
Company base case: revised in response to clarification questions	Bevacizumab	[redacted]	
	Ranibizumab	[redacted]	[redacted]
	Faricimab	[redacted]	[redacted]
	Aflibercept	[redacted]	[redacted]
+ Injection frequency for bevacizumab gamma equal assumed to that of ranibizumab	Bevacizumab	[redacted]	
	Ranibizumab	[redacted]	[redacted]
	Faricimab	[redacted]	[redacted]

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Scenario	Drug	Total cost	Incr. cost [a]
	Aflibercept	[redacted]	[redacted]
+ Lowest available NHS cost for ranibizumab (including biosimilars)	Bevacizumab	[redacted]	
	Ranibizumab	[redacted]	[redacted]
	Faricimab	[redacted]	[redacted]
	Aflibercept	[redacted]	[redacted]
+ Annual incidence of bilateral disease 14% [1]	Bevacizumab	[redacted]	
	Ranibizumab	[redacted]	[redacted]
	Faricimab	[redacted]	[redacted]
	Aflibercept	[redacted]	[redacted]
EAG's preferred analysis	Bevacizumab	[redacted]	
	Ranibizumab	[redacted]	[redacted]
	Faricimab	[redacted]	[redacted]
	Aflibercept	[redacted]	[redacted]

Source: Produced by the EAG using the company's revised model submitted at clarification
[a] Incremental cost for bevacizumab gamma relative to comparator

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2 INTRODUCTION AND BACKGROUND

2.1 Introduction

This report is a critique of the company's submission (CS) to NICE from Outlook Therapeutics on bevacizumab gamma (Lytenava™) (ONS-5010) for treating neovascular (wet) age-related macular degeneration (nAMD). It identifies the strengths and weakness of the CS. Clinical experts were consulted to advise the external assessment group (EAG) and to help inform this report.

Clarification on some aspects of the CS was requested from the company by the EAG via NICE on 31st July 2024. A response from the company via NICE was received by the EAG on 15th August 2024 and this can be seen in the NICE committee papers for this appraisal.

2.2 Background

2.2.1 Background information on neovascular (wet) age-related macular degeneration (nAMD) and the care pathway

The CS provides a brief description of the current care pathway for wet age-related macular degeneration (CS Section B.1.3). Appropriately, this includes the currently available NICE-recommended anti-vascular endothelial growth factor (VEGF) treatments **aflibercept, faricimab, ranibizumab** and **brolucizumab**.

Clinical experts advising the EAG described the evolution of anti-VEGF therapy for wet AMD over the last two decades. "First generation" treatments include **bevacizumab (Avastin)**(Not recommended by NICE for wet AMD) and **ranibizumab** (NICE TA155, published in 2008; updated in 2024).[2] **Aflibercept** (NICE TA294, published in 2013),[3] launched a few years later, is a "second generation" treatment and, more recently, the "third generation" features **faricimab** (NICE TA 800, published in 2022).[4]

After its launch aflibercept became the treatment of choice but more recently faricimab has gained market share and very recently aflibercept 8mg has become available and is also increasingly used, particularly in patients unresponsive to other agents. Both EAG clinical experts commented that first line treatment of wet AMD in their centres is predominantly with faricimab. Ranibizumab (biosimilar) is rarely used now for treatment of wet AMD, instead, it is generally used in conditions where a short course of treatment is expected, such as extrafoveal choroidal neovascularization (CNV) and peripapillary choroidal neovascularization (CNV).

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The clinical experts commented on advancements made to anti-VEGF treatments over time. An ongoing area of development is the need for treatments with greater durability of effects, as this could mean patients require injections less frequently. One of the EAG's clinical experts described how the frequency of injections has decreased from the first to the third generation of anti-VEGF drugs: ranibizumab dosing is monthly, aflibercept dosing is every 2 months and faricimab dosing every 12-14 weeks. The expert commented that longer dosing intervals with faricimab has helped relieve capacity constraints in their centre, as fewer patient appointments are needed. We describe treatment regimens and dosing in more detail below (section 2.2.3).

The EAG's clinical experts also commented that they expect **aflibercept 8mg** will be prescribed for some patients. Aflibercept 8mg is a high dose formulation of aflibercept which received a marketing authorisation from the MHRA in January 2024. It has been recommended for routine NHS commissioning[5] as it is considered clinically equivalent and of at least equal cost effectiveness to the NICE recommended aflibercept 2mg formulation (TA294). One of the experts suggested that because aflibercept 8mg is a larger volume to inject, it may not be used first line in patients with wet AMD and increased risk of glaucoma (or who have glaucoma) as there is an increased risk of intraocular pressure due to the volume of the injection. (NB. The NICE scope does not refer to aflibercept 8mg and it is not included as a comparator treatment in the CS).

The EAG notes that the background sections of the CS are focused on first line treatment for wet AMD, with no consideration of treatment switching. However, the EAG's clinical experts commented that treatment switching is common in practice. If a patient has a sub-optimal response to treatment, or is unable to sufficiently extend their injection intervals, they would be considered for re-treatment using a different anti-VEGF drug. Clinicians would generally switch patients to a newer anti-VEGF (e.g. faricimab/aflibercept) than an older drug such as ranibizumab.

2.2.2 Background information on bevacizumab gamma

Bevacizumab gamma is an ophthalmic-grade formulation of the anti-VEGF treatment **bevacizumab (Avastin).** Bevacizumab gamma was approved by the Medicines and Healthcare products Regulatory Agency (MHRA) in the United Kingdom (UK) in July 2024 for the treatment of wet age-related macular degeneration (nAMD). It was also approved for this indication by the European Medicines Agency (EMA) in May 2024. The recommended dose is 1.25 mg administered by intravitreal injection every 4 weeks (monthly). This corresponds to an injection volume of 0.05 mL. Once a sufficient response is achieved a

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“treat and extend” regimen can be considered, based on the individual patient’s needs – please see section 2.2.3)

The CS describes bevacizumab gamma as a recombinant humanized monoclonal antibody (mAb) that selectively binds with high affinity to all isoforms of human VEGF and neutralizes biologic activity through a steric blocking of the binding of VEGF to its receptors Flt-1 (VEGFR-1) and KDR (VEGFR-2) on the surface of endothelial cells.

The CS notes that bevacizumab gamma is the first formulation of bevacizumab licensed for ophthalmic use. The existing formulation, bevacizumab (Avastin), is indicated for use as an intravenous treatment for systemic cancers (NB. In this report ‘bevacizumab gamma’ refers to the ophthalmic formulation of bevacizumab, i.e. the technology under appraisal, and ‘bevacizumab (Avastin)’ refers to the non-ophthalmic preparation, prescribed off-label). Bevacizumab (Avastin) is not licensed for intravitreal use in the UK and thus is not indicated for treating wet AMD. Despite this, expert clinical advice to the EAG is that bevacizumab (Avastin) is used off licence to treat wet AMD in specific situations, for example, in patients whose visual acuity is outside the range covered by NICE recommended anti-VEGF treatments (below 6/9 or over 6/96) (NB. NICE guidance for ranibizumab, aflibercept and faricimab applies to best-corrected visual acuity (BCVA) between 6/12 and 6/96).

The CS describes bevacizumab gamma as an ophthalmic-grade formulation of bevacizumab and emphasises its conformity to the stringent EU standards required for the manufacture of ophthalmic solutions. The EAG are of the understanding that bevacizumab gamma is pharmacologically identical/similar to bevacizumab (Avastin). Effectively, bevacizumab gamma can therefore be regarded as analogous to first-generation anti-VEGF treatment, such as ranibizumab. Clinical experts to the EAG agreed that bevacizumab gamma is broadly similar in mechanism of action to the other anti-VEGFs licensed to treat wet AMD (i.e. ranibizumab, aflibercept, faricimab). The drugs have similar efficacy in improving vision loss.

Although within the same therapeutic class, the treatments inhibit VEGF in slightly different ways. Clinical advice to the EAG is that, pharmacologically speaking, bevacizumab gamma is regarded as similar to ranibizumab. They explained that aflibercept is an anti-angiogenic agent with high affinity to the isoform VEGF-A, it also binds VEGF-B and platelet-derived growth factors PDGF1 and PDGF2 . Faricimab targets two distinct pathways in retinal angiogenesis, VEGF-A and Ang-2, to create a more durable effect with the aim of reducing the number of injections and patient visits required.

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For the purposes of this cost-comparison appraisal the EAG considers it reasonable to regard bevacizumab gamma as broadly similar in mechanism to the other NICE recommended anti-VEGF treatments, and similar in clinical efficacy (e.g. improving visual acuity). This is notwithstanding advancements made to the newer anti-VEGF treatments which permit longer intervals between dosing.

2.2.3 The position of bevacizumab gamma in the treatment pathway

The company proposes bevacizumab gamma as an alternative first line treatment option to other available anti-VEGF treatments (aflibercept, faricimab and ranibizumab) in an identical population - adults with neovascular AMD.

Figure 1-1 in the company submission (CS) illustrates the loading dose and subsequent dose regimens for aflibercept, faricimab and ranibizumab and the proposed dosing regimen for bevacizumab gamma. For all treatments there is an initial loading phase to achieve maximum visual acuity, reduce symptoms and disease activity. The frequency of injections in the loading phase is monthly, for up to a maximum or 3 or 4 consecutive months. This is also the case for bevacizumab gamma - the CS states that the kinetics of bevacizumab gamma efficacy indicate that 3 or more consecutive monthly injections may be needed initially.

Thereafter a **"treat and extend**" regimen is used, whereby the intervals between doses are extended incrementally to maintain improvements in visual outcomes. For example, for ranibizumab the intervals are increased stepwise by no more than 2 weeks at a time, whereas for newer treatments such as aflibercept and faricimab, intervals can be extended in increments of up to 4 weeks, to reach a maximum interval of 16 weeks. CS Figure 1-1 does not explicitly specify a treat and extend regimen for bevacizumab gamma, but states that the healthcare professional may individualise treatment intervals based on disease activity as assessed by visual acuity and/or anatomical parameters. This was based on consideration of a 'scientific bridge' proposed by the company and accepted by the regulator, in which evidence on longer term treatment intervals for bevacizumab (Avastin) could be used in lieu of similar such evidence for bevacizumab gamma. The company states that this assumption is supported by the high similarity between the two drugs. Whilst the concept of a scientific bridge for bevacizumab gamma has some credence with the regulatory bodies, the EAG is of the view that, to reduce uncertainty, direct clinical trial evidence is needed to establish the efficacy and safety of bevacizumab gamma with longer-term injection intervals. At the current time, the real-world injection intervals for bevacizumab gamma are unknown.

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Overall, the proposed dose regimen protocol for bevacizumab gamma is broadly in-keeping with the regimens used for the cost comparator drugs aflibercept and faricimab. These are the main anti-VEGF treatments used in the NHS for this indication. However, despite the scientific bridge that there is limited direct evidence that bevacizumab gamma can be extended to the same maximum intervals as aflibercept or faricimab.

Expert clinical advice to the EAG is that bevacizumab gamma is unlikely to be used as a first line treatment in practice, due to the lack of evidence for its longer-term efficacy and safety (i.e. extending the frequency of injections). One expert suggested clinicians may use it as a second-line treatment if there is insufficient response to first line anti-VEGF treatment (e.g. following aflibercept or faricimab). Another expert disagreed with this, stating that first line treatment would always be with one of the newer agents (e.g. faricimab, aflibercept) with the expectation that most patients will have a durable response. The expert could not consider switching to older, less durable treatments such ranibizumab or bevacizumab gamma (essentially both are first generation treatments).

Another suggested option would be to prescribe bevacizumab gamma first line as a loading treatment and then switch to a different anti-VEGF for maintenance. However, another clinical expert to the EAG noted that patients with a sub-optimal response to bevacizumab loading treatment would need to switch to a different treatment and undergo a second loading period followed by an extended period. This would increase the number of injections required in the first year beyond the number of injections required if a newer treatment had been used from the outset (e.g. faricimab). This expert was of the opinion that the only use of bevacizumab gamma in practice would be similar to that of ranibizumab (biosimilar) - that is, for patients where short course of treatment is required. These patients comprise only about 5-10% of the population in every service.

The dosing frequency of bevacizumab gamma is therefore key issue for consideration in this appraisal. We critique the available clinical effectiveness evidence for bevacizumab gamma, including its durability, in section 4.2 of this report. Furthermore, in section 5.1.5.1, we identify dosing frequency for bevacizumab gamma as a key driver of the cost-comparison model. We conduct scenario analyses exploring different assumptions regarding the durability of effect.

EAG comment on the background information

The background information on wet AMD provided in the CS is reasonably detailed and relevant for the purpose of NICE health technology appraisal. However, the comprehensiveness of the information is limited in places, for example, there is a

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focus on first line treatment but little consideration of the potential for treatment switching. As will become apparent in subsequent sections of this report, this reflects the company’s anticipated position of bevacizumab gamma as a first line treatment for wet AMD. The information provided in the CS generally accords with expert clinical advice to the EAG.

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3 CRITIQUE OF THE COMPANY'S DEFINITION OF THE DECISION PROBLEM

Table 3 provides the EAG's critique of the company's decision problem in relation to the final scope issued by NICE.

EAG comment on the company's decision problem

The company's decision problem adheres to the NICE scope, with a couple of exceptions: exclusion of brolucizumab as a comparator and omission of health-related quality of life outcome data. The company's justification for the former is acceptable, whilst no justification is given for the latter. However, this does not appear to undermine the case for a cost-comparison evaluation.

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Table 3 Summary of the decision problem

	Final scope issued by NICE	Company's decision problem	Rationale if different from the final NICE scope	EAG comments
Population	• Adults with wet age-related macular degeneration	Adults with wet age-related macular degeneration	N/A	The company specify a narrower population for the cost comparison analysis: adults with wet age-related macular degeneration eligible for first line treatment. Previously treated patients receiving subsequent lines of anti-VEGF treatment are not included in the cost model. The company have since clarified that bevacizumab gamma should be considered for reimbursement in all stages of the wet-AMD treatment pathway. However, first line use is expected to be a logical assumption for cost-analysis and decision making (company factual accuracy check and confidential information check of the EAG report).
Intervention	• Bevacizumab gamma	Lytenava™ (ONS-5010) bevacizumab gamma	N/A	N/A

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	Final scope issued by NICE	Company's decision problem	Rationale if different from the final NICE scope	EAG comments
Comparators	• Aflibercept • Ranibizumab (intravitreal injection) • Brolucizumab • Faricimab	• Ranibizumab • Aflibercept • Faricimab	Brolucizumab is excluded because it is not routinely used in practice, according to company's clinical experts and national audit data indicating a market share of < 1%. Due to safety concerns brolucizumab was excluded as a comparator in NICE TA800 (faricimab).	The case for excluding brolucizumab is reasonable. EAG expert clinical advisors agree. There is a weaker justification for ranibizumab as a cost comparator, as it is rarely used for patients eligible for NICE recommended anti-VEGF treatments
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	N/A	Although listed in the decision problem, health-related quality of life is not included in the CS. However, this is not a significant issue given that this appraisal is a cost-comparison rather than a cost-effectiveness analysis (which would require HRQoL data to calculate Quality Adjusted Life Years (QALYs).)

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	Final scope issued by NICE	Company's decision problem	Rationale if different from the final NICE scope	EAG comments
Economic analysis	If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost comparison may be carried out. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. 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 and cost of biosimilar and generic products should be taken into account.	N/A	A cost-comparison will be presented in line with the final NICE scope and previous cost-comparison appraisals of treatments for the same indication (TA672 and TA800).	The company's costing model uses an appropriate time horizon (effectively lifetime) and perspective for costing (NHS and personal social services). The company's base case uses an unweighted mean cost for ranibizumab, which includes biosimilar products. The base case includes a PAS discounted price for bevacizumab gamma, and the company explore the impact of potential PAS discounts for comparators. The EAG presents results from the cost comparison model with all available NHS discounts in a confidential addendum to this report.

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	Final scope issued by NICE	Company's decision problem	Rationale if different from the final NICE scope	EAG comments
Subgroups	• None specified			
Special considerations including issues related to equity or equality	• None specified			

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4 CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review(s)

The company carried out a systematic literature review to identify relevant clinical effectiveness evidence, searching for RCTs only (CS section B.3.9.1, CS Appendix D). An adequate range of databases, using appropriate search terms, and supplementary sources were searched. Searches for full text publications were performed from database inception to 25 October 2022 and updated on 30 January 2024 (CS Appendix D.1.1). Searches for conference abstracts were performed in EMBASE only from 2020 to 30 January 2024. Overall, the searches are not likely to have missed any clinical effectiveness studies unless they were published after January 2024.

The population eligibility criteria of the review (CS Appendix D Table 0-10) were the same as the company's decision problem (CS document B Table 1-1). Studies of a range of therapeutic interventions for wet AMD were searched for and eligible for the review (CS appendix D Table 0-2 to 0-10). Thus, the review's scope (CS Appendix D Table 0-10) was broader than the company's decision problem (CS document B Table 1-1), which focuses on bevacizumab gamma as the intervention and ranibizumab, aflibercept and faricimab as comparators. This is done to inform a network meta-analysis of treatments to facilitate indirect treatment comparisons – we discuss this later in this report (section 4.3) In contrast, the range of outcomes eligible for the review were narrower than the company decision problem. Namely, health-related quality of life (HRQoL) was not specified as a relevant outcome in the inclusion criteria of the review. Given that this appraisal is a cost-comparison rather than a cost-effectiveness analysis there is no requirement for HRQoL utility data to calculate Quality Adjusted Life Years (QALYs) and costs per QALY. Nonetheless, where HRQoL has been measured as an outcome in clinical trials of a health technology it is useful to consider these results alongside clinical efficacy and safety outcomes as part of the overall assessment of clinical effectiveness.

The review included 113 RCTs (reported in 206 publications) that met the broad inclusion criteria (CS Appendix D 1.1, CS Appendix D Figure 0-1). Two trials evaluated th efficacy of bevacizumab gamma - NORSE ONE and NORSE TWO. We discuss these in the next section.

EAG comment on the methods of review(s)

Generally, the systematic literature review was well conducted. It is unlikely that any relevant clinical effectiveness studies would have been missed.

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4.2 Critique of studies of bevacizumab gamma

The company's systematic literature review identified three relevant studies of bevacizumab gamma for wet AMD, from the NORSE clinical trial programme. CS sections B.3.2 to B.3.6 report the methods and results of NORSE ONE- a small "clinical experience trial" and NORSE TWO – the pivotal phase III licensing trial. A third study, NORSE THREE, is a short-term safety study focused on frequency and incidence of treatment-emergent adverse events and is mentioned only briefly in the CS.

The company consider NORSE TWO as the key source of efficacy and safety data for bevacizumab gamma; it is included in the company's indirect treatment comparison and informs the economic evaluation in this NICE appraisal.

The Company states that NORSE ONE provided valuable insight into the trial design and inclusion/exclusion criteria for NORSE TWO. However, the power and sample size were not considered clinically meaningful. It was not originally included in the company's indirect treatment comparison, but was included in an update in response to an EAG request.

In response to a clarification question from the EAG (A3), the company reported that the NORSE studies have not been published yet. However the NORSE TWO manuscript is expected to be published in late 2024.

Below we briefly summarise the key characteristics of NORSE ONE and TWO.

NORSE ONE

Design

- Proof of concept multicenter, randomized, double-masked, controlled study

Study population

- N=61 nAMD patients
- N= 31 bevacizumab gamma
- N 30 ranibizumab:

Inclusion criteria

- Active primary Subfoveal Choroidal Neovascularization lesions secondary to Age-related macular degeneration (AMD) in the study eye
- Best corrected visual acuity of 20/40 to 20/320
- Treatment naïve and non-treatment naïve patients

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Regimens

- As NORSE TWO below

Location

- 9 trial sites in Australia

NORSE TWO

Design

- A multicentre, randomized, double-masked, active controlled, pivotal phase 3 trial to evaluate the efficacy and safety of intravitreal administered bevacizumab gamma

Study population

- Adults with choroidal neovascularisation (CNV) secondary to wet AMD. A total of 228 patients were randomised to receive bevacizumab (n=113), or ranibizumab (n=115).

Inclusion criteria

- The trial inclusion criteria specified a best corrected visual acuity of 25-67 letters read (20/50 to 20/320 Snellen equivalent), and also that patients were treatment naïve.

Regimens

- The dose of bevacizumab gamma was 1.25 mg by intravitreal injection monthly in the study eye, over 12 months.
- The dose of ranibizumab was 0.5 mg by intravitreal injection in the study eye, every month for 3 months (i.e. on Days 0, 30, and 60) followed by 2 additional injections on Days 150 and 240.
- The total duration of treatment: Bevacizumab gamma:12 months, Ranibizumab:11 months

Primary outcome

- The difference in the proportion of patients who gain ≥ 15 letters from baseline in BCVA at 11 months.

Secondary outcomes

- The mean change in BCVA from baseline to 11 months.
- The proportion of patients who gain ≥ 5 or ≥ 10 letters in visual acuity at 11 months compared with baseline.
- The proportion of patients who lose fewer than 15 letters in visual acuity at 11 months compared with baseline.
- The proportion of patients with a visual acuity Snellen equivalent of 20/200 or worse at 11 months.
- Central subfield foveal thickness

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- Adverse effects of treatment

Location

- 39 clinical trial sites in the United States

Risk of bias

The company's methodological quality assessment (also referred to as risk of bias assessment) of the NORSE TWO trial was conducted using the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in healthcare. An overview of the company's assessment is presented in CS document B Table 3-6. The EAG independently critically appraised the trial using the same criteria, and we agree with the company's assessment (Table 4).

Table 4 Overview of company and EAG risk of bias judgement

Criterion	Company judgement	EAG judgement
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

Source: Partly reproduced from CS Document B Table 3-6. Additional sources: CSR sections 7.4.3, 7.7.1, 7.7.2, 7.7.9, CSR Table 7 and Table 8; CSR Figure 2; Protocol sections 5.1, 5.2 and 8.2

Both of the EAG's exert clinical advisors were of the opinion that the patient population of NORSE TWO is reasonably reflective patients they would see in clinical practice. However,

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they also noted that the disparity in the dose regimens in the trial (12 injections for bevacizumab patients over 12 months, compared to 5 injections for ranibizumab over 11 months) would favour the clinical efficacy of bevacizumab gamma. These patients would effectively be receiving twice the dosage that the ranibizumab patients would get. The experts did not consider this a reasonable comparison from a clinical perspective. The CS describes the ranibizumab dosing as consistent with the PIER study dosing regimen (the PIER trial being one of the original trials of the efficacy and safety of ranibizumab).[6 7]

EAG comment on studies of the technology of interest

NORSE TWO is a well conducted trial, considered to be at low risk of bias in terms of its methodology and design and is reflective of patients typically seen in clinical practice in England. However, the disparity in dose regimens likely over estimates the clinical efficacy of bevacizumab gamma versus ranibizumab.

4.2.1 Key efficacy results of the intervention studies

CS Section B.3.6 reports the efficacy results for NORSE TWO. For the primary efficacy endpoint, bevacizumab gamma was superior to ranibizumab, when ranibizumab was administered in a manner consistent with the PIER study dosing regimen, for the proportion of patients achieving an increase of ≥ 15 letters in BCVA from baseline to 11 months (41.7% vs 23.1%, respectively, risk difference of 0.1859 [95% CI = 0.0442, 0.3086]; p = 0.0052).

The CS reports that bevacizumab gamma was statistically superior to ranibizumab in the first three secondary outcomes tested. Further detail can be found in CS section B.3.6.

4.2.2 Key safety results of the intervention studies

Adverse event data for NORSE TWO were presented in the CS section B.3.10 and CS Appendix F. Adverse event data for NORSE ONE were provided in the CSR only (company clarification response A1). The EAG note that the company highlight that the incidence of adverse events in NORSE TWO and NORSE ONE be considered in the context that a) the number of injections was more than double that in the bevacizumab gamma arm relative to the ranibizumab arm and b) the follow-up period was 1 month longer in the bevacizumab gamma arm (CS section B.3.10, CS Appendix F and NORSE ONE CSR section 10.10.2.1.1). Key safety results are reported below.

Incidence of one or more treatment-emergent adverse events (TEAE)

- NORSE TWO: comparable across treatment arms (CS B.3.10)
- NORSE ONE: [redacted] in the bevacizumab gamma arm ([redacted]) compared to the ranibizumab arm ([redacted]; CSR section 10.2.1.1)

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Incidence of at least one serious adverse event (SAE)

- NORSE TWO: comparable across treatment arms (CS Appendix F)
- NORSE ONE: [redacted] in the bevacizumab gamma arm ([redacted]) compared to the ranibizumab group ([redacted]; CSR section 10.2.1.1)

Incidence of discontinuing due to adverse events

- NORSE TWO: less frequent in the bevacizumab gamma arm (1.8%) compared to the ranibizumab arm (4.3%; CS Appendix F)
- NORSE ONE: [redacted] treatment arms (CSR section 10.2.1.1)

Incidence of at least one ocular adverse event occurring in the study eye

- NORSE TWO: comparable across treatment arms (CS Appendix F)
- NORSE ONE: [redacted] in the bevacizumab gamma arm ([redacted]) compared to the ranibizumab arm ([redacted]) in NORSE ONE (CSR 10.2.1.2)

Incidence of at least 1 ocular TEAE in study eye related to study drug/study procedure

- NORSE TWO: greater in the bevacizumab gamma arm (18.6%) compared to the ranibizumab arm (7%, CS Appendix F)
- NORSE ONE: greater in the bevacizumab gamma arm (29.0%) compared to the ranibizumab arm (23.3%; CSR section 10.2.1.2)

Ocular adverse events that occurred twice as frequently in the bevacizumab gamma arm relative to the ranibizumab arm either NORSE TWO or NORSE ONE are reported in Table 5 below. Clinical expert advice to the EAG were that none of these events were of concern.

Table 5 Treatment emergent ocular adverse events that occurred at least twice as frequently in the bevacizumab gamma arm relative to the ranibizumab arm in NORSE TWO or NORSE ONE

	NORSE TWO		**NORSE ONE**	
System Organ Class Preferred Term[a]	**Ranibizumab (N = 115)**	**Bevacizumab gamma (N = 113)**	**Ranibizumab (N = 30)**	**Bevacizumab gamma (N = 31)**
	n (%)	n (%)	n (%)	n (%)
Cataract nuclear	0	4 (3.5)	[redacted]	[redacted]
Conjunctival haemorrhage	3 (2.6)	10 (8.8)	[redacted]	[redacted]

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	NORSE TWO		NORSE ONE	
System Organ Class Preferred Term[a]	**Ranibizumab (N = 115)**	**Bevacizumab gamma (N = 113)**	**Ranibizumab (N = 30)**	**Bevacizumab gamma (N = 31)**
Corneal abrasion	1 (0.9)	4 (3.5)	[redacted]	[redacted]
Vitreous detachment	2 (1.7)	4 (3.5)	[redacted]	[redacted]
Vitreous floaters	1 (0.9)	4 (3.5)	[redacted]	[redacted]
Vitreous haemorrhage	1 (0.9)	2 (1.8)	[redacted]	[redacted]
Intraocular pressure increased	1 (0.9)	7 (6.2)	[redacted]	[redacted]
Eye pain	2 (1.7)	1 (0.9)	[redacted]	[redacted]

Source: Partly reproduced from CS Table 3-27 and NORSE ONE CSR Table 20
[a] Adverse events were coded using Medical Dictionary for Regulatory Activities, Version 23.0

4.3 Critique of the network meta-analysis (NMA)

4.3.1 Rationale for NMA

In setting the case for a cost comparison appraisal, the CS mentions the requirement to demonstrate non-inferiority in efficacy and safety of bevacizumab gamma to the chosen comparator treatments. The NORSE TWO trial compared the efficacy and safety of bevacizumab gamma versus ranibizumab, however in the absence of direct comparisons against aflibercept and faricimab the company conducted a systematic literature review to inform a network meta-analysis (NMA) in which indirect treatment comparisons could be made.

In addition to the NMA, the CS also reports a matched-adjusted indirect comparison (MAIC) which was subsequently conducted as a sensitivity analysis, testing how sensitive the NMA results were to heterogeneity in trial characteristics, and to assess safety outcomes which were not possible to address in the NMA.

In the CS details of the NMA and the MAIC are given in section B.3.9 and appendix D. In response to an EAG clarification question (A8) the company provided a structured 387 page report providing further detailed information about the methods and results of the NMA and the MAIC.[8] The company also supplied a separate report with updated MAIC results in response to EAG clarification question A13.[9]

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In the following sub-sections of this report (4.3.2 to 4.3.8) we describe and critique the methods used to conduct the NMA, followed by a summary of the main findings (section 4.4). We then describe and critique the MAIC (section 4.5) and give a summary of its results (section 4.6).

4.3.2 Identification, selection and feasibility assessment of studies for NMA

The company did a systematic literature review to identify relevant evidence for potential inclusion in the NMA. This is the same systematic review that we discussed earlier in this report (section 4.1) conducted to identify studies of bevacizumab gamma for the CS (the company refer to this as the "clinical SLR"). It was also used to identify studies of comparator treatments for the NMA. As we commented earlier, the methods of the systematic literature review were of a good standard and the EAG is not aware of any relevant studies not identified.

4.3.2.1 Inclusion criteria

The inclusion criteria for the NMA are reported in CS Appendix D table 0-10. The criteria are broader than the decision problem but necessarily so to construct a connected network. The interventions eligible for inclusion included bevacizumab gamma plus and company's chosen cost comparison treatments (faricimab, aflibercept and ranibizumab) plus other treatments outside the scope of this appraisal (e.g. conbercept and pegaptanib). The CS states that all conceivable treatment approaches were considered for inclusion, such as fixed interval dose regimens, "pro re nata" (as needed) regimens and treat and extend regimens. Comparators could include any intervention that allows for indirect treatment comparison. Examples of eligible efficacy outcomes are given and include best corrected visual acuity and central foveal thickness. As these are presented as examples it is not clear how many other eligible efficacy outcomes there were. Examples of relevant safety outcomes were given, including proportions of patients with adverse events classified as: any AE; ocular AE, serious AE and AEs leading to treatment discontinuation. In terms of study design, only RCTs were eligible. There was no restriction on clinical trial phase (i.e. phase I to IV).

Having run the search strategies and applied the above inclusion criteria a total of **206 publications** detailing a total of **113 trials** were included in the systematic literature review. Subsequently, a second set of inclusion criteria were applied to the 206 publications "to specifically target trials relevant to the UK contexts" (company NMA report page 25; CS Section B.3.9.2). These criteria are narrower than the first set, for example excluding treatments outside the scope of the appraisal (e.g. conbercept, bevacizumab (Avastin)).

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Eligible treatments were restricted to bevacizumab gamma plus the three chosen cost comparators, given at “doses approved in the UK”. The EAG assumes “approval” is that of the regulator (the CS states “for interventions with EMA- and/or FDA-approved doses and schedules only those will be included in analysis this means approved by the regulator”). Other restrictions applied in the second set of inclusion criteria included a timepoint threshold for outcome measurements of up to 11 months to a year (assuming time equivalence between 48-56 weeks). The CS does not give an explicit justification for this particular threshold but from Table 3-2 in the NMA report it appears that only 2 of the 113 trials were subsequently excluded on this criterion. Any potential concerns about the appropriateness of the threshold therefore have little or no consequence in this review.

Both of the EAG’s expert clinical advisors were of the opinion that aflibercept 8mg should have been included in the NMA as a comparator treatment. As we have mentioned earlier in this report (section 2.2.1) aflibercept 8mg received its marketing authorisation in the UK in January 2024, and it is available for routine commissioning in the NHS.[5] It is not included in the scope of this NICE appraisal, presumably because it wasn’t available in the UK when the scope for the appraisal was being developed.

4.3.2.2 Feasibility study

Application of the second set of inclusion criteria resulted in exclusion of 91 trials, leaving a total of **22 RCTs** for inclusion in the NMA. Based on the 22 RCTs the company did a feasibility study to establish whether an NMA is possible. They considered the following factors:

- Whether an evidence network linking bevacizumab with the chosen cost comparators can be connected.
- Whether there is an even distribution of treatment effect modifiers and prognostic factors between and within studies in the network
- Whether sufficient outcome data are available from the included trials and whether the outcomes are consistently defined and measured across the trials.
- Whether further analyses such as sensitivity analysis and subgroup analyses would be necessary, for example, to explore differences in study characteristics.

The results of the feasibility assessment are presented in the NMA report section 3.3 and 3.4. A narrative summary is given describing the study population characteristics (e.g. age, BMI, race) and comparing the distribution of prognostic factors and effect modifiers across

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the studies. A similar process was followed to assess the consistency in outcome measure definitions and availability of outcome data.

The CS doesn't give an explicit conclusion on whether or not an NMA was considered feasible. However, the company expressed concerns over some of the assumptions informing the NMA, prompting them to conduct a series of MAICs – an alternative approach which requires different assumptions (see section 4.5 of this report).

4.3.2.3 Network structure

Figure 1 below reproduces, for illustration, the overall network diagram from the CS. As can be seen, the network comprises 22 RCTs, including the NORSE 2 trial of bevacizumab gamma. (NB. NORSE 1 was not originally included in the NMA, however during this appraisal they provided an updated the NMA featuring the study – details are reported in section 9 of the NMA report). Ranibizumab 0.5mg Q4W was chosen as the central comparator node connecting all the studies. Bevacizumab gamma is connected to the network via the NORSE 2 comparator arm, ranibizumab 0.5mg Q12W. This forms a node connecting to the ranibizumab 0.5mg Q12W arm in the PIER trial. The sham arm of PIER connects with the sham arm of the MARINA trial which, in turn, is directly connected to the central comparator node (i.e. ranibizumab 0.5mg Q4W). From this central node connections are made with the other trials permitting indirect comparisons between bevacizumab gamma versus aflibercept, ranibizumab and faricimab.

The CS mentions that the NMA network aligns with the 'reduced' faricimab network from NICE TA800 in which comparators not relevant to the decision problem (e.g. off-label bevacizumab, brolucizumab) were removed from the network. The EAG assumes that this was the reason why the more restrictive second set of inclusion criteria were introduced in this current appraisal - to avoid an excessively large network comprising studies with little or no relevance to the decision problem. The EAG considers the NMA inclusion criteria to be appropriate to the decision problem.

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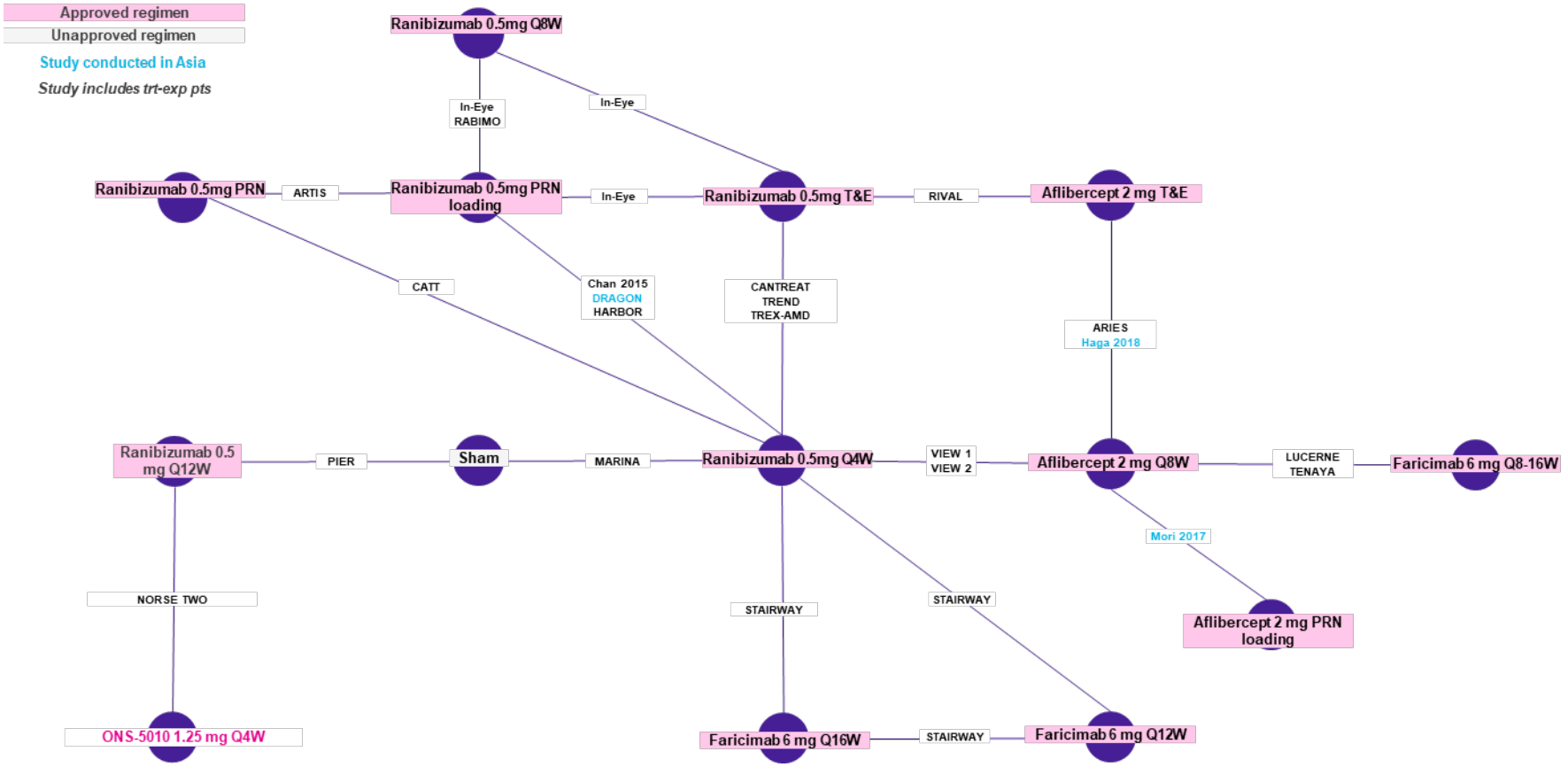

Figure 1 The overall evidence network

Source: reproduced from CS Appendix D Figure 0-2
Abbreviations: PRN, Pro re nata dosing regimen; T&E, Treat-and-extend dosing regimen; Q4W, one injection every 4 weeks; Q8W, one injection every 8 weeks; Q12W, one injection every 12 weeks; Q16W, one injection every 16 weeks.

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4.3.3 Assessment of clinical heterogeneity and similarity

The NMA feasibility exercise was an opportunity to assess potential clinical heterogeneity in the network. CS Appendix D.1.2 provides a narrative description of selected patient characteristics, including prognostic factors and effect modifiers. Below is a summary of the company's key observations:

- **Age**. The company notes that the age of study participants was "reasonably similar", ranging from 66.6 to 79 years.

- **Sex**. Large variability across the trials in percent female (27.6%-72.2%). NORSE 2 is at the higher end of the range (59.6%).

- **Body Mass Index (BMI).** Details of BMI and measures of weight were insufficiently reported by the included studies.

- **Race/ethnicity**. There was variation between studies in the proportion of White study participants, ranging from 72.8% to 98.6%. In most trials the proportion of White participants exceeded 90%, including NORSE 2 (97.8%). There was wider variation in the proportion of Asian patients – from 100% in two trials, to just 0.9% in one trial (NORSE 2). (NB. CS section B.3.9.3, page 59 states three trials with 100% Asian patients - DRAGON,[10] Haga 2018,[11] and Mori 2017,[12] whereas CS Appendix D, page 73 states there are only two such trials - Haga 2018 and DRAGON). In the remaining trials the proportion of the trial population classed as Asian was under 20%. Expert clinical advice to the EAG is that Asian patients (specifically Southeast Asia, Chinese and Japanese) tend to have lesions which are more resistant to treatment, and they require more frequent treatment. The proportion of patients of Black ethnicity ranged from 0.2% to 1.5%.

- **Choroidal neovascularisation (CNV)**. The proportion of patients with different types of CNV lesion (predominantly classic; minimally classic; occult) differed substantially between studies. The CS mentions that type of CNV can influence visual and anatomic outcomes of anti-VEGF treatment, but the CS does not elaborate on the implications for the NMA. One of the EAG clinical advisors considers the different types to broadly all respond the same way. Although there are subgroups called retinal angiomatosis proliferation and polypoidal choroidal vasculopathy that are more resistant to treatment, these subgroups may have been excluded from the trials.

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- **Treatment history**. Five of the 22 trials reported the proportion of anti-VEGF-experienced patients. In general, only a relatively small percentage of patients had been previously treated (<15%) in these studies. This included the NORSE TWO trial (3.9% patients had anti-VEGF previously). Two notable outliers, however, were the PEIR[6 7] and MARINA trials[13 14] (comparing different dosing regimens of ranibizumab versus sham injections). The proportion of previously treated patients in these trials was 56% to 57.8%. The CS does not discuss the likely implications for the results of the NMA, though in response to EAG clarification question A13 the company discuss differences between treatment naïve and treatment experienced patients. They cite literature suggesting that pre-treated nAMD patients have lower effect sizes than treatment-naïve patients. Clinical expert advice to the EAG is that patients who have had previous treatment and are then switched to another agent are more resistant to treatment. Mostly, there is an anatomical improvement by switching but usually not a visual acuity improvement.

- **Baseline visual acuity.** Reported by all studies; mean score per study ranged between 50.6 and 66.6 letters. In NORSE 2 the mean score was at the lower end of the range (51.6%).

Based on the above, the company concludes “Despite some noted variation between trials, the included studies were deemed to be broadly comparable” (CS appendix D, page 84). The EAG acknowledges there is uniformity across studies in some patient characteristics such as age, baseline visual acuity, and treatment history, but differences between studies in factors such sex, type of CNV lesion and race/ethnicity. For other factors such as BMI it is unclear whether there were differences between trials due to lack of reporting in study publications. The EAG’s expert clinical advisers mentioned additional prognostic factors not explicitly discussed by the company in relation to the NMA. These include early referral and timeliness of treatment, compliance with treatment, smoking (detrimental) and underlying fibrosis. These additional prognostic factors were not reported in the CS and therefore we do not know what impact they may have on the NMA.

EAG comment on heterogeneity/similarity

The EAG doesn’t share the company’s conclusion of “broad comparability of the trials”. Our view is that the included evidence is mixed, with some similarities, some differences and some unknowns. The implications for the NMA findings are not always clear.

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4.3.4 Risk of bias assessment for studies included in the NMA

CS Appendix D1.2 Table 0-15 reports the results of a quality assessment/risk of bias assessment of the methods used by the trials included in the NMA. The company used the criteria recommended by NICE in the evidence submission template, adapted from criteria devised by the Centre for Reviews and Dissemination at the University of York.

CS Table 0-15 presents the company's responses to each of the 7 critical appraisal questions for each of the 22 studies included in the NMA. The response categories for each question were 'Yes', 'No', 'Unclear' or 'NR' (the EAG presumes NR means 'Not reported'). There is no accompanying narrative description or summary of the results, nor are there any notes or comments explaining the choice of response.

It has not been feasible for the EAG to conduct an independent critical appraisal of all 22 studies for comparison with the company. From the EAG's examination of the company's responses (CS Table 0-15), it appears that the trials fulfilled most of the critical appraisal criteria and could be cautiously considered at low risk of bias generally. However, there were several 'unclear' responses, presumably because trial publications omitted relevant methodological information and/or ambiguity in the trial publications preventing informed judgements. The EAG is slightly concerned by the number of 'unclear' responses given to question 1 ("Was the method used to generate random allocations adequate?") (n=5 of 22 trials). Our concern increases at the 8 (of 22) trials with an 'unclear' response and the 3 trials with a 'No' response to question 2 ("Was the allocation adequately concealed?"). Both questions 1 and 2 assess the likelihood of selection bias (i.e. biased allocation of participants to interventions due to inadequate generation of a randomised sequence / inadequate concealment of allocations before assignment). Presence of selection bias is a serious threat to the internal validity of scientific studies. Responses to question 3 ("Were the groups similar at the outset of the study in terms of prognostic factors, e.g. severity of disease?") were more encouraging – a 'yes' response was given to all but one study. This suggests that randomisation and allocation concealment may not have been compromised and therefore the studies not necessarily at increased risk of selection bias.

Responses to question 4 ("Were the care providers, participants and outcome assessors blind to treatment allocation?") were notably mixed, a 'yes' response was made for 8 studies, an 'unclear' response given to 5 trials, and a 'no' response for the remaining 7 trials. The company's responses given to questions 5 to 7 (covering attrition, selective reporting, and intention to treat analysis, respectively) were generally favourable and give little cause for concern.

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EAG comment on the studies included in the NMA

Even though, generally, the trials appear to be at low risk of bias (based on the company's critical appraisal judgments) the EAG urges a degree of caution in the interpretation of the NMA findings given that some of the critical appraisal judgments remain unclear.

4.3.5 Statistical methods of the NMA

The company conducted a Bayesian NMA using the *multinma* package in R. As noted in Figure 1, the evidence network was constructed around the common comparator ranibizumab 0.5mg Q4W. Non-informative priors were used for the treatment effects and between-study standard deviation. The company conducted a scenario analysis excluding the two outlier studies exclusively in Asian patients. This is appropriate because people from certain parts of Asia (Southeast Asia, China and Japan) have a less favourable prognosis.

4.3.6 Choice between random effects and fixed-effect model

The company fitted both random effects and fixed-effect NMA models and observed the deviance information criterion (DIC) statistics and the total residual deviance to determine model goodness of fit (Company NMA report, appendix F). Due to "anticipated heterogeneity" across the studies the company opted to report NMA results based on random effects models. The results of fixed-effect models are not reported in CS Document B or Appendices, but are available in the NMA report. Model fit, in terms of DIC, between fixed and random effects models "did not differ meaningfully" (NMA report, section 6) supporting the company's preference for random effects in order to be conservative.

EAG comment on the statistical methods used in the NMA

The company appropriately followed a standard Bayesian statistical approach to conduct the NMA, and the model parameters selected are appropriate for the evidence available. The reporting of the NMA methods and results is transparent.

4.3.7 Data inputs to the NMA

Data inputs to the NMA are reported in the separate NMA report, section 5. These include number of patients, mean change from baseline values (e.g. in BCVA) and accompanying standard deviations and standard errors, per study arm, per time point. For dichotomous outcomes input data included number of patients achieving the relevant outcome.

The CS reports there was substantial missing data for standard deviation values for the outcome of BCVA (at 3, 6, 9, and 12 months) and CVT (at 12 months). This necessitated

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imputation of BCVA for 13 studies and CVT for 12 studies, which is likely to have led to an underestimation of uncertainty across these endpoints.

The company noted the response data for the sham injection arms of the PIER and MARINA trials were lower than for the other treatments for the proportion of patients gaining or losing 15 letters. Whether these differences could be attributed to random variation or differences in the populations is uncertain. However, as MARINA reported less favourable event rates compared to PIER it would appear that higher relative treatment effects for the sham vs ranibizumab 0.5mg Q4W vs sham vs ranibizumab 0.5mg Q12W arms would be conservative for bevacizumab gamma.

4.3.8 Summary of EAG critique of the NMA

The NMA was conducted using standard statistical methods and assumptions, and was informed by a comprehensive systematic literature review. It is unlikely that any relevant studies were missed by the search. The company conducted a comprehensive feasibility assessment to inform the planning of the systematic review. This identified clinical heterogeneity in the network resulting in uneven distribution of certain prognostic factors across the trials.

The studies were judged as being at low risk of bias overall, but in a number of instances a complete critical appraisal was not possible due to lack of detail in trial publications. Substantial missing outcome data resulted in heavy reliance on statistical imputation in the NMAs.

Low event proportions in the sham arms of PIER and MARINA contributed to unstable estimates of relative treatment effects of bevacizumab gamma to other competing interventions.

4.4 Results of the NMA

Below we present a summary of the results of the NMA. For some outcomes, such as mean change in BCVA, results were reported at multiple timepoints (i.e. 3, 6, 9 and 12 months). For brevity we present results for the final timepoint only (i.e. 12 months). More detailed results are available in the CS and the NMA report.

We summarise the ‘original’ NMA results as presented in the CS; these are prior to an update to the NMA during this NICE appraisal to include the NORSE ONE trial. We highlight instances where the NMA results differ in the updated analysis. Where reference is made to

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statistical significance this is based on the credible intervals. All results are based on random effects models unless stated otherwise.

As mentioned in the CS, caution is advised in the interpretation of the results, particularly for continuous outcomes such as visual acuity, due to the reliance on imputation of missing data for measures of dispersion.

4.4.1 Mean change in BCVA at 12 months

- Bevacizumab gamma 1.25mg Q4W demonstrated a statistically greater mean difference in BCVA at 12 months when compared to ranibizumab (RAN) 0.5mg Q12W and SHAM.
- No differences were observed between bevacizumab gamma 1.25 Q4W and any other treatments
- The findings do not change under the fixed-effect model.
- The results of the updated NMA (with the addition of NORSE ONE) were similar except that bevacizumab gamma was no longer statistically superior to RAN 0.5mg Q12W.
- The results of sensitivity analysis which removed studies including Asian patients only were similar to the base case results.

4.4.2 Proportion of patients gaining at least 15 letters at 12 months

- There was a statistically larger proportion of patents gaining at least 15 letters, favouring bevacizumab gamma 1.25mg Q4W compared to RAN 0.5mg Q12W.
- When expressed as odds ratios relative to ranibizumab 0.5 mg Q4W (the central comparator in the network), none of the treatments were statistically superior to RAN 0.5 mg Q4W.
- Under the fixed-effect model
- The results of the updated NMA (with the addition of NORSE ONE) were similar except that bevacizumab gamma was no longer statistically superior to RAN 0.5mg Q12W
- The conclusions of the base case analysis did not change under the sensitivity analysis removing studies including Asian patients only.

4.4.3 Proportion of patients losing less than 15 letters at 12 months

- There was a statistically larger proportion of patents losing fewer than 15 letters at 12 months among bevacizumab gamma 1.25mg Q4W patients compared to patients on SHAM.
- Under the fixed-effect model there was also statistical superiority for bevacizumab gamma compared to RAN 0.5mg Q12W in proportion of patents losing fewer than 15 letters at 12 months.

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- The results of the updated NMA (with the addition of NORSE ONE) were similar.

4.5 Critique of the Matched Adjusted Indirect Comparison (MAIC)

The unanchored matching adjusted indirect comparison (MAIC) method is used for pairwise indirect treatment comparison between single arms from different studies. Data used to inform the company's MAIC are:

- The bevacizumab gamma arm of NORSE TWO for the company base case;
- pooled bevacizumab arms of NORSE ONE and TWO, and of NORSE ONE (treatment-naïve population) and NORSE TWO for the two company sensitivity analyses; and
- summary data for the selected comparator trials of aflibercept, faricimab and ranibizumab.

However, as the NICE Decision Support Unit (DSU) Technical Support document 18 (Methods for population-adjusted indirect comparisons in submissions to NICE) cautions,[15] there is an assumption in an unanchored MAIC that absolute outcomes can be predicted from the covariates. This means that it is assumed that all effect modifiers and prognostic factors are accounted for, but in practice this very strong assumption is usually considered impossible to meet. The failure to meet this assumption leads to an unknown amount of bias in the unanchored estimate.

CS document B section 3.9.4 and CS Appendix D1.3, company clarification responses A9, A11 and A13 and the CS MAIC Report provide details relating to the series of MAICs carried out for this appraisal. Results of the company sensitivity analyses are reported in the CS MAIC Report and company clarification response A13 only.

4.5.1 Rationale for MAIC

In response to a clarification question (A9) the company elaborated on the rationale for conducting a MAIC, namely:

- To conduct an analysis which could overcome the problem that no robustly connected network was available to tie ONS-5010 to the rest of the comparator network (in this case no multilevel network meta-regression would be possible), and
- To perform an analysis without the assumptions that the sham arms in PIER and MARINA are equivalent, and to get around the very low event rates in placebo arms which added uncertainty to the NMA.

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4.5.2 Selection of studies for the MAICs

Bevacizumab gamma

The company's preferred source of individual patient data for bevacizumab gamma is the NORSE TWO trial (company clarification response A13). However, the EAG consider that NORSE ONE trial is also a relevant additional source of individual patient data for bevacizumab gamma for the MAICs. Following request by the EAG (clarification question A13), the company carried out **two sensitivity analyses** using individual patient data from:

- the pooled bevacizumab arms of NORSE ONE and TWO
- the pooled bevacizumab gamma arms of NORSE ONE (treatment-naïve population) and NORSE TWO.

Comparator trials

CS Appendix D 1.3 describes the selection of comparator studies for the MAICs. For each comparator the company selected a reference trial, or pooled set of trials. Where applicable the selected trial was the primary trial used in prior NICE technology appraisals. Overall, there were 10 main comparators. In addition, data from the HARBOR trial was used as a sensitivity analysis for RAN 0.5mg Q4W. The list of comparators and the selected trials are shown in Table 6 below:

Table 6 Selected comparator trials for the MAICs

Comparator	Selected comparator trial(s)
Afilbercept 2mg Q8W	VIEW 1/VIEW 2 [TA294]
Aflibercept 2mg TREX	RIVAL
Faricimab 6mg Q12W	STAIRWAY
Faricimab 6mg Q16W	STAIRWAY
Faricimab 6mg Q8W-Q16W	LUCERNE/TENAYA [TA800]
Ranibizumab 0.5mg TREX	TREND
Ranibizumab 0.5mg PRN	CATT
Ranibizumab 0.5mg Q8W	In-EYE
Ranibizumab 0.5mg PRN loading	HARBOR
Ranibizumab 0.5mg Q4W	MARINA [TA155]
Ranibizumab 0.5mg Q4W	HARBOR (sensitivity analysis only)

Source: Partly reproduced from CS document B Table 3-16, CS MAIC report Appendix C
PRN, pro re nata dosing regimen; Q4W, one injection every 4 weeks; Q8W, one injection every 8 weeks; Q12W, one injection every 12 weeks; Q16W, one injection every 16 weeks; TA, NICE Technology Appraisal; TREX, treat-and-extend dosing regimen

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CS document B Table 3-16 provides the names of the selected trials, and of other trials evaluating the same comparators that were not selected for the MAICs.

The EAG considers the appropriate comparator trials were selected for the MAICs.

4.5.3 Identification of prognostic factors and treatment effect modifiers to be included in the MAIC

CS Appendix D.1.3 and CS Appendix D.1.3 Table 0-18 lists prognostic factors and treatment effect modifiers. These included patient characteristics (e.g. age, sex, race); disease related characteristics (e.g. BCVA, lesion size, retinal thickness); medical history (e.g. history of smoking, history of arterial thromboembolic events). References were only provided for BCVA, age, sex and race (CS Appendix D.1.3 Table 0-18). The EAG found that one of these references, a review by Phan et al., 2021,[16] provided information for some of the other prognostic factors and treatment effect modifiers listed. Appendix 1, Table 18 (in this report) provides a comparison of prognostic factors identified in the review by Phan et al., 2021,[16] with factors listed in the CS MAIC Report, and their inclusion status in the MAIC.

Of the prognostic factors and treatment effect modifiers identified, only four had data available to enable them to be included in the MAICs for the purpose of matching patients from NORSE TWO (and pooled bevacizumab arms of NORSE ONE and TWO, and of NORSE ONE (treatment-naïve population) and NORSE TWO for the company sensitivity analyses) to the comparator trials. In order of matching (CS Appendix D Table 0-18), these were:

- BCVA at baseline
- Age at baseline
- Sex
- Race

Considering the justifications for including each variable in the MAICs in CS Appendix D Table 0-18, the EAG agrees that BCVA at baseline should be matched first followed by age at baseline. However, the EAG believes that the justification for race and sex, alongside EAG clinical expert opinion, would support race being matched next followed by sex last.

CS Appendix D Table 0-17 shows the baseline characteristics for studies included in the MAICs except for the pooled bevacizumab arms of NORSE ONE and TWO, and of NORSE ONE (treatment-naïve population) and NORSE TWO used in the company sensitivity analyses. A revised and more complete version of this table is CS MAIC Report Table 2 2.

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CS Appendix D1.3 states that all selected studies had data for the four selected prognostic factors and treatment effect modifiers included in the MAICs i.e. BCVA at baseline, age at baseline, sex, and race. However, according to CS MAIC Report Table 2.2, one selected study of ranibizumab (In-EYE), does not report data on sex and race. The EAG examined the references for this study and found data on sex but not race.[17] The EAG note this study was carried out in Spain.

4.5.4 Statistical methods for the MAIC

Statistical methods for the MAICs are detailed in CS Appendix D1.3 and appear to follow guidance from NICE Decision Support Unit (DSU) Technical Support document 18 (Methods for population-adjusted indirect comparisons in submissions to NICE).[15]

The MAICs were built using R software, and the programming code was supplied to the EAG (company clarification response A11).

4.5.5 Planned analyses comparing bevacizumab gamma to aflibercept, faricimab and ranibizumab

CS Appendix D Table 0-19 reports outcomes analysed for the MAICs were:

- Mean change in BCVA from baseline at 3 months, 6 months, 9 months and 12 months,
- Gain of ≥5 letters, ≥10 letters and ≥15 letters,
- Loss of <15 letters,
- Ocular adverse events

4.5.6 Comparison of weighted-bevacizumab gamma and comparator patient characteristics

Number of matching variables used

The EAG considers that all selected studies for the MAICs had data for all four matching variables (BCVA, age at baseline, sex and race), with the exception of one study of RAN 0.5mg Q8W (In-EYE), which had data for three matching variables (section 4.5.3).

However, Table 7 below shows there was inconsistency in the number of matching variables used in the MAICs across the different comparisons:

- all four variables for 5 main comparisons and the sensitivity analysis of RAN 0.5mg Q4W)

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- three variables (BCVA at baseline, age at baseline and race) for three comparisons (faricimab 6mg Q12W, faricimab 6mg Q16W, and RAN 0.5mg treat-and-extend (TREX)). It is unclear to the EAG why sex was omitted from the matching procedure and what the effect of including sex would be on the results of the three MAICs.
- two variables (BCVA at baseline and age and baseline) for one comparison (RAN 0.5mg Q8W). As mentioned in section 4.5.3 above, there was ambiguity within the CS as to whether sex and race were reported for this study. The EAG considers that data were available for sex but not race. Again, it is unclear to the EAG what the effect of matching on sex would be on the results of the MAIC.
- one variable (best-corrected visual acuity) for one comparison (aflibercept 2mg TREX). The company report that matching on the other variables did not converge.

Effective sample size

The effective sample size post-matching varied across comparisons (Table 7), ranging from 7.08% to 93.18% of patients receiving bevacizumab gamma in NORSE TWO (CS Appendix D Tables 0-20 to 0-39), 38.57% to 97.94% of the pooled number of patients receiving bevacizumab gamma in NORSE ONE and NORSE TWO (CS MAIC Report section 9); and 13.74% to 96.91% of the pooled number of patients receiving bevacizumab gamma in NORSE ONE (treatment-naïve population) and NORSE TWO (CS MAIC Report section 10).

Distribution of weights

For the majority of comparisons, the distribution of weights were at least somewhat skewed and had at least several large outliers (Table 7). Only two comparisons, RAN 0.5mg PRN loading and RAN 0.5mg Q4W, had no outliers. These two comparisons also had the highest effective sample sizes post matching (>90%).

Table 7 Matching variables used, distribution of rescaled weights and effective sample size after matching

Comparator	Matched variables	Effective Sample Size %	Distribution of rescaled weights
Afilbercept 2mg Q8W (VIEW 1/VIEW 2)	4[a]	45.36[b], 58.72[c], 52.58[d]	Skewed[b,c,d]; >5 large outliers[b,c,d]
Aflibercept 2mg TREX (RIVAL)	1[e]	14.27[b], 41.42[c], 18.77[d]	Skewed[b,c,d] Several large outliers[b,c,d]
Faricimab 6mg Q12W (STAIRWAY)	3[f]	43.91[b], 81.23[c], 54.30[d]	Somewhat skewed[b,c,d]; Several large outliers[b,c,d]

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Comparator	Matched variables	Effective Sample Size %	Distribution of rescaled weights
Faricimab 6mg Q16W (STAIRWAY)	3[f]	43.91[b], 81.23[c], 54.30[d]	Somewhat skewed[b,c,d]; Several large outliers[b,c,d]
Faricimab 6mg Q8W-Q16W (LUCERNE/TENAYA)	4[a]	11.53[b], 39.56[c], 20.51[d]	Very skewed[b,c,d] >10 very large outliers[b,c,d]
Ranibizumab 0.5mg TREX (TREND)	3[f]	17.18[b], 50.22[c], 25.88[d]	Skewed[b,c,d] Several large outliers[b,c,d]
Ranibizumab 0.5mg PRN (CATT)	4[a]	7.08[b], 38.57[c], 13.74[d]	Very skewed[b,c,d] >10 very large outliers[b,c,d]
Ranibizumab 0.5mg Q8W (In-EYE)	2[g]	28.38[b], 66.99[c], 38.81[d]	Somewhat skewed[b,c,d]; >5 large outliers[b,c,d]
Ranibizumab 0.5mg PRN loading (HARBOR)	4[a]	93.18[b], 97.94[c], 96.91[d]	Somewhat skewed[b,c,d] No outliers[b,c,d]
Ranibizumab 0.5mg Q4W (MARINA)	4[a]	85.78[b], 94.65[c], 91.49[d]	Symmetrical[b,c,d] None[b,c,d]
Ranibizumab 0.5mg Q4W (HARBOR)[h]	4[a]	78.50[b,i]	Not reported

Source: Partly reproduced from CS document B Table 3-16, CS Appendix D Tables 0-20 to 0-39, CS Appendix D Figures 0-14 to 0-23, and CS MAIC Report sections 8, 9 and 10
PRN, pro re nata dosing regimen; Q4W, one injection every 4 weeks; Q8W, one injection every 8 weeks; Q12W, one injection every 12 weeks; Q16W, one injecton every 16 weeks; TREX, treat and extend
[a] Best-corrected visual acuity at baseline, age at baseline, sex and race; [b] of patients receiving bevacizumab gamma in NORSE TWO; [c] of the pooled number of patients receiving bevacizumab gamma in NORSE ONE and NORSE TWO; [d] of the pooled number of patients receiving bevacizumab gamma in NORSE ONE (treatment-naïve population) and NORSE TWO; [e] matched on best-corrected visual acuity at baseline only as matching on further characteristics did not converge; [f] Best-corrected visual acuity at baseline, age at baseline, and race only; [g] Best-corrected visual acuity at baseline and age at baseline only; [h] comparator sensitivity analysis; [i] MAIC not reported for bevacizumab gamma sensitivity analyses.

4.5.7 Summary of EAG critique of the MAIC

It is unclear whether the MAICs was conducted correctly for four of the ten main comparisons. For three of these comparisons matching was only performed for three of the four variables for which data were available, and for one comparison for two of three variables for which data were available. The principle of including all prognostic factors and treatment effect modifiers in the analysis has not been met and cannot be met because of the limited information on baseline characteristics for the bevacizumab gamma and comparator studies. However, if it had been possible to match more baseline characteristics the reduction in effective sample sizes would likely have been greater. The severe

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limitations of the MAICs should be considered when viewing the results in section 4.3.8 below.

4.5.8 Results of the MAIC

Of the outcomes analysed (section 4.5.5), the following were available for all comparisons:

- Mean change in BCVA from baseline at 12 months
- Proportion of patients gaining at least 15 letters
- Proportion of patients losing fewer than 15 letters

These three outcomes are the same outcomes as those reported for the NMA in CS section 3.9.4. The EAG therefore focuses on the results of the MAICs for these outcomes only.

For each comparison, the company report relative treatment effect estimates for the unweighted generalised linear model (GLM), weighted GLM and bootstrapped GLM (CS document B section 3.9.4, CS MAIC Report section 3 and appendices D and E). Although not explicitly stated, the reporting of results in CS section B.3.9.4 and the CS MAIC Report suggest the company consider the weighted GLM to be the primary analysis. However, the EAG consider that the bootstrapped GLM gives the most reliable estimate of uncertainty. As such, Table 8 and Table 9 below report the results of the bootstrapped GLM in terms of whether the comparison of bevacizumab gamma against the specified comparator shows:

- a statistically significant difference in favour of bevacizumab gamma, denoted as “favoured”, i.e. confidence intervals for the relative treatment effect estimates exclude zero (for mean difference) or one (for odds ratio) in favour of bevacizumab gamma.
- a statistically significant difference in favour of the specified comparator, denoted as “disfavoured”, i.e. confidence intervals for the relative treatment effect estimates exclude zero (for mean difference) or one (for odds ratio) in favour of the comparator.
- or no statistical difference, denoted as “no difference”, i.e. confidence intervals for the relative treatment effect estimate exclude zero (for mean difference) or one (for odds ratio)

These tables also indicate whether the relative treatment effect estimate of the weighted GLM, unweighted GLM and NMA random effects model results were inconsistent with that of the bootstrapped GLM. A summary for each of the three outcomes is also given below:

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Mean change in BCVA from baseline at 12 months

Of the 10 main comparisons, bevacizumab gamma 1.25mg Q4W demonstrated a statistically greater mean change in BCVA from baseline at 12 months for aflibercept 2mg TREX, faricimab 6mg Q12W, faricimab 6mg Q16W and for all dose regimens of ranibizumab. It should be noted that these findings were inconsistent with the results of NMA random effects model, which found no difference.

The results of the sensitivity analyses using pooled data from NORSE ONE and TWO were similar with the exception that there was no longer a difference between bevacizumab gamma and faricimab 6mg Q12W and faricimab Q16W. This was consistent with the results of NMA random effects model.

Sensitivity analyses using pooled data from NORSE ONE (treatment-naïve population) and NORSE TWO were also similar with the exception that there was no longer a difference between bevacizumab gamma and faricimab 6mg Q12W, and now faricimab 6mg Q16W demonstrated a statistically greater mean change in BCVA from baseline at 12 months compared to bevacizumab gamma. The latter finding is inconsistent with the results for the weighted and unweighted GLM of the MAIC, and the results of NMA random effects, which all found no difference.

Proportion of patients gaining at ≥15 letters

A statistically larger proportion of patients gaining at least 15 letters, favouring bevacizumab 1.25mg Q4W compared to RAN 0.5mg PRN loading dose and RAN 0.5mg Q4W only. These findings were inconsistent with the results of NMA random effects model, which found no difference.

The results of the sensitivity analyses using pooled data from NORSE ONE and TWO were similar with the exception that there was no longer a statistical difference between bevacizumab 1.25mg Q4W compared to RAN 0.5mg PRN loading dose and to RAN 0.5mg Q4W only. Furthermore, a statistically larger proportion of patients gaining at least 15 letters now favoured faricimab 6mg Q16W compared to bevacizumab gamma 1.25mg Q4W. This latter finding was inconsistent with the results for the weighted and unweighted GLM of the MAIC, and the results of NMA random effects, which all found no difference.

Sensitivity analyses using pooled data from NORSE ONE (treatment-naïve population) and NORSE TWO found no difference between bevacizumab gamma 1.25mg Q4W compared to all comparators except RAN 0.5mg PRN loading dose. This result was inconsistent with the

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NMA random effects model, which found no difference between bevacizumab gamma 1.25mg Q4W compared to RAN 0.5mg PRN loading dose.

Proportion of patients losing < 15 letters

There was a statistically larger proportion of patents losing fewer than 15 letters at 12 months among bevacizumab 1.25mg Q4W patients compared to all comparators except faricimab 6mg Q12W as the model did not converge, and RAN 0.5mg PRN, which found no difference. The odds ratios for all comparisons were large with extremely wide confidence intervals.

The results of both sensitivity analyses (using pooled data from NORSE ONE and TWO and using pooled data from NORSE ONE (treatment-naïve population) and NORSE TWO) were similar with the exception that the model additionally did not converge for the comparison to faricimab 16mg Q16W.

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Table 8 Results of MAICs comparing bevacizumab gamma to aflibercept and to faricimab

Comparator	**Aflibercept 2 mg Q8W**	**Aflibercept 2 mg TREX**	**Faricimab 6 mg Q12W**	**Faricimab 6 mg Q16W**	**Faricimab 6 mg Q8-Q16W**
Comparator trial	VIEW 1/ VIEW 2	RIVAL	STAIRWAY	STAIRWAY	LUCERNE/ TENAYA
NORSE TWO ONLY (COMPANY BASE CASE) - Bootstrapped GLM results					
ESS%	45.36	14.27	43.91	43.91	11.53
BCVA CFB – 11/12 months[a]	No difference[e]	Favoured[d,f]	Favoured[d,e,f]	Favoured[d,e,f]	No difference[e]
Gain ≥15 letters[b]	No difference[e]	No difference[e]	No difference	No difference	No difference[e]
Lose <15 letters[b]	Favoured[c,e,f]	Favoured[c,d,e,f]	DNC	Favoured[c,d,e,f]	Favoured[c,e,f]
POOLED NORSE ONE AND TWO (COMPANY SENSITIVITY ANALYSIS) - Bootstrapped GLM results					
ESS%	58.72	41.42	81.23	81.23	39.56
BCVA CFB – 11/12 months[a]	No difference	Favoured[d,f]	No difference	No difference	No difference[e]
Gain ≥15 letters[b]	No difference	No difference[e]	No difference	**Disfavoured**[d,e,f]	No difference[e]
Lose <15 letters[b]	Favoured[c,e,f]	Favoured[c,d,e,f]	DNC	DNC	Favoured[c,e,f]
POOLED NORSE ONE (treatment-naïve only) AND NORSE TWO (COMPANY SENSITIVITY ANALYSIS) - Bootstrapped GLM results					
ESS%	52.28	18.77	54.30	54.30	20.51
BCVA CFB – 11/12 months[a]	No difference	Favoured[d,f]	No difference	**Disfavoured**[d,e,f]	Favoured[d,f]
Gain ≥15 letters[b]	No difference[e]	No difference[e]	No difference	No difference	No difference[e]
Lose <15 letters[b]	Favoured[c,e]	Favoured[c,d,e]	DNC	DNC	Favoured[c,d,e]

Source: Partly reproduced from CS MAIC Report sections 3, 8, 9 and 10; CS SLR-NMA Technical Report sections 5.1.4, 5.2, 5.3, 9.1.4, 9.2, 9.3,10.1.4, 10.2, and10.3
BCVA, best corrected visual acuity; CFB, change from baseline; Disfavoured, confidence intervals exclude 0 (mean difference) or 1 (odds ratio) in favour of the specified comparator; DNC, did not converge ; ESS, effective sample size; Favoured, confidence intervals exclude 0 (mean difference) or 1 (odds ratio) in favour of bevacizumab gamma; GLM generalised linear model; No difference, no statistically significant difference between bevacizumab gamma and the specified comparator; Q8W, one injection every 8 weeks; Q12W, one injection every 12 weeks; Q16 W, one injection every 16 weeks; Q8-16W, one injection every 8 to 16 weeks; TREX, treat-and-extend dosing regimen

[a] *Relative effect measure mean difference;* [b] *relative effect measure odds ratio;* [c] *estimate highly unstable due to comparing values above 95% in both groups;* [d] *inconsistent with weighted GLM result* [e] *inconsistent with unweighted GLM result;* [f] *inconsistent with NMA random effects model result;* [g] *NMA not carried out for this outcome*

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Table 9 Results of MAICs comparing bevacizumab gamma to ranibizumab

Comparator	Ranibizumab 0.5 mg TREX	Ranibizumab 0.5 mg PRN	Ranibizumab 0.5 mg Q8W	Ranibizumab 0.5 mg PRN loading	Ranibizumab 0.5 mg Q4W	Ranibizumab 0.5 mg Q4W (sensitivity analysis)
Comparator trial	TREND	CATT	In-EYE	HARBOR	MARINA	HARBOR
NORSE TWO ONLY (COMPANY BASE CASE) - Bootstrapped GLM results						
ESS%	17.18	7.08	28.38	93.18	85.78	78.50
BCVA CFB – 11/12 months[a]	Favoured[d,f]	Favoured[d,f]	Favoured[f]	Favoured[f]	Favoured[f]	No difference
Gain ≥15 letters[b]	No difference[e]	No difference[e]	No difference[e]	Favoured[f]	Favoured[d,e,f]	No difference
Lose <15 letters[b]	Favoured[c,d,e,f]	No difference[c]	Favoured[c,d,e,f]	Favoured[c,d,e,f]	Favoured[c,d,e,f]	No difference[c]
POOLED NORSE ONE AND TWO (COMPANY SENSITIVITY ANALYSIS) - Bootstrapped GLM results						
ESS%	50.22	38.57	66.99	97.94	94.65	N/A
BCVA CFB – 11/12 months[a]	Favoured[d,f]	Favoured[d,f]	Favoured[f]	Favoured[f]	Favoured[f]	N/A
Gain ≥15 letters[b]	No difference[e]	No difference[e]	No difference[e]	No difference	No difference	N/A
Lose <15 letters[b]	Favoured[c,f]	Favoured[c,e,f]	Favoured[c,e,f]	Favoured[c,d,e,f]	Favoured[c,e,f]	N/A
POOLED NORSE ONE (treatment-naïve only) AND NORSE TWO (COMPANY SENSITIVITY ANALYSIS) - Bootstrapped GLM results						
ESS%	25.88	13.74	38.81	96.91	91.49	N/A
BCVA CFB – 11/12 months[a]	Favoured[f]	Favoured[e,f]	Favoured[f]	Favoured[f]	Favoured[f]	N/A
Gain ≥15 letters[b]	No difference[e]	No difference[e]	No difference[e,]	Favoured[f]	No difference	N/A
Lose <15 letters[b]	Favoured[c,e,g]	Favoured[c,d,e,g]	Favoured[c,e,g]	Favoured[c,d,e,g]	Favoured[c,d,e,g]	N/A

Source: Partly reproduced from CS MAIC Report sections 3, 8, 9 and 10; CS SLR-NMA Technical Report sections 5.1.4, 5.2, 5.3, 9.1.4, 9.2, 9.3,10.1.4, 10.2, and 10.3
BCVA, best corrected visual acuity; CFB, change from baseline; disfavoured, a statistically significant difference in favour of the specified comparator; DNC, did not converge; ESS, effective sample size; Favoured, a statistically significant difference in favour of bevacizumab gamma; GLM generalised linear model; No difference, no statistically significant difference between bevacizumab gamma and the specified comparator; PRN, pro re nata dosing regimen; Q4W, one injection every 4 weeks; Q8W, one injection every 8 weeks; TREX, treatment and extend dosing regimen

[a] *Relative effect measure mean difference;* [b] *relative effect measure odds ratio;* [c] *estimate highly unstable due to comparing values above 95% in both groups;* [d] *inconsistent with weighted GLM result* [e] *inconsistent with unweighted GLM result;* [f] *inconsistent with NMA random effects model result;* [g] *NMA not carried out for this outcome*

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5 COST COMPARISON

5.1 EAG critique of the company's cost comparison

5.1.1 Model structure and assumptions

The structure of the company's cost-comparison model is illustrated in CS B.4.2.2 Figure 4-1. The structure is consistent with that in the faricimab appraisal (TA800).[4] The EAG agrees that this structure is appropriate.

CS section B.4.2.11 includes a list of model assumptions used in the company's base case analysis. The assumptions mean that the only differences between treatments that impact on the incremental cost estimates are the dosing frequency and drug prices. This is consistent with the opinion of clinical experts advising the EAG, who stated that the drugs have similar effects on visual acuity, but that they differ in the durability of effect (interval between injections).

We note that the model does not allow for switching between treatments, the company state that switching is unusual (response to clarification question A5). However, clinical experts advised that treatment switching is common (estimated at around 50% in the long term), due to drug side effects or the need to extend the interval between treatments. The EAG note that the TA800 cost-comparison model for faricimab also omitted consideration of treatment sequencing and switching. The impact of this on long-term incremental treatment costs is uncertain.**Key features of the cost analysis**

Features of the cost analysis are defined in CS B.4.2.1. We note the following issues:

Population: "adults (aged >18 years) eligible for first-line treatment of neovascular age-related macular degeneration" (CS Table 4-1) This is does not align with the license indication for bevacizumab gamma, the stated population in CS Table 1-1 or in the NICE scope, which do not specify eligibility for first-line treatment (see section 2.2.3 above). The company's model estimates costs from initiation of first-line anti-VEGF treatment and includes treatment discontinuation.

Comparators: Aflibercept, ranibizumab and faricimab. The EAG considers this to be acceptable. Aflibercept and ranibizumab were accepted comparators in the faricimab appraisal (TA800).[4] The company excluded brolucizumab on the basis of its low market share, and safety concerns (CS B.1.3), and clinical experts advising the EAG agreed that brolucizumab is rarely used in current practice.

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Perspective: The company state that the perspective for costing is that of the UK NHS and Personal Social Services (PSS). An NHS and PSS perspective is appropriate for the NICE Reference Case, but NICE does not have a remit for the whole UK[18]. However, the model actually uses NHS England unit costs (see section 5.1.7), which is appropriate.

Currency year: We note that the currency year specified in CS Table 4-1 (2024) is not accurate. In response to Clarification Question B3, the company corrected the statement in CS B.4.2.6 that costs were inflated to 2024 prices. The company's revised model uses the most recent sources that are available for costing (2024 for drugs and 2022/23 NHS Cost Collection for other resources). The EAG considers this to be appropriate.

We agree with other features of the analysis in CS Tables 4-1, including.

- **Time horizon**: effectively lifetime (maximum age 100 years)
- **Cycle length**: one-year with a half-cycle correction
- **Discounting**: 3.5% (as in TA800); scenario with no discounting (Table 14)

5.1.3 Patient characteristics

Parameters for the modelled patient population are shown in CS Table 4-3. We agree with the company's assumptions regarding baseline demographics, which were based on the population in NORSE TWO: starting age of 79 years (scenario 75 years) and 41% male.

5.1.3.1 Prevalence of bilateral disease

The company use a 7.3% prevalence of bilateral disease at baseline, derived from NICE guideline NG82, and accepted by the committees in TA800 and TA672. One of our clinical experts stated that this figure is high and suggested a value of less than 5%. We report a scenario using a baseline prevalence of bilateral disease of 5% (Table 15).

5.1.3.2 Incidence of bilateral disease

The company's model uses an annual incidence of bilateral disease of 1.39%, sourced from a UK AMD database that was reported in the NICE guideline (NG82). However, we note that NG82 (section 10.1.2.2.1) reports that 42% of patients develop nAMD in the fellow eye over 3 years, equating to a monthly incidence of 1.39% (as used in TA800), or an annual incidence of 14% (Zarranz-Ventura et al. (2014)).[1] An annual incidence of 14% is supported by clinical advice to the EAG, because both of our clinical experts commented that about 50% of patients develop bilateral disease by year five. We prefer to use an annual incidence of bilateral disease of 14% in our base case (Table 16).

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5.1.4 Mortality

The company assume equal mortality across treatment arms to reflect equivalent efficacy (CS B.4.2.4). The model uses general population mortality rates, adjusted for the cohort age and sex (ONS UK 2018-2020).[19] Although not the most recent data, the EAG consider this choice of year range to be appropriate, as it excludes peak Covid-19 pandemic period.

The company adjust the general population mortality rates to account for a higher risk of death in patients with nAMD: relative risk 1.09, based on a meta-analysis by Wang et al (2017).[20] The EAG notes excess mortality for people with nAMD was not applied in TA800, so we report a scenario RR=1 (Table 15).

5.1.5 Resource utilisation inputs

ealthcare resource inputs used in the company's base case are reported in CS Table 4-4.

5.1.5.1 Treatment dosing frequency

The key clinical driver of the model is treatment injection frequency (CS B.4.2.5). We note that the Year 1 and Year 2 treatment dosing frequencies for faricimab, aflibercept and ranibizumab are the same as those accepted in TA800, and that the Year 3+ dosing frequency matches the TA800 committee's preferred assumption (Table 10). The model applies the same dosing frequency for incident disease in the fellow eye (i.e. injections are more frequent in the first and second year after diagnosis of nAMD in the fellow eye than in subsequent years).

Table 10 Treatment dosing frequency per year

Treatment	Dosing frequency per year		
	Year 1	Year 2	Year 3+
Bevacizumab gamma	[redacted]	[redacted]	[redacted]
Faricimab	6.79	4.69	4.00
Aflibercept	8.00	5.63	4.00
Ranibizumab	9.13	7.14	4.00

Source: Partly reproduced from CS Table 4-4

In their base case, the company assumes that bevacizumab gamma [redacted]. The company conducted a scenario analysis with bevacizumab gamma [redacted] (Table 14). We also report an EAG scenario with the dosing frequency for bevacizumab gamma set to equal that of faricimab (Table 15).

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Clinical advice to the EAG is that the ranibizumab dosing schedule is more appropriate for bevacizumab gamma, as bevacizumab and ranibizumab are both 'first generation' anti-VEGF treatments that are less durable than aflibercept (second generation) and faricimab (third generation). The clinical experts commented that longer-acting treatments are needed to decrease the burden on both NHS resources and patients. They stated that as faricimab is the most durable of the current treatments, it is their preferred choice for first-line therapy in the NHS. If a patient does not respond to faricimab, the experts stated that they would use aflibercept as second-line treatment, but not ranibizumab as they would prefer to avoid older generation treatments. An expert also noted that as the higher 8 mg dose of aflibercept is now on the market, this would be considered as an alternative to faricimab to achieve a long interval between treatments.

The clinical experts also highlighted that the treat and extend approach is used in the NHS, but that as bevacizumab gamma has not been assessed in a treat and extend strategy, it is unlikely to be used in this way. We note the company's argument that the EMA and MHRA have accepted a treat-and-extend schedule for bevacizumab gamma, based on 'bridging evidence' from prior trials of repackaged, off-label Avastin® (CS B.4.6).

One of the clinical experts advising the EAG noted that in the Netherlands, bevacizumab is used for the loading doses, then treatment is switched to faricimab or aflibercept for the extend period. They suggested that UK commissioners may be receptive to this approach, although it is a new concept and not all specialists would agree.

5.1.5.2 Treatment discontinuation rate

The economic model uses an annual treatment discontinuation rate of 8.9%, which was originally used in NICE NG82 and accepted by the committee in TA800.[4 21]

One of the clinical experts who we consulted estimated that 10% of patients would discontinue treatment each year, which we test in a scenario analysis (Table 15). We also report scenarios with discontinuation rates of 5% and 13%, as tested by the TA800 EAG (see Table 15).

The clinical experts agreed that the discontinuation rate would be the same for all treatments, as the usual reason for discontinuation is that further treatment would be futile.

5.1.6 Drug acquisition costs

The company used drug acquisition costs for the comparators from the British National Formulary (BNF), shown in CS B.4.2.6 Table 4.5. We noted some discrepancies in some of

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the comparator vial sizes given in CS Table 4.5. The company checked these against the most recent BNF entries and corrected the vial sizes, as shown in their response to clarification question B1. This correction had no effect on the results of the economic model because the cost of each vial remained the same.

Bevacizumab gamma is available in the NHS with a confidential simple Patient Access Acheme (PAS) discount of [redacted], reducing the net price of £470 per 25mg/ml vial to [redacted]. The CS analyses use the PAS discount for bevacizumab and list price for comparator drugs. We report results with all available PAS and Medicines Procurement Supply Chain (MPSC) discounts, in a separate confidential addendum to this EAG report.

The EAG notes that the ranibizumab drug cost used in the model (£523.45 per vial) is calculated as an unweighted mean of the costs of the branded product (Lucentis) and biosimilars (Ongavia, Byooviz, Ranivisio, and Ximluci). The EAG prefers to use the lowest available cost for ranibizumab (i.e. Ximluci at £495.90 per 2.3mg/0.23ml vial).

Clinical advice to the EAG is that an 8mg formulation of aflibercept is now available in the NHS and its use is governed by clinician preference. However, data for the 8mg formulation for aflibercept is not presented in the cost-comparison model and our clinical experts thought it would provide a useful comparison.

5.1.7 Healthcare resource use and costs

Model inputs to estimate NHS resource use and costs are described in CS Table 4.6. The EAG considers that appropriate costing codes have been used:

- **Diagnostic testing**: weighted mean of HRG codes: RD30Z, RD31Z & RD32Z (Contrast Fluoroscopy Procedures with duration < 20, 20-40 and > 40 minutes), which is consistent with assumptions accepted in TA672 and TA800
- **Drug administration**: WF01A (non-consultant-led follow-up, Ophthalmology Service), as accepted in TA800
- **Monitoring**: HRG code: BZ88A (Retinal Tomography, 19 years and over); as accepted in TA800. The company assumes three monitoring visits per year for all treatments, based on clinical advice. The company explore an alternative monitoring strategy in a scenario analysis (Table 14).

The NHS costs cited in CS Table 4-6 are taken from the '2023/25 NHS Payment Scheme (amended)' (which has replaced the NHS National Tariff) (CS B.4.2.7). In response to clarification question B2, the company revised their model to include the most recent

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National Cost Collection data (National schedule of NHS costs 2022/23).[22] The EAG considers that this change is appropriate, as it reflects NICE guidance that 'reference costs' should be used for costing (NICE paragraph 4.4.9). Table 11 shows the unit costs that were used in the company's revised model.

The EAG were unable to confirm the new costs because, at the time of checking (04 Sept 2024), the 22/23 National Cost Collection data were unavailable. NHS England have removed the data due to data discrepancies.

Table 11 Updated costs used in the cost comparison model

Variable	Original costs used in the company submission	Costs used to address the clarification question
Drug administration	£69.00	£141.00
Diagnostic testing	£126.55	£218.99
Monitoring	£110.00	£158.00

Source: Partly reproduced from the company's response to clarification question B2, Table 2

These changes result in an increase in total costs of [redacted] for bevacizumab gamma; £2,558 for faricimab, £2,738 for aflibercept and £2,941 for ranibizumab. The impact on incremental costs is small (see Table 12).

The EAG notes that the costs for diagnostic testing and monitoring are the same for all treatments and so cancel out in incremental cost calculations.

Table 12 Cost results by category, company revised base case

Cost	Bevacizumab gamma	Faricimab	Aflibercept	Ranibizumab
Diagnostic testing	[redacted]	£246	£246	£246
Drug acquisition	[redacted]	£22,280	£23,300	£16,460
Drug administration	[redacted]	£3,479	£3,831	£4,229
Monitoring	[redacted]	£2,231	£2,231	£2,231
Total cost	[redacted]	£28,236	£29,608	£23,165
Incremental cost (bevacizumab gamma versus comparator)				
Revised base case	-	[redacted]	[redacted]	[redacted]
Original base case	-	[redacted]	[redacted]	[redacted]
Difference	-	[redacted]	[redacted]	[redacted]

Source: Partly reproduced from the company's response to clarification question B2, Table 3

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5.1.7.1 One-stop versus two-stop clinics

The company's economic model approximates a 'two-stop' clinical model (i.e. separate visits for treatment administration and monitoring). The model assumes that monitoring visits are equal across treatment arms, as specified by the TA800 committee. Our clinical experts noted that there is variation across the UK in use of one-stop and two-stop clinic models.

One of our clinical experts stated that their clinic operates a one-stop model, which requires a different staff mix: the scan is conducted by a trained technician/ophthalmic science practitioner; medical assessment is undertaken by a doctor or other specialist clinician; and the injection is usually delivered by a specialist nurse (doctors do around 20% of injections).

The company assume that patients have three monitoring visits per year, which is not appropriate for a one-stop model; as it assumes that treatment can be extended after 3 injections to 8 weeks, and then 12 week follow up, which is not achievable for all patients. The EAG clinical expert who operates with a two-stop clinic approach, thought that three monitoring visits would be the minimum number per year. Both experts suggested that 5 monitoring visits per year would be more realistic. The EAG notes that increasing the number of monitoring visits per year has no effect on the incremental costs, because monitoring costs are common to all comparators (Table 12).

5.1.7.2 Resource use for bilateral disease

The company assume that drug administration for bilateral disease costs 1.5 times the cost for unilateral disease, which is consistent with assumptions in TA672 and TA800. The EAG agree with this approach. Our clinical experts explained that if a patient has bilateral disease and the treatment cycle for the eyes is synchronised, both eyes are injected at the same clinic visit. The experts stated that a clinic visit for treatment of both eyes is not much longer than for treatment of one eye.

In contrast, if the disease develops in the eyes at different times, separate visits will often be required to accommodate different dosing schedules for each eye. The aim is to synchronise treatment after Year 1 or Year 2, depending on how the second eye responds. The EAG consider the company have modelled this appropriately.

The company use the same monitoring costs for unilateral and bilateral disease, which is in line with TA672. Monitoring costs are assumed to be the same for all treatments. Increasing monitoring costs to account for bilateral treatment would increase total costs but have no effect on incremental costs between bevacizumab gamma and comparators.

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5.1.8 Adverse reaction costs and resource use

The company do not include costs for treating adverse reactions (CS B.4.2.8). They justify this on the basis that no statistically significant or clinically significant differences in safety were observed in trials that compared bevacizumab gamma and ranibizumab (NORSE ONE, NORSE TWO, CATT and IVAN). This approach is consistent with TA800, where the committee accepted that the probability of adverse events was the same across all treatments and regimens, so safety is assumed to be equivalent. The EAG accept the assumption of identical adverse event rates between treatments for the purpose of costing.

5.2 EAG model checks

The company summarise their model validation approach in CS B.4.2.10. EAG checks of the company's cost-comparison model included: comparison of all parameter values against the CS and stated source; checking the calculations in the Excel spreadsheet; and double programming the model, i.e. we constructed a duplicate version to check it produced the same results.

We noticed a minor error in the way the half-cycle correction is applied: the drug acquisition, administration and monitoring costs in the last cycle were not halved in the company's model. However, the effect of this on the model results is negligible.

When using the original costs for diagnostic testing, treatment administration and monitoring in the company's revised base case, we were able to reproduce the original model results. We confirm that evidence sources and the values applied in the economic model are consistent with their original sources, with the exception of the incidence rate for bilateral disease (see section 5.1.3.2 above) which we corrected in the EAG preferred analysis (Table 16).

5.3 Company and EAG cost comparison results

5.3.1 Company base case

The total per-patient costs for the company's original base case are given in CS Table 4.8. Following their response to clarification questions, the company updated their model to use the most recent National Cost Collection unit costs (see section 5.1.7 above). Results of the revised company base case are shown in Table 13.

These results suggest that bevacizumab gamma (with a PAS price discount) is cost saving relative to the comparators (all at list price). However, the EAG notes that these analyses are not meaningful for decision-making as they do not include the PAS discounts for the

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comparators. Results using the PAS prices for all treatments are presented in a separate confidential addendum to this report.

Table 13 Total and incremental per-patient costs: company' revised base case

Costs	Bevacizumab gamma	Faricimab	Aflibercept	Ranibizumab
Diagnostic testing	[redacted]	£246	£246	£246
Drug acquisition	[redacted]	£22,280	£23,300	£16,460
Drug administration	[redacted]	£3,479	£3,831	£4,229
Monitoring	[redacted]	£2,231	£2,231	£2,231
Total cost	[redacted]	£28,236	£29,608	£23,165
Incremental cost [a]	-	[redacted]	[redacted]	[redacted]

Source: Partly reproduced from the company's response to clarification question B2, Table 3
[a] Incremental cost for bevacizumab gamma relative to comparator

5.3.2 Company sensitivity and scenario analyses

The company's sensitivity analysis inputs are listed in CS Table 4-10 and the results are described in CS B.4.4.1. The company provided updated tornado diagrams in their response to clarification question B2 (Figures 1 to 3).

The company's scenario analyses are described in CS B.4.4.1:

1. Company estimates of comparator PAS discounts
2. Discount rate set to 0%
3. Alternative monitoring frequency: six monitoring visits in year one, five in year two, and four in year three onwards (versus three per year in the base case).
4. Alternative starting age of 75 years (replicates population estimates from TA800)
5. Increased injection frequency for bevacizumab gamma [redacted]
6. Threshold analysis of varied comparator discounts

We report results for the company's scenarios using their revised model in Table 14. Results with confidential price discounts for comparators are reported in an addendum to this report.

Table 14 Company scenario analysis: revised company model

Scenario	Drug	Total cost	Incr. cost [a]
Revised company base case	Bevacizumab	[redacted]	-
	Ranibizumab	£23,165	[redacted]

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Scenario		Drug	Total cost	Incr. cost [a]
		Faricimab	£28,236	[redacted]
		Aflibercept	£29,608	[redacted]
2	Discount rate of 0%	Bevacizumab	[redacted]	-
		Ranibizumab	[redacted]	[redacted]
		Faricimab	[redacted]	[redacted]
		Aflibercept	[redacted]	[redacted]
3	Alternative monitoring frequency (6 monitoring visits in Year 1, 5 in Year 2, and 4 in Year ≥ 3)	Bevacizumab	[redacted]	-
		Ranibizumab	[redacted]	[redacted]
		Faricimab	[redacted]	[redacted]
		Aflibercept	[redacted]	[redacted]
4	Alternative starting age: 75 years	Bevacizumab	[redacted]	-
		Ranibizumab	[redacted]	[redacted]
		Faricimab	[redacted]	[redacted]
		Aflibercept	[redacted]	[redacted]
5	Increased injection frequency for bevacizumab gamma [redacted]	Bevacizumab	[redacted]	-
		Ranibizumab	[redacted]	[redacted]
		Faricimab	[redacted]	[redacted]
		Aflibercept	[redacted]	[redacted]

Source: Produced by the EAG using the company's revised model submitted in response to clarification questions.
[a] Incremental cost for bevacizumab gamma relative to comparator

5.3.3 EAG scenario analyses

Results for additional EAG scenarios are shown in Table 15. Results with confidential price discounts for comparators are reported in an addendum to this report.

Table 15 EAG scenario analysis: revised company model

Scenario		Drug	Total cost	Incr. cost
Revised company base case		Bevacizumab	[redacted]	-
		Ranibizumab	£23,165	[redacted]
		Faricimab	£28,236	[redacted]
		Aflibercept	£29,608	[redacted]
1	Use faricimab injection frequency for bevacizumab gamma	Bevacizumab	[redacted]	-
		Ranibizumab	[redacted]	[redacted]

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Scenario		Drug	Total cost	Incr. cost
		Faricimab	[redacted]	[redacted]
		Aflibercept	[redacted]	[redacted]
2	Use the lowest cost for ranibizumab (£495.90 per vial)	Bevacizumab	[redacted]	-
		Ranibizumab	[redacted]	[redacted]
		Faricimab	[redacted]	[redacted]
		Aflibercept	[redacted]	[redacted]
3	Baseline bilateral disease of 5%	Bevacizumab	[redacted]	-
		Ranibizumab	[redacted]	[redacted]
		Faricimab	[redacted]	[redacted]
		Aflibercept	[redacted]	[redacted]
4	Annual discontinuation rate of 5%, for all treatments	Bevacizumab	[redacted]	-
		Ranibizumab	[redacted]	[redacted]
		Faricimab	[redacted]	[redacted]
		Aflibercept	[redacted]	[redacted]
5	Annual discontinuation rate of 10%, for all treatments	Bevacizumab	[redacted]	-
		Ranibizumab	[redacted]	[redacted]
		Faricimab	[redacted]	[redacted]
		Aflibercept	[redacted]	[redacted]
6	Annual discontinuation rate of 13%, for all treatments	Bevacizumab	[redacted]	-
		Ranibizumab	[redacted]	[redacted]
		Faricimab	[redacted]	[redacted]
		Aflibercept	[redacted]	[redacted]
7	Remove increased RR of mortality of 1.09	Bevacizumab	[redacted]	-
		Ranibizumab	[redacted]	[redacted]
		Faricimab	[redacted]	[redacted]
		Aflibercept	[redacted]	[redacted]

Source: Produced by the EAG using the company's revised model submitted in response to clarification questions.
[a] Incremental cost for bevacizumab gamma relative to comparator

5.3.4 EAG's preferred assumptions

We have identified three key aspects of the company's base case with which we disagree. Our preferred model assumptions are:

1. Ranibizumab injection frequency for bevacizumab gamma

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2. Lowest cost for ranibizumab, rather than the average
3. Annual incidence of bilateral disease 14%

The cumulative effect these assumptions is shown in Table 16. In the EAG base case, bevacizumab gamma is cost-saving relative to all included comparators, based on the PAS discounted price for bevacizumab gamma and list price for all other treatments.

Table 16 Cumulative change from company's base case to the EAG preferred analysis

Scenario	Drug	Total cost	Incr. cost [a]
Company base case: revised in response to clarification questions	Bevacizumab	[redacted]	-
	Ranibizumab	£23,165	[redacted]
	Faricimab	£28,236	[redacted]
	Aflibercept	£29,608	[redacted]
+ Injection frequency for bevacizumab gamma assumed equal to that of ranibizumab	Bevacizumab	[redacted]	-
	Ranibizumab	[redacted]	[redacted]
	Faricimab	[redacted]	[redacted]
	Aflibercept	[redacted]	[redacted]
+ Lowest available NHS cost for ranibizumab (including biosimilars)	Bevacizumab	[redacted]	-
	Ranibizumab	[redacted]	[redacted]
	Faricimab	[redacted]	[redacted]
	Aflibercept	[redacted]	[redacted]
+ Annual incidence of bilateral disease 14%	Bevacizumab	[redacted]	-
	Ranibizumab	[redacted]	[redacted]
	Faricimab	[redacted]	[redacted]
	Aflibercept	[redacted]	[redacted]
EAG's preferred analysis	Bevacizumab	[redacted]	-
	Ranibizumab	[redacted]	[redacted]
	Faricimab	[redacted]	[redacted]
	Aflibercept	[redacted]	[redacted]

Source: Produced by the EAG using the company's revised model submitted in response to clarification questions.
[a] Incremental cost for bevacizumab gamma relative to comparator

5.3.5 Scenario analyses on the EAG's assumptions

We performed scenario analyses on our base case to investigate the impact of changing some of our model assumptions to reflect the company's preferences. The change that has

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the greatest impact on the results is change to the assumed injection frequency for bevacizumab gamma (scenario 1).

Table 17 EAG scenario analyses, EAG base case

Scenario		Drug	Total costs	Incr. costs [a]
EAG base case		Bevacizumab	[redacted]	-
		Ranibizumab	[redacted]	[redacted]
		Faricimab	[redacted]	[redacted]
		Aflibercept	[redacted]	[redacted]
1	Injection frequency for bevacizumab gamma [redacted]	Bevacizumab	[redacted]	-
		Ranibizumab	[redacted]	[redacted]
		Faricimab	[redacted]	[redacted]
		Aflibercept	[redacted]	[redacted]
2	Use the average vial cost for ranibizumab (£523.45 per vial)	Bevacizumab	[redacted]	-
		Ranibizumab	[redacted]	[redacted]
		Faricimab	[redacted]	[redacted]
		Aflibercept	[redacted]	[redacted]

Source: Produced by the EAG using the company's revised model submitted in response to clarification questions.
[a] Incremental cost for bevacizumab gamma relative to comparator

5.4 EAG conclusions on the cost comparison analysis

The structure of the company's model is consistent with the cost-comparison model that was used to inform the appraisal of faricimab for treatment of nAMD (TA800).

The company's results suggest that, compared with the currently approved comparators, bevacizumab gamma is associated with lifetime cost savings for patients with nAMD. The EAG disagrees with three of the assumptions in the company's model, listed in section 5.3.4. However, our preferred assumptions still result in bevacizumab gamma having lower total costs than faricimab, aflibercept and ranibizumab when using the discounted PAS price for bevacizumab gamma and list prices for the comparators (Table 16).

We report results for the company's and EAG's analysis using all available NHS price discounts for bevacizumab gamma and the included comparators in a confidential addendum to this report.

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6 EQUALITIES AND INNOVATION

This was not discussed within the CS. The EAG have not identified any equality issues and our clinical experts did not raise any concerns.

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7 EAG COMMENTARY ON THE ROBUSTNESS OF EVIDENCE SUBMITTED BY THE COMPANY

The structure and key assumptions of the company's costing model are consistent with the approach and committee's preferred assumptions in the NICE appraisal for faricimab (TA800). The model results are driven by two sets of parameters: the injection frequency for bevacizumab gamma; and drug acquisition costs. There are uncertainties over other model parameters (including the monitoring frequency, rates of bilateral disease, mortality and treatment discontinuation), but these have little or no impact on incremental costs, because these parameters are assumed not to differ between treatments.

There are some structural uncertainties related to the restriction of the model to assessment of first-line treatment, and assumption that patients do not switch between different anti-VEGF treatments. The relative costs of bevacizumab gamma and the comparators when initiated after previous anti-VEGF treatment would depend on treatment frequencies after switching, which are uncertain.

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9 APPENDICES

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Appendix 1 – Prognostic factors included in the MAIC

Table 18 Comparison of prognostic factors identified in a review with factors listed in the CS MAIC Report, and their inclusion status in the MAIC

Prognostic factors/effect modifiers	Reported in Phan et al., 2021[a] (strength of evidence)	Comment on prognostic factors/effect modifier's association with visual outcomes	Listed in CS MAIC Report as relevant treatment effect modifiers	Included in MAIC
BCVA at baseline	Yes (strong)	Patients presenting with lower VA gain more VA during treatment but are more likely to respond poorly. Those with good initial VA are more likely to maintain good final VA in both the short and long term	Yes	Yes
CNV lesion size at baseline	Yes (strong)	A larger lesion size is associated with lower VA gains	Yes	No - comparator trials report different measures
Age at baseline	Yes (strong)	Older age is associated with worse visual outcomes	Yes	Yes
Gender	Yes (insufficient)	Regularly included as a risk factor in analyses but no significant associations found between	Yes	Yes

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Prognostic factors/effect modifiers	Reported in Phan et al., 2021[a] (strength of evidence)	Comment on prognostic factors/effect modifier's association with visual outcomes	Listed in CS MAIC Report as relevant treatment effect modifiers	Included in MAIC
		gender and the visual response to anti-VEGF treatment		
Ethnicity	Yes (insufficient)	No direct relationship between ethnicity and visual outcome. Outcomes related to ethnic background may be tied to CNV lesion sub-type due to the higher prevalence of PCV seen within Black and Asian populations compared to White populations. PCV has been found to be associated with poor anatomic responses to ranibizumab treatment.	Yes	Yes
Smoking	Yes (mixed)	Current and previous smoking maybe associated with worse outcomes	Yes	No - excluded due to lack of data
Genetics	Yes (mixed)	The presence of certain AMD risk alleles (CFH & ARMS2) and VEGF polymorphisms may influence visual response	Yes ("ARMS2 variants", "CFH variants")	No - excluded due to lack of data
CNV lesion type	Yes (mixed)	Classic & pre-dominantly classic lesions may be associated with worse visual outcomes due to worse presenting VA.	Yes ("Distribution of CNV type (classic vs occult)")	No - excluded due to lack of data

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Prognostic factors/effect modifiers	Reported in Phan et al., 2021[a] (strength of evidence)	Comment on prognostic factors/effect modifier's association with visual outcomes	Listed in CS MAIC Report as relevant treatment effect modifiers	Included in MAIC
Retinal thickness	Yes (mixed)	Markedly thinner or thicker retinas associated with worse VA gain	No	N/A
Retinal Exudation – Intraretinal Fluid (IRF), Subretinal Fluid (SRF) and Subretinal Hyperreflective Material (SHRM)	Yes (mixed)	IRF (particularly sub-foveal) associated with worse visual outcomes SRF at baseline associated with better VA gains, residual SRF associated with poorer outcomes	No	N/A
Pigment Epithelial Detachments (PED)	Yes (mixed)	Presence of PED at baseline associated with worse visual outcomes. Response of PED not associated with VA gain	Yes ("PParesence of PED")	No - excluded due to lack of data
Retinal Pigment Epithelium (RPE) Atrophy	Yes (mixed)	Presence associated with worse long-term VA gain	No	N/A
Haemorrhage	Yes (mixed)	Sub-retinal haemorrhage may lead to worse visual outcomes through scar formation	Yes ("Haemorrhage")	No - excluded due to lack of data
Subretinal Fibrosis	Yes (not reported)	The presence of scar has also been associated with worse visual outcomes in trials,	No	N/A
History of arterial thromboembolic events	No		Yes	No - excluded due to lack of data

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Prognostic factors/effect modifiers	Reported in Phan et al., 2021[a] (strength of evidence)	Comment on prognostic factors/effect modifier's association with visual outcomes	Listed in CS MAIC Report as relevant treatment effect modifiers	Included in MAIC
CNV area	No		Yes	No - excluded due to lack of data
Family history of AMD	No		Yes	No - excluded due to lack of data

Source: Partly reproduced from CS MAIC Report and Phan et al., 2021
CNV, choroidal neovascularization; IRF, intraretinal fluid; PED, pigment epithelial detachment; RPE, Retinal Pigment Epithelium; SRF, subretinal fluid; VA, visual acuity; VEGF, vascular endothelial growth factor;
[a] Review of prognostic factors cited as reference in CS MAIC repor

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