NICE National Institute for Health and Care Excellence

Cost Comparison Appraisal

Bevacizumab gamma for treating wet age-related macular degeneration [ID6320]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

COST COMPARISON APPRAISAL

Bevacizumab gamma for treating wet age-related macular degeneration [ID6320]

Contents:

The following documents are made available to stakeholders:

Access the **final scope** and **final stakeholder list** on the NICE website.

1. **Company submission** from Outlook Therapeutics:
   a. Full submission
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**

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

4. **External Assessment Report** prepared by Southampton Health Technology Assessments Centre

5. **External Assessment Group response to factual accuracy check of EAR**

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal: cost-comparison

Bevacizumab gamma for treating wet age-related macular degeneration [ID6320]

Document B

Company evidence submission

July 2024

File name	Version	Contains confidential information	Date
ID6320 – Document B – cost comparison-company-evidence-submission-template (conf. visible)	**V1.0**	**Yes**	**17th July 2024**

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Tables and figures

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List of abbreviations

AE	Adverse event	mL	Millilitre
AMD	Age-related macular degeneration	NA	Not applicable
(n)AMD	(Neovascular) age-related macular degeneration	NCT	National Clinical Trial
ANOVA	Analysis of variance	NEI	National Eye Institute
Anti-VEGF	Anti-vascular endothelial growth factor	NHS	National Health Service
BCVA	Best-corrected visual acuity	NI	Non-inferiority
BNF	British National Formulary	NICE	National Institute for Health and Care Excellence
CHMP	Committee for Medicinal Products for Human Use	NMA	Network meta-analysis
CI	Confidence interval	NR	Not reported
CNV	Choroidal neovascularisation	OCT	Optical coherence tomography
CRC	Central Reading Center	ONS	Office for National Statistics
CSFT	Central subfield retinal thickness	ONS-5010	Bevacizumab gamma
CSR	Clinical study report	PAS	Patient Access Scheme
CST	Central subfield thickness	PCV	Polypoidal choroidal vasculopathy
DAA	Disease activity assessment	PICOS	Population, intervention, comparator, outcome and study type framework
DIC	Deviance information criterion	PPS	Per protocol analysis set
DSA	Deterministic sensitivity analysis	PRN	Pro re nata dosing regimen
eCRF	Electronic case report form	PRNX	Pro re nata and extend dosing regimen
EMA	European Medicines Agency	PSS	Personal Social Services
EQ-5D	5-dimension European Quality of Life questionnaire	PSSRU	Personal Social Services Research Unit
ERG	Evidence Review Group	q12w	One injection every 12 weeks
ETDRS	Early Treatment Diabetic Retinopathy Study chart	q8w	One injection every 8 weeks
EURETINA	European Society of Retina Specialists	QALY	Quality-adjusted life year
FA	Fluorescein angiography	qXw	One injection every X weeks
Fab	Fragment, antigen-binding	RAN	Randomised analysis set
FAS	Full analysis set	RCT	Randomised controlled trial
Fc	Fragment crystallizable	RE	Random-effects
FDA	Food and Drug Administration	RPE	Retinal pigment epithelium
FE	Fixed-effects	SAE	Serious adverse event
FFA	Fluorescein angiography	SAF	Safety analysis set
FTA	Fast track appraisal	scFv	Single-chain variable fragment
HES	Hospital Episodes Statistics	SD	Standard deviation
HRG	Healthcare resource group	SE	Standard error
HRQoL	Health-related quality of life	SLR	Systematic literature review
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals	SmPC	Summary of Product Characteristics
Ig	Immunoglobulin	SRF	Sub-retinal fluid
IRF	Intra-retinal fluid	TA	Technology appraisal
ITT	Intention to treat	TFC	Treatment Function Code
IVT	Intravitreal	T&E	Treat-and-extend dosing regimen
kDa	Kilodalton	UK	United Kingdom
LOCF	Last observation carried forward	US	United States of America
LP	Loading phase	VA	Visual acuity
LS	Least squares	VAT	Value-added tax
LSM	Least squares mean	VEGF	Vascular endothelial growth factor
LSMD	Least squares mean difference	VEGFR	Vascular endothelial growth factor receptor
MAIC	Matching-adjusted indirect comparison	VFQ	Visual function questionnaire
mg	Milligram	VH	Variable domain, heavy-chain
MHRA	Medicines & Healthcare Products Regulatory Agency	VL	Variable domain, light-chain

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

B.1.1 Decision problem

This cost-comparison submission covers the full EU (and MHRA) marketing authorisation for bevacizumab gamma in the following indication:

> Lytenava™ is indicated in adults for treatment of neovascular (wet) age-related macular degeneration (nAMD).[1, 2]

The MHRA marketing authorisation for the UK, was granted on the 5th July 2024, and is consistent with EMA license published on the 22nd May 2024.[2]

The whole population detailed in the license and final scope has been included for consideration in this submission, namely, adults with wet age-related, macular degeneration. The Royal College of Ophthalmologists, Macular Society, and Royal National Institute of the Blind, have all agreed with the population in their responses to the draft remit and draft scope for this technology appraisal [ID6320].[3]

The decision problem addressed within this submission is presented in (Table 1-1) and is consistent with the NICE final scope. Any differences between the decision problem addressed within this submission and the NICE final scope are outlined in (Table 1-1).

The relevant comparators to bevacizumab gamma in this appraisal are aflibercept, faricimab and ranibizumab (all intravitreal injections), as the three licensed, and NICE recommended therapies most commonly used for this indication in the UK.

The relevant population for bevacizumab gamma in this appraisal is interchangeable with the full populations for which aflibercept, faricimab and ranibizumab are recommended by NICE in TA155, TA294, and TA800.[4-7]

Table 1-1 The decision problem

	Final scope issued by NICE 20th June 2024[8]	**Decision problem addressed in the company submission**	**Rationale if different from the final NICE scope**
Population	Adults with wet age-related macular degeneration	Adults with wet age-related macular degeneration	N/A – in line with the final NICE scope
Intervention	Lytenava™ (ONS-5010) bevacizumab gamma	Lytenava™ (ONS-5010) bevacizumab gamma	N/A – in line with the final NICE scope
Comparator(s)	• Aflibercept • Ranibizumab (intravitreal injection) • Brolucizumab • Faricimab	• Ranibizumab • Aflibercept • Faricimab	Brolucizumab has been excluded from the submission, as clinical experts have confirmed to Outlook Therapeutics that it is not routinely used in clinical practice, as reflected by the second annual report of the National Ophthalmology Database (NOD) AMD Audit, which indicated a market share usage of less than 1%.[9-11] The safety concerns raised in the Direct Healthcare Professional Communication from Novartis and EMA in October 2021 has resulted in minimal use in routine clinical practice of brolucizumab for nAMD in the UK.[12] As discussed in TA800, concerns about serious adverse effects with brolucizumab including intraocular inflammation, retinal vasculitis and occlusion, typically precludes use of brolucizumab as a first-line treatment.[4, 13] The TA800 technical team confirmed the appropriateness of excluding brolucizumab. Additionally, the brolucizumab appraisal concluded similar effects to ranibizumab and aflibercept.[4]

Outcomes	• visual acuity (the affected eye) • overall visual function • central subfield foveal thickness (CSFT) • adverse effects of treatment • health-related quality of life	• visual acuity (the affected eye) • overall visual function • central subfield foveal thickness (CSFT) • adverse effects of treatment • health-related quality of life	In line with TA155, TA294, TA672 and TA800, loss and gain of letters in BCVA outcomes from baseline over time will be presented.[4-7]
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).[4, 5, 14]

	The cost effectiveness analysis should include consideration of the benefit in the best and worst seeing eye.		

No subgroups within the population are considered separately.

B.1.2 Description of the technology being evaluated

Bevacizumab gamma (Lytenava™) is an ophthalmic-grade formulation of the anti-VEGF treatment bevacizumab, and has been approved as a new active substance by the EMA and MHRA. [1, 2] UK clinicians have broad experience of using bevacizumab as Avastin®, (*predominantly in an oncology setting*) but the introduction of bevacizumab gamma will provide the first opportunity to use a formulation of bevacizumab which is licensed for ophthalmic use, and which conforms to the stringent EU standards required for the manufacture of ophthalmic solutions.

Avastin® (bevacizumab) is a monoclonal antibody targeting all isoforms of VEGF-A, but is only approved for use in systemic cancers, via intravenous use. The Summary of Product Characteristics (SmPC) states in section 4.4 "*Avastin® is not formulated for intravitreal use*".[15] Off-label, re-packaged Avastin® (bevacizumab) for the treatment of nAMD is unlicensed for intravitreal use in the UK. Repackaged, off-label bevacizumab should not be implied as a safe or appropriate option for patients with wet-AMD by inclusion in this appraisal and is not routinely available to clinicians for the treatment of newly diagnosed wet AMD patients due to specific commissioning restrictions.[16-18]

Lytenava™ (bevacizumab gamma) is 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. Following intravitreal injection, the binding of bevacizumab gamma to VEGF prevents the interaction of VEGF with its receptors on the surface of endothelial cells, reducing endothelial cell proliferation, vascular leakage, and new blood vessel formation in the retina. Table 1-2 shows how bevacizumab gamma conforms to the stringent EU standards required for the manufacture of ophthalmic solutions.[19-21] This well-controlled pharmaceutical manufacturing operation will allay concerns that compounding pharmacies increase the risk of rare but potentially devastating endophthalmitis. [12] Repackaged Avastin® (bevacizumab) produced at UK compounding pharmacies is not manufactured to the same EU ophthalmic quality standards and intravitreal use is out-with both EU and MHRA marketing authorisation. Studies have also shown reduced potency driven by variability in protein concentration of bevacizumab samples aliquoted for wet-AMD – for example, Yannuzzi et al. showed 81% of samples had

lower protein concentrations than required, with statistically significant variations in protein concentration among samples and increased probability of adverse events. [22]

Table 1-2 A comparison of manufacturing to EU ophthalmic quality standards

Ophthalmic Solution Requirement	Off-label compounded repackaged IV solution of oncological Avastin® matching ophthalmic approval requirements	Lytenava™ (bevacizumab gamma) ophthalmic solution for intravitreal injection
Sterile per Ph. Eur. 2.6.1	Unknown	Yes
Particulates per USP <789> for ophthalmic solutions	Unknown	Yes
GMP	Unknown	Yes
Bacterial endotoxins per PH. Eur. 2.6.14	No	Yes
EMA approved ophthalmic package consistent with Ph. Eur. 0522	No	Yes
EMA reviewed stability data supporting shelf life	No	Yes
ph EMA approved and consistent with Ph. Eur. 0522	No	Yes
Potency EMA approved specifications for shelf life	No	Yes
Osmolarity specification for ophthalmic solution	No	Yes

Sources: 1. USP general Chapter <771> OPHTHALMIC PRODUCTS—QUALITY TESTS USP40-NF35, second supplement, June 1, 2017; 2: Aldrich, Dale S.et.al.; Ophthalmic Preparations USP STIMULI TO THE REVISION PROCESS Vol. 39(5) [Sept.–Oct. 2013]; 3: Missel PJ. et.al, Design and evaluation of ophthalmic pharmaceutical products. In: Florence, AT, Siepmann J. Modern Pharmaceutics—Applications and Advances. New York: Informa; 2009:101–189.[19-21]

Abbreviations: EMA – European Medicines Agency; EU – European Union; FDA – Food and Drug Administration; GMP – Good Manufacturing Practice; IV – intravenous; pH – potential of hydrogen; Ph. Eur. – European Pharmacopoeia ; USP – United States Pharmacopeia

Bevacizumab gamma received a centralised Marketing Authorisation granted by the European Commission and Marketing Authorisation granted by the Medicines and Healthcare products Regulatory Agency (MHRA) in the United Kingdom (UK) for the treatment of wet age-related macular degeneration (nAMD). [1, 23]

Table 1-3 Technology being evaluated

UK approved name and brand name	Bevacizumab gamma (Lytenava™)
Mechanism of action	Bevacizumab gamma is a recombinant humanised IgG1 monoclonal antibody (mAb) for human vascular endothelial growth factor (VEGF). Bevacizumab gamma binds VEGF and prevents the interaction of VEGF to its receptors (Flt-1 and KDR) on the surface of endothelial cells. Bevacizumab gamma is a human VEGF inhibitor that binds to all isoforms of VEGF-A. By inhibiting VEGF-A, bevacizumab gamma suppresses endothelial cells proliferation, neovascularization, and vascular permeability. Inhibition of

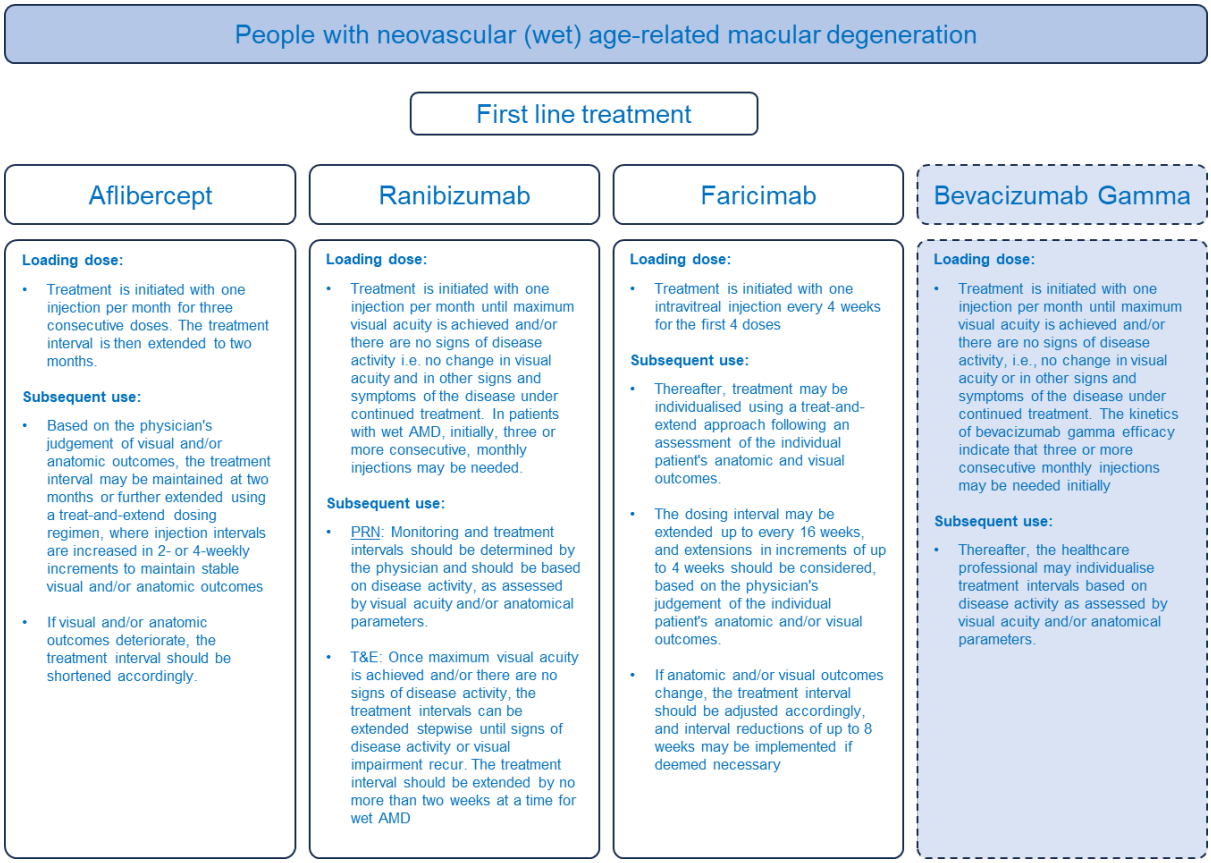
	angiogenesis works to block the growth of abnormal blood vessels in the back of the eye.[1, 2]
Marketing authorisation/CE mark status	EMA Marketing authorisation issued: 27th May 2024 EMA product number: EMEA/H/C/005723[1] MHRA Marketing Authorisation issued: 27th July 2024 MHRA Marketing Authorisation number: PL 59162/0001[2]
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Lytenava™ is indicated in adults for treatment of neovascular (wet) age-related macular degeneration (nAMD).[1 2]
Method of administration and dosage[1] **(EU SmPC)**	This medicinal product must be administered by a qualified healthcare professional, experienced in intravitreal injections. 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. “Treatment is initiated with one injection per month until maximum visual acuity is achieved and/or there are no signs of disease activity, i.e., no change in visual acuity or in other signs and symptoms of the disease under continued treatment. The kinetics of bevacizumab gamma efficacy indicate that three or more consecutive monthly injections may be needed initially. Thereafter, the healthcare professional may individualise treatment intervals based on disease activity as assessed by visual acuity and/or anatomical parameters.” Monitoring and treatment intervals should then be determined by the healthcare professional and should be based on disease activity, including clinical examination, functional testing or imaging techniques (e.g. optical coherence tomography or fluorescein angiography). If visual and anatomical outcomes indicate that the patient is not benefiting from continued treatment, the medicinal product should be discontinued. Treatment should also be withheld if clinically indicated
Additional tests or investigations	No additional tests or investigations are required beyond those already undertaken with other anti-VEGF products

List price and average cost of a course of treatment	The list price for one treatment with bevacizumab gamma is £470 The SmPC enables clinicians to extend the injection interval following the initial three or more consecutive monthly injections. Patients are therefore estimated to receive [redacted] injections in year one, [redacted] injections in year two, and [redacted] injections in all subsequent years (in line with the agreed injection frequency of [redacted] described in NICE TA800),[4] implying an average (list price) cost of [redacted] in year one, and cumulatively, [redacted], and [redacted], for two and three years of treatment respectively.
Patient access scheme/commercial arrangement (if applicable)	A patient access scheme has been approved by PASLU, [redacted]

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

Based on the EU and MHRA marketing authorisations for this indication, bevacizumab gamma is positioned as an alternative option to other anti-VEGF treatment options (aflibercept, faricimab and ranibizumab), covering an identical population of adults with neovascular (nAMD), as presented in (Figure 1.1), below.[1, 23]

Figure 1-1 Proposed treatment pathway



Although brolucizumab (Beovu®) is approved for use in the UK, clinical experts have confirmed to Outlook Therapeutics that it is not routinely used in clinical practice[10] - reflected by a market share of <0.1% in the latest NOD AMD audit report 2024,[9, 11] and restricted predominantly by the concerning safety profile.[12] Brolucizumab was not included as a comparator of relevance in the faricimab cost-comparison TA800,[4] based on concerns regarding serious adverse effects including intraocular inflammation, retinal vasculitis and occlusion, typically precluding the use of brolucizumab as a first-line treatment. The TA800 technical team confirmed the appropriateness of excluding brolucizumab from the faricimab NICE appraisal.[4] Also of relevance, the brolucizumab appraisal TA672 concluded similar effects to ranibizumab and aflibercept.[5]

B.1.4 Equality considerations

Outlook Therapeutics does not foresee any specific equity issues to be considered as part of this appraisal but would reiterate that visual impairment resulting from nAMD is recognised as a disability in the UK (as highlighted in prior NICE appraisals in wet AMD).

The Royal College of Ophthalmologists agreed in their response to the draft remit and draft scope for this appraisal [ID6320],[3] that no clinically relevant groups can be identified in whom outcomes are expected to be different. This appraisal would not exclude people with protected characteristics.

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

Relevant comparators to bevacizumab gamma have been appraised by NICE via both cost-comparison and cost-utility methods. This appraisal of bevacizumab gamma will use a cost-comparison methodology, and as such the key clinical conclusion should be non-inferiority to comparators in the key endpoints of relevance for nAMD.

It is also relevant to discuss the justification of treatment intervals, since these have been a critical area of prior appraisal discussions.

B.2.1 Clinical outcomes and measures

The comparators for bevacizumab gamma in this appraisal are the licensed anti-VEGF therapies aflibercept, ranibizumab and faricimab. All three therapies have been evaluated by NICE and recommended for patients with nAMD in NICE TA294 (aflibercept, published 2013),[7] NICE TA155 (ranibizumab, published 2020 and updated 2024)[6] and NICE cost-comparison TA800 (faricimab, published in 2022).[4, 14]

The indirect comparisons described in section B.3.9. confirm non-inferiority of bevacizumab gamma versus the above comparators, based on consistent trial endpoints.

Table 2-1 Clinical outcomes and measures appraised in NICE comparator appraisals

	Outcome	• Measurement scale	• Used in cost-effectiveness model?	Source
NICE TA800 Faricimab for nAMD [4]	Visual acuity (study eye)	• Mean change in BCVA from baseline over 40, 44 and 48 weeks • Proportion of patients gaining ≥15 or ≥10 letters in BCVA from baseline averaged over Weeks 40, 44, and 48 and over time • Proportion of patients avoiding loss of ≥15 or ≥10 letters in BCVA from baseline averaged over Weeks 40, 44, and 48 and over time • Proportion of patients gaining ≥15 letters from baseline or achieving BCVA of ≥84 letters	The cost-effectiveness case was built on non-inferiority to comparators aflibercept and ranibizumab, informed by an NMA which analysed the following: • Mean change from baseline in BCVA score • Proportion of patients gaining at least 15 letters, and at least 10 letters • Proportion of patients avoiding loss of at least 15 letters, and at least 10 letters	TENAYA, LUCERNE [24]

		averaged over Weeks 40, 44, and 48 and over time		
	Visual function	• Change from baseline in CST at Week 52/56/60 • Change from baseline in CST over time • Change from baseline in total area of CNV lesion at Week 48 • Change from baseline in total area of leakage at Week 48	The cost-effectiveness case was built on non-inferiority to comparators, informed by an indirect comparison which analysed the mean change in CST:	TENAYA, LUCERNE [24]
	Adverse events	• Incidence and severity of ocular adverse events • Incidence and severity of non-ocular adverse event	The cost-effectiveness case was built on non-inferiority to comparators, informed by an indirect comparison which analysed the following: • Overall treatment discontinuation/withdrawal • Overall ocular AEs rate • Overall ocular SAE rate	TENAYA, LUCERNE [24]
	HRQoL	• Change from baseline in NEI VFQ-25 composite over time	Not used	TENAYA, LUCERNE [24]
NICE TA294 Aflibercept for nAMD [7]	**Outcome**	• **Measurement scale**	**Used in cost-effectiveness model?**	**Source**
	Visual acuity (study eye)	• Proportion of patients losing <15 ETDRS letters from baseline at Week 52 (& Week 96) • Mean change in BCVA from baseline at Week 52 (and Week 96) • Proportion of patients gaining >15 letters from baseline to Week 52 (and Week 96)	Yes to all	VIEW 1, VIEW 2 [25]

	Visual function	• Change in CNV area from baseline to Week 52 (and Week 96) • Mean change in CSFT from baseline to Week 52 (and Week 96)	No to all	VIEW 1, VIEW 2 [25]
	Adverse events	• Ocular AEs; non-ocular AEs	No (ocular AEs only explored in scenario analysis)	VIEW 1, VIEW 2 [25]
	HRQoL	• Change in total NEI VFQ-25 from baseline to Week 52 (and Week 96) • Change in EQ-5D from screening	• No • Yes	VIEW 1, VIEW 2 [25] VIEW 2 only
NICE TA155 Ranibizumab for nAMD [6]	**Outcome**	• **Measurement scale**	**Used in cost-effectiveness model?**	**Source**
	Visual acuity (study eye)	• Proportion of patients losing <15 ETDRS letters from baseline to 12 months (and 24 months) • Gain of more than 15 ETDRS letters of visual acuity from baseline to 12 months (and 24 months) • Mean change in visual acuity (mean number of ETDRS letters lost or gained) from baseline to 12 months (and 24 months)	Yes to all	MARINA, ANCHOR, PIER

	Visual function	• Mean change in area of leakage from CNV and total area of CNV from baseline over time	Yes	MARINA, ANCHOR, PIER
	Adverse events	• Ocular AEs; non-ocular AEs	Yes (only ocular AEs deemed clinically & economically important)	MARINA, ANCHOR
	HRQoL	• Change in total NEI VFQ-25 from baseline over time	No	MARINA, ANCHOR, PIER

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

B.2.2 Resource use assumptions

An overview of key economic input decisions from relevant prior appraisals is given below. TA800 (faricimab) is likely to provide the most relevant and up-to-date input preferences to this appraisal, given the recent publication date, and similar evaluation methodology.[4] While preferences from all relevant appraisals are included, we specifically focus on TA800 in Table 2-2 and Table 2-3 below.

Faricimab for treating wet age-related macular degeneration (NICE TA800) published June 2022. [4]

Comparative efficacy and safety data for faricimab was presented following a network meta-analysis (NMA) versus aflibercept and ranibizumab. Results of the NMA demonstrated faricimab to be associated with comparable visual outcomes (BCVA) and comparable anatomical outcomes (decreasing retinal thickness) with a lower or similar injection frequency than the agreed standard of care. Adverse events were also found to be comparable for faricimab and relevant comparators.

As such, the company's economic base case was primarily driven by an assumption of fewer injections and monitoring visits needed for faricimab compared with comparators. The Committee was cautious that in NHS clinical practice, faricimab may have a similar dosing regimen as aflibercept and ranibizumab, noting potential inconsistencies in clinical practice and chance of error in busy clinical settings.

Aflibercept solution for injection for treating wet age-related macular degeneration NICE TA294) published July 2013. [7]

Comparative efficacy and safety data was presented following a NMA of published outcomes for aflibercept 2 mg every 8 weeks with ranibizumab 0.5 mg in a 'treatment as needed' regimen. Results described three endpoints (namely, maintained vision, improved vision, and mean change from baseline in BVCA) over both a 12- and 24-month timeframe. No statistically significant differences were shown between the two treatment options. Furthermore, no statistically significant differences in safety outcomes were observed. When applied to the manufacturer's Markov model, the similarities between treatment options evident in the NMA, largely precluded any difference in QALY gain (0.01 QALYs), and as such treatment and monitoring costs, as well as injection frequencies were presented as the primary drivers of cost-effectiveness.

Of note, the ERG preferred to equalise both the number of injections given in the first year of treatment, and the likelihood of a one-stop service, where assessment and treatment clinics

run in parallel.[26] By contrast, a two-stop service separates the administration and monitoring visits.[26]

Ranibizumab and pegaptanib for the treatment of age-related macular degeneration (NICE TA155) pub. Aug 2008 – updated 2012. [6]

The manufacturer's submission compared the use of ranibizumab with best supportive care for patients with minimally classic or occult no classic lesions, and with both PDT with verteporfin and best supportive care for patients with predominantly classic lesions. The different types of wet AMD were analysed separately based on results from RCTs (ANCHOR for comparison with PDT in predominantly classic lesions, MARINA for comparison with best supportive care in minimally classic lesions, and PIER for reduced- frequency dosage in all lesion types). Because the ANCHOR trial did not include a sham injection arm, comparison between treatment with ranibizumab and best supportive care for patients with predominantly classic lesions was made through indirect comparison using data from a study (TAP) in which PDT was compared with best supportive care.

Again, clinical outcomes were not highlighted as key drivers of cost-effectiveness, with injection frequency, duration of treatment, longer-term outcomes and administration costs being highlighted as the primary drivers.

Table 2-2 describes the key economic inputs used in the relevant prior NICE assessment of faricimab.

Table 2-2 Faricimab (TA800) key assumptions and inputs [4, 14]

Input	Values	Justification/ source	Critique
Injection frequencies	Faricimab • Year 1 = 6.79 • Year 2 = 4.69 • Year ≥ 3 = 3.25 Aflibercept • Year 1 = 8.00 • Year 2 = 5.63 • Year ≥ 3 = 4.00 Ranibizumab • Year 1 = 9.13 • Year 2 = 7.14 • Year ≥ 3 = 4.00	Faricimab • Injection frequencies in years one and two were derived from the pooled analysis of the TENAYA and LUCERNE studies • The calculation of year 3+ frequencies was redacted from the submission but noted elsewhere to be 3.25/year Aflibercept and ranibizumab • Frequencies were taken from the NMA described in TA800	Due to the lack of longer-term data, NICE preferred to apply a consistent 3yr+ frequency of 4 injections per year for all treatment options
Monitoring visits	Assumed to be conducted during the	This assumption is aligned with the economic assessment conducted in the NICE clinical	Accepted

	injection administration visit	guidelines for AMD (NG82),[27] where it was assumed that for all continuous regimens, no additional monitoring visits would be required.	
Treatment discontinuation	Years 1 and 2 redacted (but assumed equal for all treatment options Years 3+ = 0.089	Years 1 and 2: • Pooled TENAYA and LUCERNE data (with NMA confirmation of similarity between treatments Years 3+ • NG82	The ERG accepted the year 3+ discontinuation rate of 8.9% with a scenario analysis of 13%, but proposed alternative year 1 and 2 value (redacted)
Diagnostic testing	£130.74	NHS Reference Schedule 2019/2020, based on confirmation of testing approach via NG82	Accepted
Treatment administration	The base case analysis assumes that, in addition to drug acquisition costs, the cost of an injection administration visit comprises of an outpatient consultant-led visit (£101.80), an injection administration cost (IVT) (£54.54) and an OCT procedure (£125.88)	Consultant led outpatient visit • NHS reference costs 19/20: Consultant led non-admitted follow-up (ophthalmology) WF01A, service code 130 OCT • NHSE reference schedule 19/20. Outpatient procedure code for Retinal Tomography: BZ88A (ophthalmology) IVT injection • TA346	The ERG proposed a risk of double counting, proposing that the consultant OP cost covers the consultant doing something. A revised base case was proposed to remove the separate consultant OP cost element from the administration cost, or alternatively to remove the OCT cost element instead.
Treatment acquisition cost	Faricimab • Redacted Aflibercept • £816.00 Ranibizumab • £551.00	List prices available via the BNF, with scenario analyses exploring the impact of confidential patient access schemes	Accepted

Commentary from the committee papers of the most recent cost-comparison appraised by NICE in nAMD (TA800), resulted in the following conclusions from the scrutiny panel:

Cost-comparison was appropriate methodology because faricimab is likely to be similarly clinically effective compared with comparators.

The scrutiny panel requested that the following assumptions (Table 2-3), were applied to the original model submitted by the company:

Table 2-3 TA800: Scrutiny panel preferred assumptions for the model [4]

	NICE scrutiny panel recommendations	**Bevacizumab gamma model baseline**
Discontinuation rate	50% at 5 years	Treatment discontinuation rates are assumed to be 8.9% annually for all treatments based on the discontinuation rate of year 3 onwards in the faricimab appraisal TA800. This value approximates a 50% discontinuation rate by year five.
Clinic costs	Non-consultant led appointments for treatment and monitoring.	**Administration cost:** Treatment Function Code (TRC) Ophthalmology Service WF01A*[28, 29] **Monitoring cost:** HRG code: BZ88A – (Retinal Tomography 19 years and over) Outpatient procedure (£110)
Injection visit frequency Year 1	Year 1 injections based on the loading phases for each treatment as per SmPC, followed by a treat and extend (T&E) regimen for all treatments.	Values reflect those agreed in TA800 for [redacted]. The initial loading phase of 3 or 4 consecutive monthly injections (4 is taken as a conservative estimate), followed by T&E, where a minimum [redacted] interval provides an additional conservative estimate [redacted] in the first year. This total of [redacted] injections for bevacizumab gamma in the first year, aligns with the agreed frequency for

		[redacted] injections in the most recent NICE TA800.
Injection visit frequency Subsequent years	Number of injections should be the same for all treatments in subsequent years based on T&E regimen.	The injection frequency agreed for [redacted] in TA800 was [redacted] injections in year 2, and 4 injections in year 3. The model follows these conservative estimates, averaging approx. [redacted] between injections in year 2 and approx. [redacted] between injections from year 3 onwards.
Injection visit resource cost	Replace consultant cost with non-consultant led visit and remove OCT at injection visits.	WF01A – Follow-up attendance – single professional (£69)*
Monitoring visit frequency	Monitoring visits should be the same across arms.	HRG code: BZ88A Outpatient procedure (£110) applied the same across arms

*Cost of Outpatient attendances – unit price, 2024/25. The unit costs applied to follow-up attendance (single professional) are the same for both consultant-led and non-consultant-led attendances. Treatment Function Code (TRC) WF01A.[28, 29]

The key drivers of the cost-effectiveness from TA800, TA294, TA672 and TA155, relevant to the cost comparison analysis, have been explored in scenario analyses and are presented in Section B.4.4.[4-7, 14]

B.3 Clinical effectiveness

B.3.1 Identification and selection of relevant studies

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

B.3.2 List of relevant clinical effectiveness evidence

Results from the NORSE trial program provides key evidence supporting bevacizumab gamma – with NORSE TWO specifically providing the pivotal data informing this submission.

Bevacizumab gamma was licensed in Europe based on a mixed marketing authorisation, with evidence from prior trials of bevacizumab (Avastin®) submitted to EMA to provide further evidence. This additional evidence is specifically relevant for the understanding of likely treatment intervals modelled in this appraisal.

The evidence submitted to EMA from prior Avastin® trials is included in this submission under the heading “Supportive Evidence”. For context, the rationale for the mixed marketing authorisation approach is given below:

‘As-needed’ dosing was not specifically evaluated during the clinical development of bevacizumab gamma, however, a scientific bridge was demonstrated, which included physicochemical and biological-functional parameters, showing a high similarity between Avastin® and bevacizumab gamma. Further confirmation comes from the human PK evaluations. This clinical PK comparison of the two products as well as modelling data demonstrated and confirmed the high level of similarity.

This bridge therefore allows the consideration of published intravitreal Avastin® data to inform expected bevacizumab gamma outcomes.

Both bevacizumab (Avastin®) and ranibizumab (Lucentis®) have been shown to have comparable outcomes with respect to visual acuity regardless of monthly or as-needed dosing[30-33]. Evidence from the pivotal clinical trial (NORSE 2) can therefore be viewed in the context of previous studies of bevacizumab in nAMD (namely, CATT, IVAN, and LUCAS) where monthly dosing and extended dosing regimens were shown to deliver similar efficacy and safety. [30, 31, 34-37]

Studies have concluded that bevacizumab has equivalent effects on visual acuity at one year, when administered according to a treat-and-extend protocol, with one year outcomes comparable to those of other clinical trials with monthly treatment.[37] Accordingly, in alignment with the approved anti-VEGFs, the EU and MHRA have supported a treat-and-extend dosing schedule for bevacizumab gamma, based on scientifically bridging to repackaged, off-label Avastin® (bevacizumab) within strictly controlled clinical trial protocols.

This scientific bridge is the basis for the mixed marketing authorisation approval of bevacizumab gamma by the EMA (and subsequently the MHRA), allowing the following SMPC wording:

"[…] the healthcare professional may individualise treatment intervals based on disease as assessed by visual acuity and/or anatomical parameters." [1]

The clinical development programme for bevacizumab gamma was multinational, involving study centres recruiting patients in Europe, the US, and Australia. Intravitreal bevacizumab gamma was investigated in three clinical trials: NORSE ONE (ONS-5010-001, NCT03844074)[38]; NORSE TWO (ONS-5010-002, NCT03834753)[39]; and NORSE THREE (ONS-5010-003, NCT04516278)[40]. Together, these trials represent the primary sources of evidence for the marketing authorisation for bevacizumab gamma in this indication.

A brief overview of the NORSE ONE, NORSE TWO and NORSE THREE trials is presented in Table 3.1.

Relevant clinical effectiveness evidence for bevacizumab gamma

For completeness, NORSE ONE and THREE have been included in the table below. NORSE THREE included the primary endpoint of frequency and incidence of treatment-emergent adverse events as specified in the decision problem. However, no further evidence of clinical effect in the NORSE THREE study (or the NORSE ONE study) is considered relevant to this appraisal.

Table 3-1 Clinical effectiveness evidence for bevacizumab gamma

Study	NORSE ONE (ONS-5010-001) NCT03844074	NORSE TWO (ONS-5010-002) NCT03834753	NORSE THREE (ONS-5010-003) NCT04516278
Title	A Clinical Effectiveness Study Examining the Efficacy and Safety of	A Clinical Effectiveness Study Examining the Efficacy and Safety of	A 3-month Study to Assess the Safety of ONS-5010 in

Study	NORSE ONE (ONS-5010-001) NCT03844074	NORSE TWO (ONS-5010-002) NCT03834753	NORSE THREE (ONS-5010-003) NCT04516278
	ONS-5010 in Subjects with Neovascular Age-related Macular Degeneration (AMD)	ONS-5010 in Subjects with Neovascular Age-related Macular Degeneration (AMD)	Subjects with Visual Impairment Due to Retinal Disorders
Study design	Proof-of-concept (Phase 3) Multicenter, randomized, double-masked, controlled study	Pivotal trial (Phase 3) Multicenter, randomized, double-masked, active controlled	Safety trial (Phase 3) Prospective, multicenter, open label, nonrandomized
Population	Adults aged 50 years and older Active primary subfoveal choroidal neovascularization lesions secondary to AMD in the study eye n=61	Adults aged 50 years and older Active primary subfoveal choroidal neovascularization lesions secondary to AMD in the study eye n=228	Adults aged 18 years and older Active clinical diagnosis of: AMD, BRVO & DME Total n=197
Intervention(s)	Bevacizumab gamma solution for intravitreal injection administered at a dose of 1.25 mg		
Comparator(s)	Ranibizumab solution for intravitreal injection administered at a dose of 0.5 mg		None
Indicate if study supports application for marketing authorisation (yes/no)	Yes	Yes	Yes
Reported outcomes specified in the decision problem	BCVA (the affected eye) Overall visual function? Central subfield foveal thickness Adverse effects of treatment	BCVA (the affected eye) Overall visual function? Central subfield foveal thickness Adverse effects of treatment	Adverse effects of treatment

Key: AMD – age-related macular degeneration; DRVO - diabetic macular edema; BRVO - branch retinal vein occlusion

Rationale for use in the model

Given that this appraisal is conducted via a cost-comparison route, there is a fundamental assumption of clinical similarity between bevacizumab gamma and the agreed comparators. Therefore, while patient characteristics from NORSE TWO are used in the model, the assumption of clinical similarity avoids the need for differential outcomes in all endpoints to be included. Rather, the results of NORSE TWO are used to inform an indirect treatment comparison and series of MAIC analyses to justify non-inferiority and a simplified model. Results of NORSE TWO are further used to support the modelled injection intervals, via the previously described bridging trials, supporting the likely similarities in outcomes expected for a flexible dosing regimen in light of the NORSE TWO Q4W dosing. [41]

Rationale for non-use in the model

The phase 3, NORSE ONE, study was not used to inform the economic model (via establishment of clinical similarity with comparators via indirect comparison).[42] NORSE ONE was a small "clinical experience trial" not intended to be assessed statistically. In this study ONS-5010 demonstrated an effect and was safe and well tolerated. NORSE ONE provided valuable insight into the trial design and inclusion/exclusion criteria for NORSE TWO. The power and sample size were not considered clinically meaningful, and this will be discussed in greater detail in B.3.3.

NORSE THREE was a 3-month phase 3, safety trial enrolling nAMD, DME and RVO patients.[43] Due to the mixed population, short duration and absence of efficacy data, NORSE THREE was not considered relevant to the indirect comparison informing the cost-comparison model.

Supportive evidence (from prior bevacizumab (Avastin®) trials)

The trial design of NORSE TWO was influenced by comparator dosing regimens across global jurisdictions. Since a Q4W dosing schedule for bevacizumab gamma was selected, the question of effectiveness when used with extended treatment intervals requires further evidence.

Three large trials of bevacizumab (Avastin®) have sought to investigate the outcomes associated with longer treatment intervals. The below publications were presented to the EMA as part of the licensing evidence package:

- "CATT" - Ranibizumab and Bevacizumab for Neovascular Age-Related Macular Degeneration [30, 44]

- "IVAN" - Alternative treatments to inhibit VEGF in age-related choroidal neovascularisation: 2-year findings of the IVAN randomised controlled trial [31, 45]

- "LUCAS" - Comparison of Ranibizumab and Bevacizumab for Neovascular Age-Related Macular Degeneration According to LUCAS Treat-and-Extend Protocol [37]

Baseline characteristics compared with relevant, peer-reviewed literature reports of ophthalmic bevacizumab (repackaged, off-label Avastin®) using monthly dosing

Characteristics of participants at baseline for each of the relevant trials IVAN, CATT, LUCAS and NORSE TWO are summarised in Table 3-4 below.[30, 31, 37, 39, 41, 44, 45]

Table 3-2 Baseline characteristics of IVAN, CATT, LUCAS and NORSE TWO

Study name	NORSE TWO	IVAN	CATT	LUCAS
Study location	US	UK	US	Norway
Diagnosis	Active primary CNV secondary to AMD	Active nAMD	Active CNV secondary to AMD	previously untreated neovascular AMD
Total number of subjects (all interventions)	228	610	1185	441
Mean age (years)	78.9	77.7	79.3	78.4
Mean BCVA (ETDRS letters read)	51.6	61.4	60.5	61
Naïve to previous anti-VEGF therapy, n (%)	219 (96.1)	610 (100)	1185 (100)	100%
Information relating to preparation of intravitreal bevacizumab	ONS-5010 (bevacizumab gamma) packaged in single-use glass vials	Commercially available bevacizumab repackaged in prefilled syringes		Commercially available vial

Rationale for use in the model

'As needed' dosing of anti-VEGF treatments after the initial loading phase is commonplace in UK clinical practice. Given the Q4W dosing in NORSE TWO, the above studies were used in conjunction with the scientific bridge to support similar clinical outcomes for monthly or 'as needed' dosing. This logic is applied in the indirect comparison and also justifies the potential dosing intervals of up to Q12W explored in the cost-comparison model.

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

The trial methodology of the NORSE ONE and NORSE TWO trials are summarised below, in line with the NICE user guide.[46] As outlined above in B.3.2, NORSE TWO is the only study informing the economic model (both directly, and via indirect comparison), enrolling similar patients, and assessing similar endpoints, to comparator studies. NORSE THREE is excluded, since this 3-month safety trial, was not designed to show clinical effectiveness.

NORSE TWO study design

The NORSE TWO Phase 3 Pivotal Trial was a double-masked, active comparator-controlled, one year study in 228 adults (≥50 years) with CNV secondary to nAMD.

The primary objective of the NORSE TWO study was to evaluate the efficacy of intravitreal injections of bevacizumab gamma as compared with ranibizumab in preventing vision loss, as measured by the difference in proportion of subjects who gain ≥ 15 letters from baseline in BCVA at 11 months. The safety and tolerability of intravitreal injections of bevacizumab gamma administered monthly from baseline to 12 months was also evaluated. Table 3.2 below provides a summary of methodologies for NORSE ONE and NORSE TWO.

Table 3-3 NORSE TWO study design

Trial number	NORSE ONE (ONS-5010-001) NCT03844074	**NORSE TWO** (ONS-5010-002) NCT03834753
Relevance to economic model	NO	**YES**
Trial design	Proof-of-concept (Phase 3) Multicenter, randomized, double-masked, controlled study	Pivotal trial (Phase 3) Multicenter, randomized, double-masked, active controlled
Eligibility criteria for participants	**Inclusion Criteria: (NORSE ONE & TWO)** Active primary Subfoveal Choroidal Neovascularization lesions secondary to Age-related macular degeneration (AMD) in the study eye	
	Inclusion Criteria:	**Inclusion Criteria:**

	Best corrected visual acuity of 20/40 to 20/320 Treatment naïve and non-treatment naïve patients	Best corrected visual acuity of 25-67 letters read (20/50 to 20/320 Snellen equivalent) Treatment naïve patients only
	Study eye must: • Have active leakage on Fluorescein Angiogram involving the fovea • Have oedema involving the fovea • Be free of scarring, fibrosis, or atrophy involving the central foveal zone **Exclusion Criteria: (NORSE ONE & TWO)** • Previous subfoveal focal laser photocoagulation in the study eye • Any concurrent intraocular condition in the study eye that may require medical or surgical intervention or contribute to vision loss within 1 year	
Settings and locations where the data were collected	61 nAMD patients 9 trial sites in Australia	228 nAMD patients 39 clinical trial sites in the US
Trial drugs	**Bevacizumab gamma:** 1.25 mg by intravitreal injection monthly in the study eye **Ranibizumab:** 0.5 mg by intravitreal injection in the study eye, every month for 3 months (ie, on Days 0, 30, and 60) followed by 2 additional injections on Days 150 and 240[a] *a Subjects in the ranibizumab group underwent sham procedures at visits when they did not receive an active (ranibizumab) injection.*	
Duration of Treatment	Bevacizumab gamma: 12 months Ranibizumab: 11 months	
Number of subjects on study drugs	Bevacizumab gamma: 31 Ranibizumab: 30	Bevacizumab gamma: 113 Ranibizumab: 115
Primary outcomes (including scoring methods and timings of assessments)	**Primary Outcome Measures:** • To evaluate the efficacy of intravitreal injections of bevacizumab gamma as compared with ranibizumab in preventing vision loss, as measured by the difference in proportion of subjects who gain ≥ 15 letters from baseline in best-corrected visual acuity (BCVA) at 11 months • To evaluate the safety and tolerability of intravitreal injections of bevacizumab gamma administered monthly from baseline to 12 months **Method of assessment:** *BCVA to be assessed as letters read using the Early Treatment Diabetic Retinopathy Study (ETDRS) charts.* • *A positive change represents an improvement in visual acuity.*	
	Secondary Outcome Measures:	

	To evaluate the efficacy of intravitreal injections of bevacizumab gamma as compared with ranibizumab in preventing vision loss, as measured by the following: 1. The mean change in BCVA from baseline to 11 months 2. The proportion of subjects who gain ≥ 5 or ≥ 10 letters in visual acuity at 11 months compared with baseline. 3. The proportion of subjects who lose fewer than 15 letters in visual acuity at 11 months compared with baseline. 4. The proportion of subjects with a visual acuity Snellen equivalent of 20/200 or worse at 11 months 5. The mean change from baseline in visual acuity over time up to 11 months **Method of assessment: (1-4 above)** *BCVA to be assessed as letters read using the ETDRS charts.* • *A positive change represents an improvement in visual acuity. (1-3)* • *A negative change represents a decrease in visual acuity. (4)*

a Subjects in the ranibizumab group underwent sham procedures at visits when they did not receive an active (ranibizumab) injection.

NORSE ONE was not used to inform the indirect comparison or economic model: Firstly, due to the relatively small number of subjects (61 subjects, 30 in the bevacizumab gamma group); secondly, since it was not powered to show a significant difference in subjects gaining three lines of BCVA; and thirdly, due to the uneven distribution of baseline attributes (a mixed population of treatment-naïve and previously treated nAMD subjects), as well as baseline visual acuity.

Study methodology NORSE TWO

NORSE TWO was a multicentre, randomized, double-masked, controlled study designed to evaluate the efficacy and safety of intravitreally administered bevacizumab gamma. Approximately 220 eligible subjects with nAMD were to be enrolled.

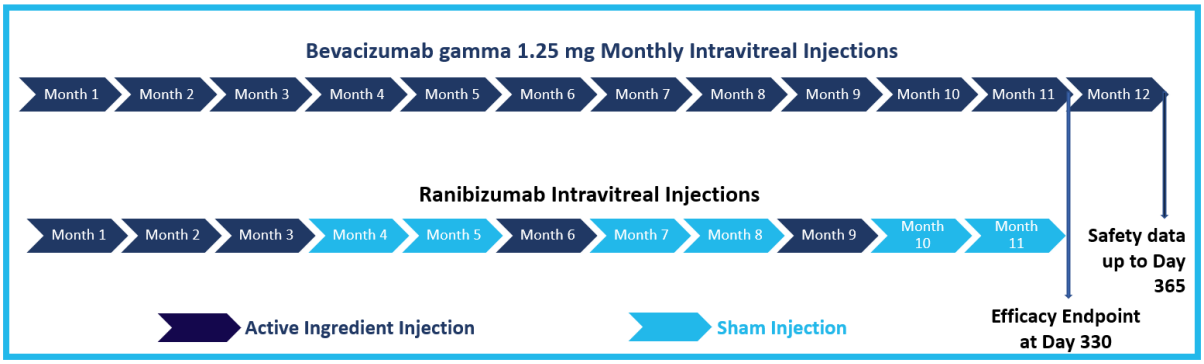
Following a screening period of up to 28 days, eligible subjects were randomized in a 1:1 ratio to receive bevacizumab gamma or ranibizumab in the study eye. Note that only one eye was designated as the study eye and the injection was performed by an unmasked physician. Prior to randomization, the investigator was to receive and review clinical laboratory tests for eligibility and also to receive confirmation of subject eligibility from the medical image reviewer.

Subjects randomized to receive bevacizumab gamma were administered a monthly intravitreal injection of 1.25 mg of bevacizumab gamma in the study eye for up to 12 months until study completion. Subjects randomized to ranibizumab, received 0.5 mg of ranibizumab

by intravitreal injection in the study eye every month for 3 months (ie, on Days 0, 30, and 60) followed by 2 additional injections, 90-days apart, on Days 150 and 240. Subjects in the ranibizumab group underwent sham procedures at visits when they did not receive an active (ranibizumab) injection.

The end of study visit differed depending on which treatment group the subject was randomized to, concluding at Day 330 for the ranibizumab group and at Day 365 for the bevacizumab gamma group, at which time the subjects reverted to the investigator's standard of care.

Figure 3-1 Study schema for NORSE TWO



Safety and efficacy assessments were conducted throughout the dosing and evaluation phases of the study. The efficacy evaluation period was 11 months (through Day 330) for both study groups, whereas the safety evaluation period was 11 months (through Day 330) for the ranibizumab group and 12 months (through Day 365) for the bevacizumab gamma group. The determination of efficacy was based on BCVA and on measurements of central foveal thickness (CFT) by spectral domain-optical coherence tomography (SD-OCT). Safety was assessed by a review of adverse events (AEs), post-injection assessments (including gross visual assessments [finger counting, hand motion, light perception] 15 minutes post-injection and intraocular pressure [IOP] measurements 30 minutes post-injection), findings from the review of body systems, vital sign measurements, clinical laboratory test results, ongoing measurements of IOP, slit-lamp biomicroscopy, dilated ophthalmoscopy, and fundus autofluorescence, and fluorescein angiography. All investigators performing the ocular assessments were masked to study drug assignment.

Baseline characteristics NORSE TWO

The baseline characteristics were evenly distributed across study arms, and no significant difference was observed.

Table 3-4 NORSE TWO Baseline characteristics

	Bevacizumab gamma (n=113)	Ranibizumab (n=115)
Female n (%)	67 (59.3)	69 (60.0)
Age in years	79 (54 - 97)	80 (55 - 98)
Race n (%)		
White	110 (97.3)	113 (98.3)
Black	2 (1.8)	0
Asian	1 (0.9)	1 (0.9)
Other	0	1 (0.9)
Study eye n (%)		
Right eye	49 (43.4)	51 (44.3)
Baseline BVCA mean (SD)	52.1 (12.16)	51.1 (12.96)
Baseline BVCA mean (SD)	430.0 (150.85)	423.7 (114.77)

Supportive evidence (from prior bevacizumab (Avastin®) trials)

The methodologies of supportive trials presented to the EMA as part of the mixed marketing authorisation, are briefly summarised below, including a comparison to the methods employed for NORSE TWO.[41]

Table 3-5 Comparison of relevant bevacizumab trials

Study name	**NORSE TWO**		**IVAN**		**CATT**		**LUCAS**	
Drug	Bevacizumab gamma	IVR	IVB	IVR	IVB	IVR	IVB	IVR
Intervention	1.25mg, monthly	0.5 mg, monthly for 3 months + 2 injections 90-days apart	1.25 mg, monthly Or 1.25mg 'discontinuous' (up to 3 months)	0.5 mg, monthly Or 0.5mg 'discontinuous' (up to 3 months)	1.25 mg, monthly Or 1.25mg 'as needed'	0.5 mg, monthly Or 0.5mg 'as needed'	1.25 mg Treat & extend	0.5 mg Treat & extend
Subjects treated	113	115	Monthly n=127 Discontinuous n=127	Monthly n=134 Discontinuous n=137	Monthly n=277 As needed n=291	Monthly n=294 As needed n=295	213	218
Key efficacy endpoints across studies								
Proportion with BCVA gain ≥ 15 letters from baseline, n/N (%)								
Mean (SD) change from baseline in BCVA								

CATT = Comparison of Age-related Macular Degeneration Treatment Trials; CNV = choroidal neovascularization; IVAN = Randomized Controlled Trial of Alternative Treatments to Inhibit VEGF in Age-related Choroidal Neovascularization; IVB = intravitreal bevacizumab; IVR = intravitreal ranibizumab; nAMD = neovascular age-related macular degeneration

The overall study designs are considered appropriate for the comparison of both medicinal products and administration schemes and the overall quality of the studies is considered high – notably, in a Cochrane review article by Solomon et al. from 2019, which investigated the ocular and systemic effects of intravitreal anti-VEGF injections for nAMD, the overall risk for bias in studies CATT and IVAN was considered low.[47]

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

NORSE TWO Statistical methods

All statistical processing was performed using SAS® version 9.4 or later. Descriptive statistics were used to provide an overview of the efficacy and safety results. Categorical variables were summarized by the frequency counts and percentages for each response category, while continuous variables were summarised using the sample size, mean, median, standard deviation (SD), standard error of the mean (SE) (where applicable), minimum, and maximum values. Two-sided, 95% confidence intervals (CIs) were provided for all endpoints when applicable. Where inferential testing was conducted, unless otherwise stated, the statistical tests were 2-sided with an alpha level of 0.05.

The following study populations were defined for this study:

- Primary efficacy evaluations were conducted using the ITT population, which consisted of all randomized subjects.
- Supportive efficacy evaluations were conducted using the PP population, which included all subjects in the ITT population who had at least 1 post-dose BCVA assessment and were compliant with all critical study criteria.
- Safety evaluations were conducted using the safety population, which included all subjects who were randomized and received at least 1 administration of study drug during the study.

Efficacy Analysis:

The difference in the proportion of subjects who gained ≥ 15 letters in visual acuity between the bevacizumab gamma and ranibizumab groups was analysed using a Fisher's exact test. The difference in proportions and the associated 95% CI was reported. Subjects who discontinued due to an AE, lack of- efficacy, or use of rescue therapy were categorized as non-responders, whereas subjects who discontinued for other reasons and had a missing Month 11 BCVA were treated as missing.

The first secondary efficacy endpoint (change from baseline in BCVA to 11 months) was analysed using both a fixed and an adaptive approach to a trimmed means method of

analysis. Complementary analyses to the first secondary analysis included an analysis of covariance (ANCOVA) model, with study drug group as a fixed effect and the baseline BCVA as a continuous covariate; an ANCOVA employing a multiple imputation method; and a repeated measures analysis of the change in BCVA from baseline over time. The remaining secondary efficacy endpoint analyses were performed using a Fisher's exact test to compare the bevacizumab gamma and ranibizumab groups. If the primary efficacy analysis and the first secondary efficacy analysis were significant, a hierarchical testing method was used to control the Type 1 error at an overall 2-sided alpha level of 0.05. To control for multiplicity in the remaining secondary efficacy endpoints, the analyses were conducted in a stepwise manner, with endpoints analysed in the order presented in the criteria for evaluation description, above. Note that the testing process terminated whenever a statistical test for a step was not significant (ie, all subsequent tests for the remaining steps were considered not significant).

B.3.5 Critical appraisal of the relevant clinical effectiveness evidence

An overview of the quality assessment for NORSE TWO is presented in Table 3-6 below.[41] Please refer to Appendix D for the full quality assessment.

Table 3-6 Critical appraisal of NORSE TWO

Study question	**NORSE TWO (NCT03834753)**
Was randomisation carried out appropriately?	Yes
Was the concealment of treatment allocation adequate?	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes
Were there any unexpected imbalances in drop-outs between groups?	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	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

NORSE TWO was a well conducted clinical trial, as demonstrated in critical appraisal in Table 3-6 above. No specific limitations have been published.

B.3.6 Clinical effectiveness results of the relevant studies

Primary endpoint results for NORSE TWO

The study provided substantial evidence of clinical efficacy and met its primary efficacy endpoint, demonstrating that bevacizumab gamma was superior to ranibizumab, when ranibizumab was administered in a manner consistent with the PIER study dosing regimen, for the proportion of subjects achieving an increase of ≥ 15 letters in BCVA from baseline to 11 months (41.7% vs 23.1%, respectively, with a risk difference of 0.1859 [95% CI = 0.0442, 0.3086]; p = 0.0052).

Table 3-7 Subjects Gaining ≥ 15 Letters from Baseline to 11 Months

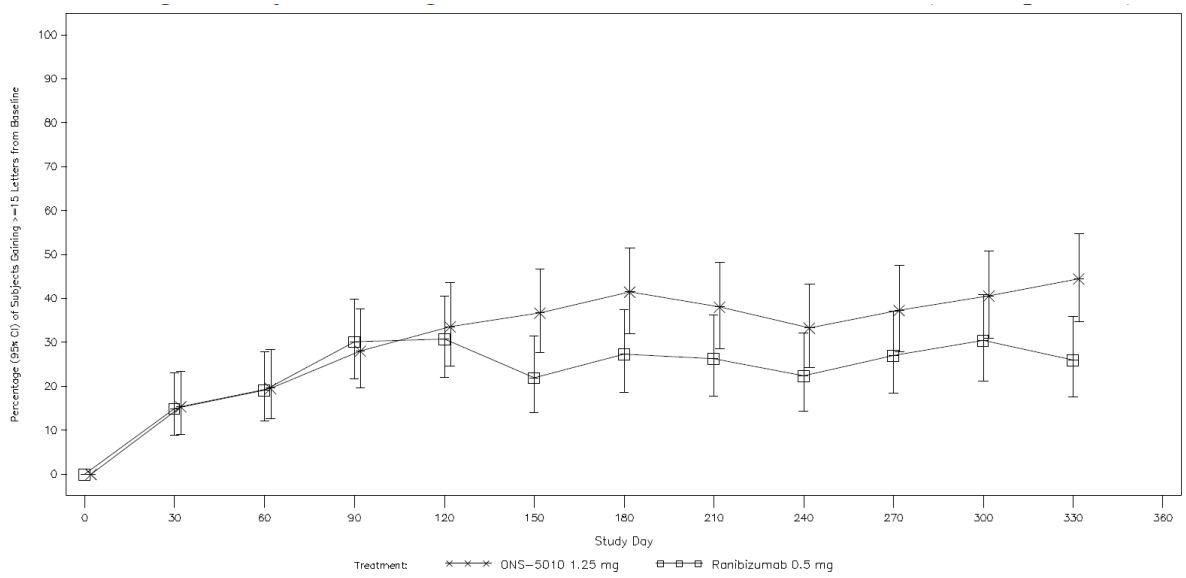
	Ranibizumab (N=115)	**Bevacizumab gamma (N=113)**
Number of subjects, n/N (%)	24/104 (23.1)	45/108 (41.7)
Risk difference		0.1859
95% CI [a]		0.0442, 0.3086
p-value [b]		0.0052

CI = confidence interval; ITT = intent-to-treat; n = number of subjects with ≥ 15 letter increase; N = number of subjects with Month 11 assessment

a Exact 95% CI for risk difference; b P-value from Fisher's exact test. A hierarchical testing method was used to control Type 1 error at an overall 2-sided 0.05 level.

Subjects who received rescue/prohibited therapy or withdrew from study drug administration due to an adverse event or lack of efficacy were considered non-responders. Subjects who had missing 11-month values and did not receive rescue/prohibited therapy or withdrew from study drug administration due to an adverse event or lack of efficacy were treated as missing.

Figure 3-2 Percentage of Subjects Gaining ≥ 15 Letters - Baseline Over Time



CI = confidence interval

The difference between study drug groups was significant, favouring bevacizumab gamma, for the first secondary efficacy endpoint (change from baseline in BCVA to 11 months) using both trimmed means approaches. Specifically, the LS mean change in BCVA from baseline to 11 months using the trimmed means fixed approach was 19.310 letters in the bevacizumab gamma group and 14.575 letters in the ranibizumab group (least squares [LS] mean difference of 4.735 [95% CI = 1.306, 8.163]; p = 0.0035). Similarly, the LS mean change in BCVA from baseline to 11 months using the trimmed means adaptive approach was 13.640 letters in the bevacizumab gamma group and 5.770 letters in the ranibizumab group (LS mean difference = 7.870 [95% CI = 4.536, 12.599]; p = 0.0001).

Secondary endpoint results for NORSE TWO

Table 3-8 BCVA change from Baseline to 11 Months by Trimmed Means Fixed and Adaptive Approaches (ITT Population)

	Ranibizumab (N=115) n=96	**Bevacizumab gamma** (N=113) n=104
Mean (SD)	5.8 (14.80)	11.2 (12.19)
Median	6.0	12.0
Min,max	-42,42	-47,40
Trimmed Means Fixed Approach		
LS mean [a,b]	14.575	19.310
LS mean difference (95% CI)		4.735 (1.306, 8.163)
p-value		0.0035

Trimmed Means Fixed Approach		
LS mean [a,c]	5.770	13.640
LS mean difference (95% CI)		7.870 (4.536, 12.599)
p-value		0.0001

CI = confidence interval; ITT = intent-to-treat; LS = least squares; max = maximum; min= minimum; SD = standard deviation

Summary statistics were based on observed changes in best-corrected visual acuity from baseline to 11 months. Observations were ranked based on baseline adjusted 11-month scores. The p-values to test the LS mean differences were determined by taking the proportions of values in a 10,000-permutation distribution more extreme than the observed effect. The 95% CI surrounding the LS mean difference was determined by adding the 2.5 and 97.5 percentiles from the same permutation distribution to the observed LS mean difference.

[a] The LS mean values and LS mean difference were estimated from and analysis of covariance model using the subset of values greater than the percentile floor.

[b] The trimmed means fixed approach compared the 50% best (> median) observations in each study drug group. Those observations with missing data at 11 months had values worse than the median imputed to calculate the adjusted median in which the best 50% were subset.

c The trimmed means adaptive approach assigns a percentile floor in the study drug group based on the greatest proportion of dropouts observed between the 2 groups. Those observations with missing data at 11 months had values worse than the percentile floor imputed to calculate the adjusted floor in which the best observations were subset.

There was a significant difference favouring bevacizumab gamma when compared with ranibizumab in the sequential testing of the first 3 remaining secondary efficacy endpoints (ie, the proportions of subjects who gained ≥ 5 letters and ≥ 10 letters in BCVA from baseline to 11 months, and the proportion of subjects who lost < 15 letters in BCVA from baseline to 11 months). In the bevacizumab gamma group, 74 subjects (68.5%) gained ≥ 5 letters in BCVA, 61 subjects (56.5%) gained ≥ 10 letters in BCVA, and 101 subjects (93.5%) lost < 15 letters in BCVA from baseline to 11 months. In the ranibizumab group,

53 subjects (51.0%), 36 subjects (34.6%), and 86 subjects (82.7%) were included in the same respective BCVA responder categories. For each of these fixed-sequence secondary endpoints, the difference between study drug groups was significant (p ≤ 0.0185). The proportion of subjects with a visual acuity Snellen equivalent of 20/200 or worse at 11 months (ie, the final secondary efficacy endpoint in the fixed sequence) was lower in the bevacizumab gamma group (13.0% [14 subjects]) compared with the ranibizumab group (24.0% [25 subjects]); however, the treatment difference did not quite achieve statistical significance at a 0.05 alpha level (p = 0.0505).

Table 3-9 Secondary Efficacy Endpoints: Responder Analyses (ITT Population)

Parameter, n/N (%)	Ranibizumab (N=115)	Bevacizumab gamma (N=113)
Subjects gaining ≥ 5 letters from baseline at 11 months, n/N (%)	53/104 (51.0)	74/108 (68.5)
Risk difference		0.1756
95% CI [a]		0.0315, 0.3052
p-value [b]		0.0116
Subjects gaining ≥ 10 letters from baseline at 11 months, n/N (%)	36/104 (34.6)	61/108 (56.5)
Risk difference		0.2187
95% CI [a]		0.0726, 0.3487
p-value [b]		0.0016
Subjects losing < 15 letters from baseline at 11 months, n/N (%)	86/104 (82.7)	101/108 (93.5)
Risk difference		0.1083
95% CI [a]		0.0168, 0.2044
p-value [b]		0.0185
Subjects with a visual acuity Snellen equivalent of 20/200 or worse at 11 months, n/N (%) [c]	25/104 (24.0)	14/108 (13.0)
Risk difference		-0.1108
95% CI [a]		-0.2187, -0.0050
p-value [b]		0.0505

CI = confidence interval; ITT = intent-to-treat; n = number of subjects meeting criterion, N = number of subjects with Month 11 assessment

[a] Exact 95% CI for risk difference.

[b] P-value from Fisher's exact test. A hierarchical testing method was used to control Type 1 error at an overall 2-sided alpha of 0.05.

[c] 20/200 is the visual acuity Snellen equivalent of 35 letters.

Subjects who received rescue/prohibited therapy or withdrew from study drug administration due to an adverse event or lack of efficacy were considered nonresponders. Subjects who had missing 11-month values and did not receive rescue/prohibited therapy or withdrew from study drug administration due to an adverse event or lack of efficacy were treated as missing.

The first and second complementary analyses of the secondary efficacy endpoint, which used an ANCOVA and an ANCOVA with multiple imputation, consistently showed a greater improvement in BCVA in the bevacizumab gamma group compared with the ranibizumab group at 11 months ($p \leq 0.0043$). The third complementary analysis, which used a repeated measures analysis of the first secondary efficacy endpoint, showed an improvement in BCVA as early as Day 30, with a greater improvement in the bevacizumab gamma group compared with the ranibizumab group starting at Day 150 that was maintained through Day 300 in the ITT population ($p \leq 0.0272$ at each time point).

Table 3-10 First and Second Complementary Analyses of the Change in BCVA from Baseline Over Time by Repeated Measures Analysis (ITT Population)

BCVA Change from Baseline to 11 Months [a]	**Ranibizumab** (N=115) n=96	**Bevacizumab gamma** (N=113) n=104
ANCOVA		
Mean (SD)	5.8 (14.80)	11.2 (12.19)
Median	6.0	12.0
Min,max	-42, 42	-47, 40
LS mean (SE)	5.807 (1.3519)	11.226 (1.2989)
95% CI	3.141, 8.473	8.665, 13.788
LS mean difference		5.419 (1.8748)
95% CI		1.722, 9.117
p-value [a]		0.0043
ANCOVA with multiple imputation b		
Mean (SD)	5.8 (14.80)	11.2 (12.19)
Median	6.0	12.0
Min,max	-42, 42	-47, 40
LS mean (SE)	5.131 (1.3632)	11.191 (1.3112)
95% CI	2.459, 7.803	8.621, 13.761
LS mean difference		6.060 (1.8927)
95% CI		2.350, 9.770
p-value [a]		0.0014

ANCOVA = analysis of covariance; BCVA = best-corrected visual acuity; CI = confidence interval; ITT = intent-to-treat; LS = least squares; max = maximum; min = minimum; SD = standard deviation; SE = standard error

Summary statistics are based on observed changes from baseline to 11 months.

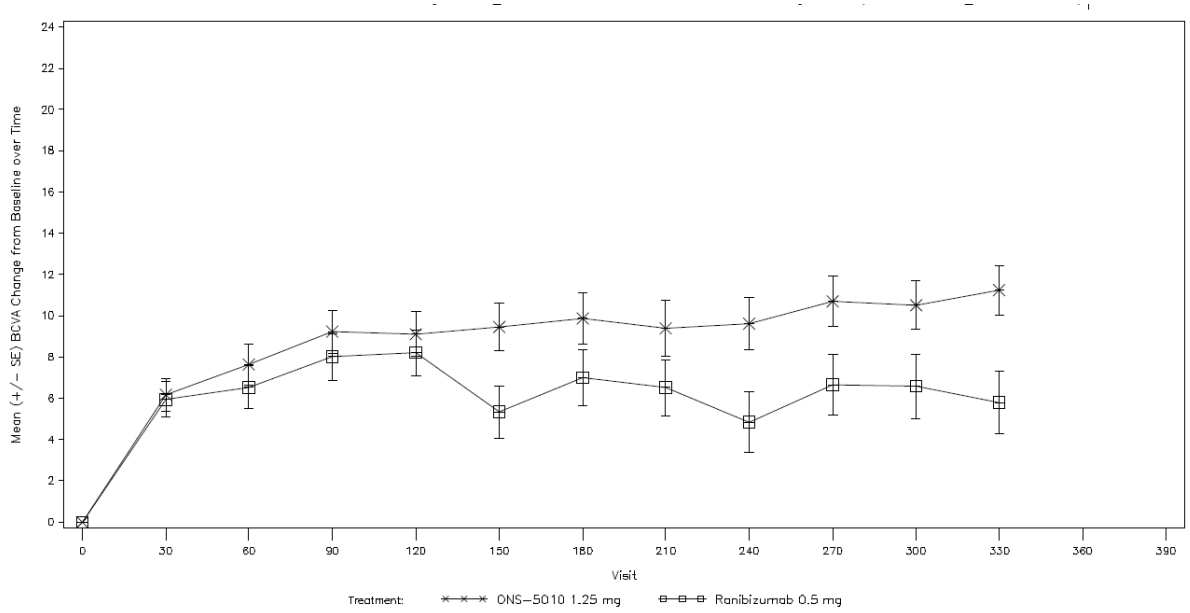
a P-value using an ANCOVA with study drug group as fixed effect and baseline BCVA as a continuous covariate. The p-value tested the difference in LS mean values between study drug groups.

b Missing 11-month BCVA values were replaced using the multiple imputation method with a set of plausible values that represented the uncertainty of the correct value based on the observed time matched data at all other visits. The multiple imputation was completed by 2 steps: (1) impute these intermittent missing data using Markov chain Monte Carlo methods to get a monotone missingness data pattern and, (2) use the regression method to impute missing data.

This method of imputation assumed that missing data were missing at random.

c The 95% CIs and the p-values are based on the overall estimates from 100 imputations, testing the ONS-5010 group versus the ranibizumab group using the difference between Month 11 and baseline.

Figure 3-3 Third Complementary Analysis of the Change in BCVA from Baseline Over Time by Repeated Measures Analysis (ITT Population)



BCVA = best-corrected visual acuity; ITT = intent-to-treat; SE = standard error

Across all sensitivity analyses of the first secondary efficacy endpoint, there was a consistently greater improvement in BCVA in the bevacizumab gamma group compared with the ranibizumab group at 11 months, indicating that the results of the first secondary efficacy endpoint were free from bias due to missing data.

The results of primary and secondary efficacy analyses in the overall ITT and PP populations were consistent with those observed among subjects naive to anti-VEGF therapy, who comprised the majority (> 71.5%) of the respective study populations with efficacy data at 11 months. Given the small number of subjects who had previously received anti-VEGF treatment (n = 4-5 in each study drug group), comparisons with the treatment naive population were not informative.

In the analysis of the exploratory efficacy endpoint, there was no notable difference between study drug groups in the mean absolute change from baseline in CFT at 11 months.

The efficacy analyses conducted using the PP population were generally similar to the analyses conducted using the ITT population, further confirming the efficacy conclusions of the study.

Based on the planned 'mixed marketing authorisation' process undertaken by the EMA, several older studies of intraocular bevacizumab were submitted, providing further evidence on the parent molecule's clinical outcomes.

Supportive evidence (from prior bevacizumab (Avastin®) trials)

While the NORSE TWO trial demonstrated superiority over ranibizumab, the IVAN, and CATT trials confirmed that bevacizumab (repackaged, off-label Avastin®) is similar to ranibizumab in the treatment of nAMD. All trials ultimately concluded that bevacizumab, either as UK repackaged, off-label Avastin® (IVAN) or US repackaged, off-label Avastin® (CATT) and bevacizumab gamma (NORSE TWO), is a highly effective treatment for nAMD.

Table 3-11 demonstrates that outcomes from NORSE TWO are in line with prior Avastin® trials.

Table 3-11 NORSE TWO compared with relevant, peer-reviewed literature reports of ophthalmic bevacizumab (repackaged, off-label Avastin®)

Study name	NORSE TWO		IVAN		CATT	
Drug	Bevacizumab gamma	IVR	IVB	IVR	IVB	IVR
Intervention	1.25mg, monthly	0.5 mg, monthly for 3 months + 2 injections 90-days apart	1.25 mg, monthly[a] Or 1.25mg 'discontinuous' (up to 3 months)	0.5 mg, monthly[a] Or 0.5mg 'discontinuous' (up to 3 months)	1.25 mg, monthly Or 1.25mg 'as needed'	0.5 mg, monthly Or 0.5mg 'as needed'
Subjects treated	113	115	Monthly n=127 Discontinuous n=127	Monthly n=134 Discontinuous n=137	Monthly n=277 As needed n=291	Monthly n=294 As needed n=295
Key efficacy endpoints						
Proportion with BCVA gain ≥ 15 letters from baseline, n/N (%)	45/108 (41.7)	24/104 (23.1)	40/274 [b] (14.6)	64/287 [b] (22.3)	83/265 [d] (31.3)	97/284 [d] (34.2)
Mean (SD) change from baseline in BCVA[c]	11.2 (12.19)	5.8 (14.80)	4.7 (12.5)	6.4 (12.8)	8.0 (15.8)	8.5 (14.1)

CATT = Comparison of Age-related Macular Degeneration Treatment Trials; CNV = choroidal neovascularization; IVAN = Randomized Controlled Trial of Alternative Treatments to Inhibit VEGF in Age-related Choroidal Neovascularization; IVB = intravitreal bevacizumab; IVR = intravitreal ranibizumab; nAMD = neovascular age-related macular degeneration
[a] Ranibizumab was administered for this study in accordance with the US Food and Drug Administration approved PIER study dosing regimen (Regillo 2008).

[b] The IVAN study results are presented for each study drug overall, regardless of treatment regimen (ie, continuous + prn); therefore, N is the total number randomized to each study drug with available data at 1 year, and not subjects randomized only to the continuous administration
[c] 11 months in NORSE TWO, and 1 year in the CATT and IVAN
[d] Results describe the monthly arm of CATT, after one year of treatment

Table 3-12 Additional Efficacy Endpoints: Proportion of Subjects with ≥ 5 and ≥ 10 Letter Gains and < 15 Letter losses from Baseline for Patients Treated with bevacizumab gamma and repackaged, off-label Avastin® Across Randomized, Controlled, Clinical Studies

Parameter	NORSE TWO Bevacizumab gamma (N = 113)	IVAN repackaged, off-label Avastin® (N = 296)	CATT repackaged, off-label Avastin® (N = 265)
Proportion with BCVA gain ≥ 10 letters from baseline at 1 year, %	56.5	NR	37.0 [a]
Proportion with BCVA gain ≥ 5 letters from baseline at 1 year, %	68.5	NR	18.9 [a]
Proportion with BCVA loss < 15 letters from baseline at 1 year, %	93.5	NR	94.0 [a]

[a] Results describe the monthly arm of CATT, after one year of treatment

In the IVAN study, 610 subjects with active nAMD were randomized to receive intravitreal injections of either repackaged, off-label Avastin® (bevacizumab) 1.25 mg (n = 296) or Lucentis (ranibizumab) 0.5 mg (n = 314). After the initial 3 injections were administered, 149 and 157 subjects, respectively, in the bevacizumab and ranibizumab groups were allocated to receive continuous treatment with their assigned study drug.[31] Of note, however, the data for this study are presented for all subjects who received each study drug, regardless of treatment regimen (ie, assigned injections or continuous treatment). At 1 year, the increase in mean BCVA from baseline was 4.7 versus 6.4 letters, respectively, in the bevacizumab and ranibizumab groups. At this time point, 40 of 274 subjects (14.6%) in the bevacizumab group and 64 of 287 subjects (22.3%) in the ranibizumab group had gained ≥ 15 letters from baseline in BCVA. The mean decrease from baseline in foveal thickness, as measured by OCT, was −139 µm in the bevacizumab group and −155 µm in the ranibizumab group. The median number of treatments was 11 in the bevacizumab group and 10 in the ranibizumab group. Overall, bevacizumab was similar to ranibizumab in regard to the improvements in vision. At 2 years, a meta-analysis of pooled data from both the IVAN and CATT studies confirmed the non-inferiority of bevacizumab to ranibizumab. [45]

The Comparison of AMD Treatments Trials (CATT) compared the relative safety and effectiveness of Lucentis with repackaged, off-label Avastin® in a multicenter clinical study and determined that both treatments are equally effective in improving vision when administered monthly or on an as-needed basis.[30] In the CATT study, subjects with active

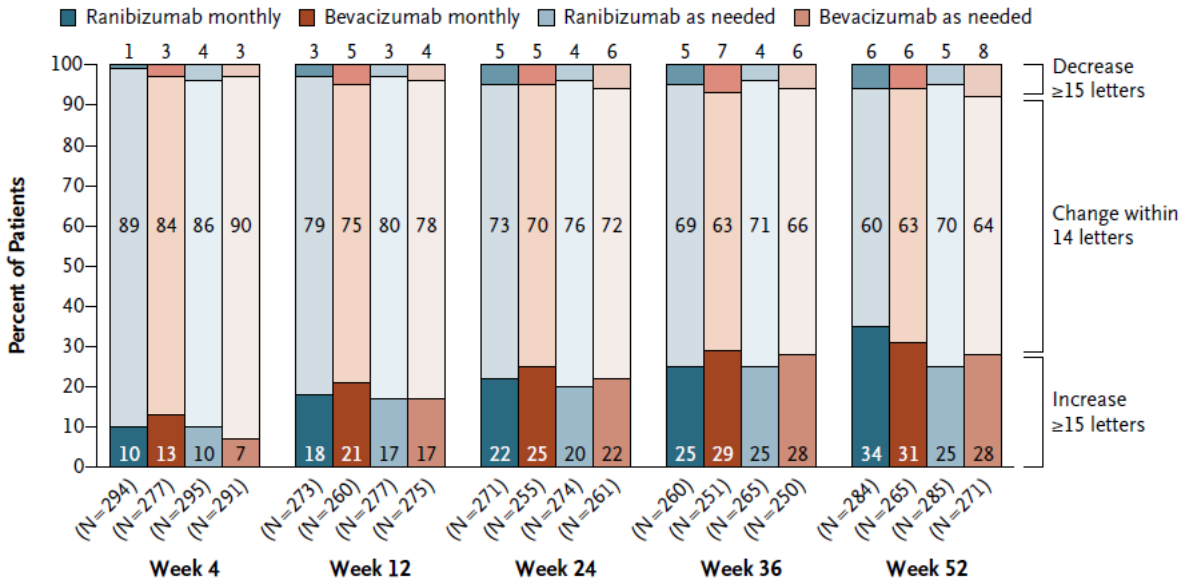
CNV secondary to nAMD and LUCAS 2015 used a "treat-and-extend" protocol for both drugs.

Summary of supportive evidence:

The IVAN study demonstrated that for BCVA, bevacizumab was neither non-inferior nor inferior to ranibizumab (mean difference −1·37 letters, 95% CI −3·75 to 1·01; p=0·26). Discontinuous treatment was neither non-inferior nor inferior to continuous treatment (−1·63 letters, –4·01 to 0·75;p=0·18). Frequency of arterial thrombotic events or hospital admission for heart failure did not differ between groups given ranibizumab (20 [6%] of 314 participants) and bevacizumab (12 [4%] of 296; odds ratio [OR] 1·69, 95% CI 0·80–3·57; p=0·16), or those given continuous (12 [4%] of 308) and discontinuous treatment (20 [7%] of 302;0·56, 0·27–1·19; p=0·13). Meta-analysis of CATT and IVAN confirm the above conclusions.

The CATT study demonstrated that one-year results for visual acuity could be achieved with less-than-monthly regimens for both drugs. Ranibizumab given as needed was equivalent to ranibizumab given monthly, with a mean difference of 1.7 letters.
Bevacizumab given as needed was equivalent to bevacizumab given monthly at all time points through 36 weeks (with mean differences all within 1.6 letters); at 52 weeks, the difference of 2.1 letters yielded an inconclusive comparison.

Figure 3-4 Proportion of patients with changing visual acuity from the CATT study



The LUCAS study demonstrated that bevacizumab and ranibizumab had equivalent effects on visual acuity at 1 year when administered according to a treat-and-extend protocol. The visual acuity results at 1 year were comparable to those of other clinical trials with monthly treatment. The numbers of serious adverse events were small.

Relevance to this appraisal:

'As-needed' dosing was not specifically evaluated during the clinical development of bevacizumab gamma, however, a scientific bridge was demonstrated, which included physico-chemical and biological-functional parameters, showing a high similarity between Avastin® and bevacizumab gamma. Further confirmation comes from the human PK evaluations. This clinical PK comparison of the two products as well as modelling data demonstrated and confirmed the high level of similarity.

This bridge therefore allows the consideration of published intravitreal Avastin® data to inform expected bevacizumab gamma outcomes.

Both bevacizumab (Avastin®) and ranibizumab (Lucentis®) have been shown to have comparable outcomes with respect to visual acuity regardless of monthly or as-needed dosing[30-33]. Evidence from the pivotal clinical trial (NORSE 2) can therefore be viewed in the context of previous studies of bevacizumab in nAMD (namely, CATT, IVAN, and LUCAS) where monthly dosing and extended dosing regimens were shown to deliver similar efficacy and safety. [30, 31, 34-37]

Considering the similarity between Lytenava™ (bevacizumab gamma) and repackaged, off-label intravitreal Avastin® (bevacizumab), and the general mode of action of anti-VEGFs, the results of these studies can be extrapolated to Lytenava™ (bevacizumab gamma), concluding that treat and extend dosing would confer similar results with respect to functional and anatomical outcomes as monthly dosing, but with a reduced treatment burden.

The posology of treat and extend dosing has been accepted by the EMA in the marketing authorisation and associated SmPC, where the treatment intervals may be individualised by the prescribing clinician.[1] Wording below is taken from the EU SmPC for Lytenava™ (bevacizumab gamma).

> "Treatment is initiated with one injection per month until maximum visual acuity is achieved and/or there are no signs of disease activity, i.e., no change in visual acuity

or in other signs and symptoms of the disease under continued treatment. The kinetics of bevacizumab gamma efficacy (see section 5.1 EU SmPC) indicate that three or more consecutive monthly injections may be needed initially. **Thereafter, the healthcare professional may individualise treatment intervals based on disease activity as assessed by visual acuity and/or anatomical parameters."**

Also of relevance, is the notion that intravitreal use of Avastin® may have under-performed versus what may be expected of bevacizumab gamma, given the proven variability in protein concentration seen in samples of aliquoted, repackaged Avastin®. Yannuzzi et al. showed 81% of samples had lower protein concentrations than required, with statistically significant variations in protein concentration among samples and increased probability of adverse events. [22]

Lastly, a naïve comparison of relevant anti-VEGF treatment options, across clinically important endpoints is presented in Table 3-13, below.

Table 3-13 Efficacy results following treatment with bevacizumab gamma and UK approved anti-VEGF therapies

PARAMETER	LYTENAVA Bevacizumab gamma	LUCENTIS (TA155) Ranibizumab			EYLEA (TA294) Aflibercept		VABYSMO (TA800) Faricimab	
	NORSE TWO (N=113)	ANCHOR (N = 140)[1]	MARINA (N = 240)[2]	PIER (N = 61)[3]	VIEW 1 (N = 301)[4]	VIEW 2 (N = 306)[4]	TENAYA (N = 334)[5]	LUCERNE (N = 331)[5]
Proportion of subjects gaining ≥ 15 letters from baseline at 1 year, %	41.7	40.3	33.8	13.1	30.6	31.4	20.0	20.2
Proportion of subjects gaining ≥ 10 letters from baseline at 1 year, %	56.5	NR	NR	NR	NR	NR	37.1	39.2
Proportion of subjects gaining ≥ 5 letters from baseline at 1 year, %	68.5	NR	NR	NR	NR	NR	59.2	60.5
Proportion of subjects losing < 15 letters from baseline at 1 year, %	93.5	96.4	94.6	90.2	95.1	95.6	95.4	95.8
Proportion of subjects with a visual acuity Snellen equivalent of 20/200 or worse at 1 year, %	13.0	16.4	11.7	24.6	NR	NR	6.4	7.9
Mean letter change from baseline at 1 year	12.19	11.3	7.2	-0.2	7.9	8.9	5.8	6.6

1. Enrolled only predominantly classic lesions; 0.5mg monthly (Brown 2006)[34]
2. Enrolled only minimally classic or occult lesions; 0.5mg monthly (Rosenfeld 2006)
3. 0.5mg q12 weeks (Regillo 2008)
4. 2mg q8 weeks (Heier 2012)
5. 6mg up to q16weeks after 4 initial q4 week doses (Heier 2022)

After 1 year of treatment with bevacizumab gamma in NORSE TWO, the proportions of subjects gaining ≥ 15 letters, ≥ 10 letters and ≥ 5 letters in BCVA from baseline and mean letter change from baseline were comparable to results observed across the registration studies for the relevant comparator anti-VEGF therapies. The proportions of subjects who lost < 15 letters in BCVA from baseline in NORSE TWO was consistent with those reported in the other studies.

Overall, these comparative results provide further evidence to support the effectiveness of bevacizumab gamma in the treatment of nAMD, and reinforce the similarities in the clinical outcomes associated with all anti-VEGF treatments, with the bridging studies CATT and IVAN demonstrating the likely consistency of outcomes regardless of treatment schedule.

B.3.7 Subgroup analysis

No economic subgroup analyses are considered relevant to this appraisal. This was agreed by NICE at final scope.[8]

B.3.8 Meta-analysis

No further trials of bevacizumab gamma were structured to allow a meta-analysis.

B.3.9 Indirect and mixed treatment comparisons

NORSE TWO compared the efficacy and safety of bevacizumab gamma and ranibizumab. To inform comparisons and explore estimates of relative efficacy and safety for aflibercept, faricimab, and ranibizumab, a systematic literature review (SLR) of clinical evidence was conducted to identify relevant studies for use in an indirect comparison with bevacizumab gamma. No studies exist that directly compare bevacizumab gamma against aflibercept or faricimab in these populations, so initially a network meta-analyses (NMA) was conducted to make this comparison. A match-adjusted indirect comparison (MAIC) was subsequently conducted as a sensitivity analysis, testing how sensitive the NMA results might be to heterogeneity in the trial characteristics, as well as providing an opportunity to explore safety parameters not possible to address in the NMA.

See appendix D for full details of the methodology for the NMA and MAIC.

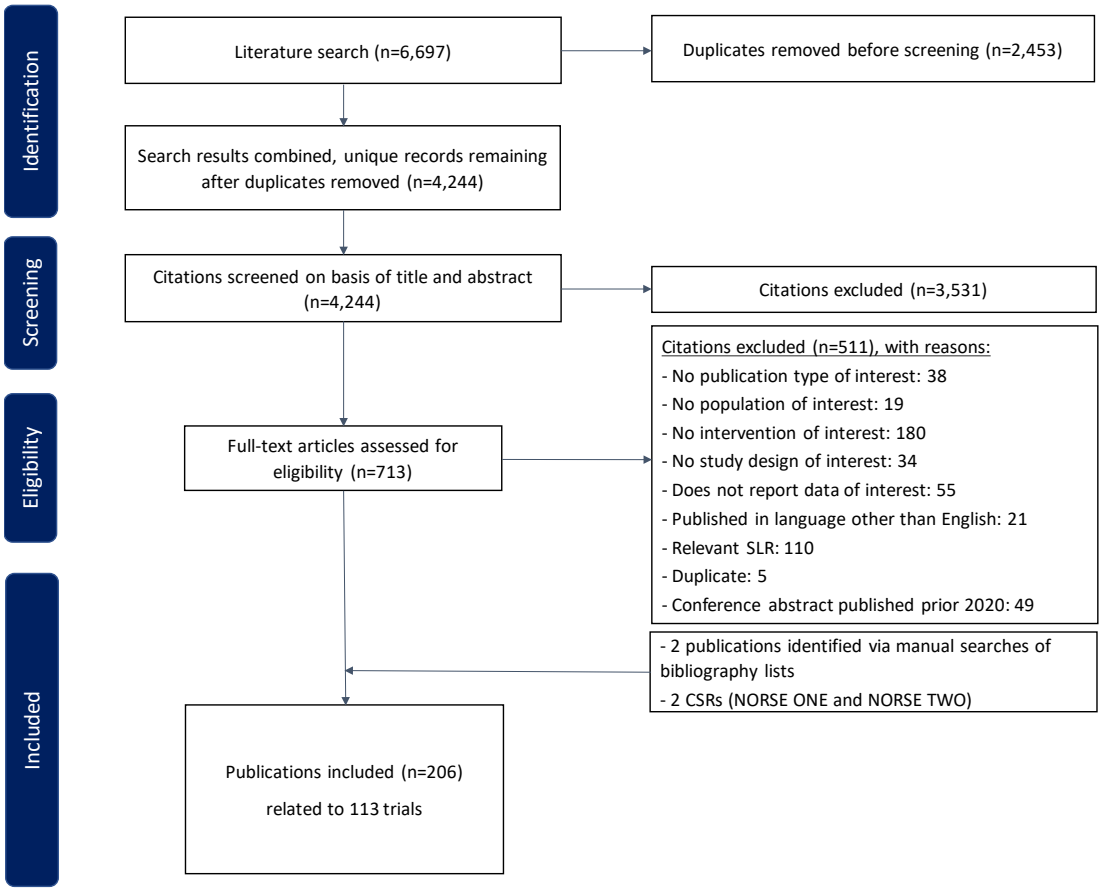
B.3.9.1 Identification and selection of relevant studies

As described in Section B.3.1, an SLR was conducted to identify relevant randomised controlled trial (RCT) evidence for the efficacy and safety data for respective pharmacological interventions for the treatment of nAMD. In total, 4,244 unique publications were screened, of which 713 were reviewed at the full text-stage. Following the exclusion of publications not meeting the criteria, a total of 206 publications reporting 113 trials were deemed eligible for inclusion in the SLR, of which 108 were full publications, 3 were conference abstracts and 2 were clinical study reports (CSRs) for the NORSE ONE and NORSE TWO trials (provided by Outlook Therapeutics) (Figure 3-4).

Following the identification of relevant studies from the clinical SLR, a feasibility assessment for inclusion within an NMA was performed to assess the efficacy and safety of bevacizumab gamma compared with the relevant comparators to this appraisal: aflibercept, faricimab and

ranibizumab. The SLR and NMA were conducted in line with the NICE guide to the methods of technology appraisal.[48] Full details are presented in Appendix D.

Figure 3-5 PRISMA flow chart of included and excluded publications from the SLR of clinical efficacy and safety (includes publications identified as part of the original SLR and SLR update)



Summary of indirect comparison approach:

To inform the comparative efficacy and safety of bevacizumab gamma, Outlook Therapeutics first explored the ability of a Network Meta Analysis (NMA) to deliver robust results. Methods and full results are presented in Appendix D, while top line results are presented here in section B.3.9.

Given the uncertainties identified when completing the NMA, Outlook Therapeutics subsequently explored conducting a matched adjusted indirect comparison (MAIC) to provide confirmatory evidence. Full results are presented later in B.3.9, with methods detailed in Appendix D.

B.3.9.2 Feasibility assessment for NMA

Following identification of relevant studies from the clinical SLR, an assessment was conducted to determine the feasibility of performing a NMA to estimate the relative effectiveness of bevacizumab gamma and the relevant comparators. The eligibility criteria for the NMA were based on the population, intervention, comparator, and outcome (PICO) criteria reported in Table 3-14.

Table 3-14 PICO framework for NMA

	Inclusion criteria for UK evidence base
Population	Adult (≥ 18 years old) patients with wet AMD, anti-VEGF experienced or naive **Excluded populations:** Trials that enrolled exclusively patients with PCV (NORSE TWO trial excluded those patients from enrollment)
Interventions	**Treatments within scope:** • ONS-5010 (bevacizumab gamma) • Aflibercept 2 mg • Faricimab 6 mg • Ranibizumab 0.5 mg **Treatments outside of scope:** • Doses of aflibercept, faricimab, and ranibizumab other than those approved in the UK • Non-opthalmic formulations of bevacizumab (not approved for wet AMD in the UK) • Brolucizumab (due to low market share in the UK) • Conbercept • Pegaptanib • Biosimilar formulations of interventions of interest • PDS **Assumptions:** • Studies investigating only a single administration of the investigational agent will be excluded from analysis. • Studies where the doses of the investigational agent are not reported, or if multiple interventions are pooled into one arm and no separate intervention-level data are reported will be excluded from analysis. • For interventions with EMA- and/or FDA-approved doses and schedules only those will be included in analysis. **Per the faricimab TA800, all conceivable treatment approaches were considered:** • Fixed interval: injections are administered on a fixed schedule every X weeks, for example, Q4W (monthly), Q8W (2-monthly), Q12W (3-monthly), Q16W (4-monthly) treatment. • PRN (pro re nata): injections are administered as needed, following a PRN definition pre-specified in the study protocol. • PRNX (pro re nata and extend): PRN with the potential to extend the assessment interval. • T&E (treat-and-extend): treat with the potential to extend the treatment interval, for example, +2-week adjustment, -2-week adjustment between treatment timings.
Comparators	• Placebo/sham • Standard of care/observation

	• Any other intervention that allows for an indirect treatment comparison (eg. to form a connected network for analysis)
Outcomes	**Timepoints for all outcomes**: 11 months, assumed time equivalence between 48-56 weeks, 11/12 months, and 1-year outcomes. **Vision outcomes:** • Mean change from baseline in BCVA score • Proportion of patients gaining letters: at least 15 letters • Proportion of patients losing letters: at least 15 letters **Anatomic outcomes:** • Mean change in retinal thickness **Safety outcomes:** • Overall ocular AEs rate

Key: AE – adverse event; AMD – age-related macular degeneration; BCVA – best corrected visual acuity; EMA – European Medicines Agency; FDA – Food and Drug Administration; PCV – polypoidal choroidal vasculopathy; PDS – port delivery service; PRN – pro re nata; PRNX (pro re nata and extend); T&E – treat and extend; VEGF – vascular endothelial growth factor.

An overview of the different treatment regimens included in the NMA is presented in Table 3-15. All regimens could either include or exclude a loading phase.

Table 3-15 Treatment doses and regimens included in the NMA

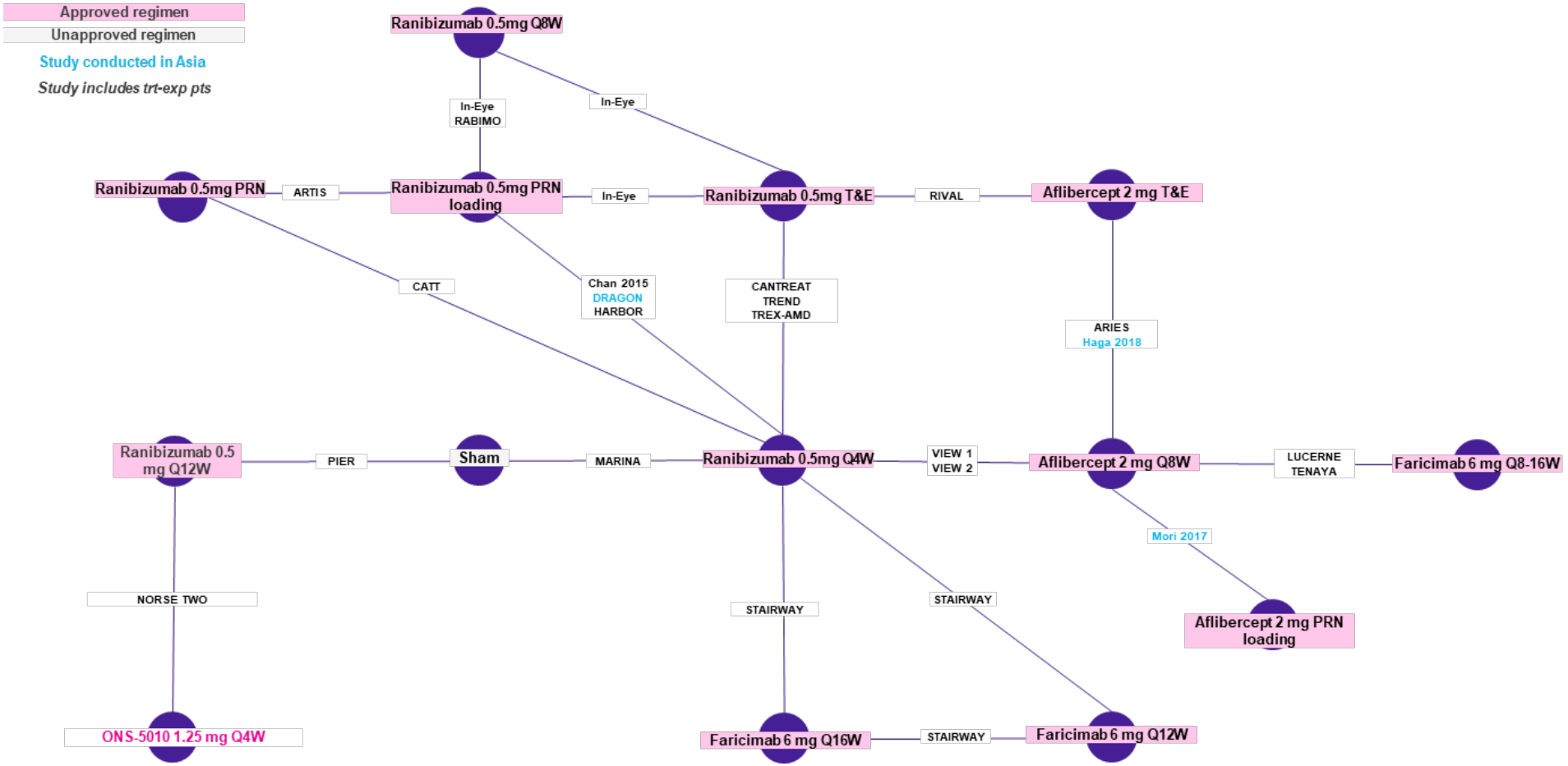
Treatment	Dose	Regimen (with or without >1 loading dose)
Aflibercept	2 mg	Q8W PRN T&E
Bevacizumab gamma	1.25 mg	Q4W
Faricimab	6 mg	Q12W Q16W Q8-Q16W
Ranibizumab IVT	0.5 mg	Q4W Q8W PRN T&E
Placebo/sham		Q4W Q12W

Key: IVT – intravitreal; PRN – pro re nata; T&E – treat and extend.

Results of the feasibility assessment showed that it was possible to develop a connected network of trials which assessed various treatments for nAMD and were similar in design to NORSE TWO. The overall network of evidence is shown in Figure 3-5. 22 RCTs comprise the network; ranibizumab (RAN) 0.5 mg Q4W is the central comparator node. The proposed UK network aligns with the faricimab network from NICE TA800, after removing repackaged

off-label bevacizumab, brolucizumab, and PDS formulations of ranibizumab. This approach is consistent with the NICE evidence review group's reduced network in TA800, which removed comparators that were not relevant to the decision problem.[4]

Figure 3-6 Overall network of evidence



Key: IVT – intravitreal; PRN – pro re nata; T&E – treat and extend.

B.3.9.3 NMA methodology

Reference node

Ranibizumab 0.5 mg Q4W was selected as the common comparator/reference node.

Models, likelihood and priors

All analyses were conducted in a Bayesian framework using a model with parameters, a likelihood distribution, and prior distributions.

Dichotomous outcomes

For dichotomous outcomes, the number of patients with the event and the number of patients in each treatment arm were extracted. A standard model with a binomial likelihood and logit function was used for dichotomous outcomes; the prior distribution for study-specific intercepts and treatment effects was $\mathcal{N}(0, 100^2)$.

Continuous outcomes

For continuous outcomes, the change from baseline (CFB) was extracted for each study arm. If the change from baseline was not provided, the raw value at the timepoint of interest and the baseline score were extracted, and the change from baseline was calculated. In cases where an SE for the CFB was not available, the following tiered approach was taken to impute the missing values:

1. Estimation of the SE of the CFB from the SD of the CFB and the follow-up (fup) arm population size (n) via the following formula:

$$SE_{CFB} = \frac{SD_{CFB}}{\sqrt{n_{fup}}}$$

2. Where SE was missing, but 95% CIs were reported, SEs were calculated as follows:

$$SE(outcome) = |(upper\ 95\%\ CI - lower\ 95\%\ CI)/3.92|$$

3. Where the SE of the CFB could not be estimated via the preceding steps, the weighted (by arm follow-up population size) mean SD of the complete case CFBs was calculated (by outcome type). The SE of the CFB was then calculated as per step 1.

4. Where no complete case data were available to estimate the baseline or follow-up measures by outcome type, they were imputed using the baseline value (for follow-

up measures) or the follow-up value (for baseline measures). The SD and SE of the CFB were then calculated as per step 1.

For continuous outcomes, mean change from baseline to follow-up was analysed using an identity link and a normal likelihood. For treatment effects and study-specific intercepts, $\mathcal{N}(0, 100^2)$ prior distributions were used.

Fixed and random effects models

Fixed and random effects models represent two different approaches to combining/pooling relative effect estimates across studies. With the fixed-effect approach, it is assumed that there is one true effect size shared by all the included studies for each treatment comparison (no heterogeneity is expected). The treatment comparison effect is calculated as the weighted average of study-specific effects, with study weights based on the inverse of the variance of each study. With the random-effects approach, it is assumed that differences in the results between studies are caused in part by true differences between the studies (some level of heterogeneity across study results is expected); the treatment effects are assumed to be normally distributed. Hence, the confidence interval for the random-effects model is often wider than the confidence interval obtained with a fixed-effect model.

Both fixed and random effects models have been considered, with the latter being preferred in the presence of heterogeneity. Where fixed and random effects models are fitted, a comparison was made by observing the deviance information criterion (DIC) statistics and the total residual deviance, to ensure that the selected model's overall fit was adequate. Given the anticipated heterogeneity across the network, only the results from the random effects models have been presented throughout the main document.

Software

All analyses were performed using R version 4.4.0. The model parameters were estimated using a Hamiltonian Markov Chain Monte Carlo (MCMC) algorithm implemented in the multinma package. The results comprise of 50,000 samples from the posterior distribution of each model, having first run and discarded 50,000 'burn-in' iterations.

Planned analysis

The base case NMA included all eligible RCTs connected to the network; while a sensitivity analysis was performed excluding three trials in 100% Asian patients (DRAGON, Haga 2018, Mori 2017).

Full details of the NMA methodology can be seen in Appendix D.

B.3.9.4 NMA results

The results of the NMA models are presented in the following sections to demonstrate the comparable efficacy and safety of bevacizumab gamma to the comparators and support the case for bevacizumab gamma being appraised using the cost-comparison framework in the fast-track appraisal process. Full results for all outcomes/timepoints as well as the sensitivity analyses can be seen within the NMA report.

Mean change in BCVA at 12 months

The base case analysis included 21 trials that reported the mean change in BCVA at 12 months, as shown in Figure 3-7. Under the random effects model, bevacizumab gamma ONS-5010) 1.25 Q4W demonstrated a statistically greater mean difference in BCVA at 12 months when compared to RAN 0.5 Q12W and sham. No meaningful differences were observed between bevacizumab gamma (ONS-5010) 1.25 Q4W and any other comparison. When considering the fixed effects model, the results remained unchanged. It should be noted that SDs for many studies were imputed, as measures of dispersion (SEs, CIs, etc.) were not well-reported. The MDs relative to RAN 0.5 mg Q4W for all interventions are shown in a forest plot (Figure 3-7). Bevacizumab gamma (ONS-5010) 1.25 Q4W has the highest SUCRA value, indicating a strong probability of being the best or among the best treatment options available.

Figure 3-7 Network of evidence – BCVA at 12 months (base case)

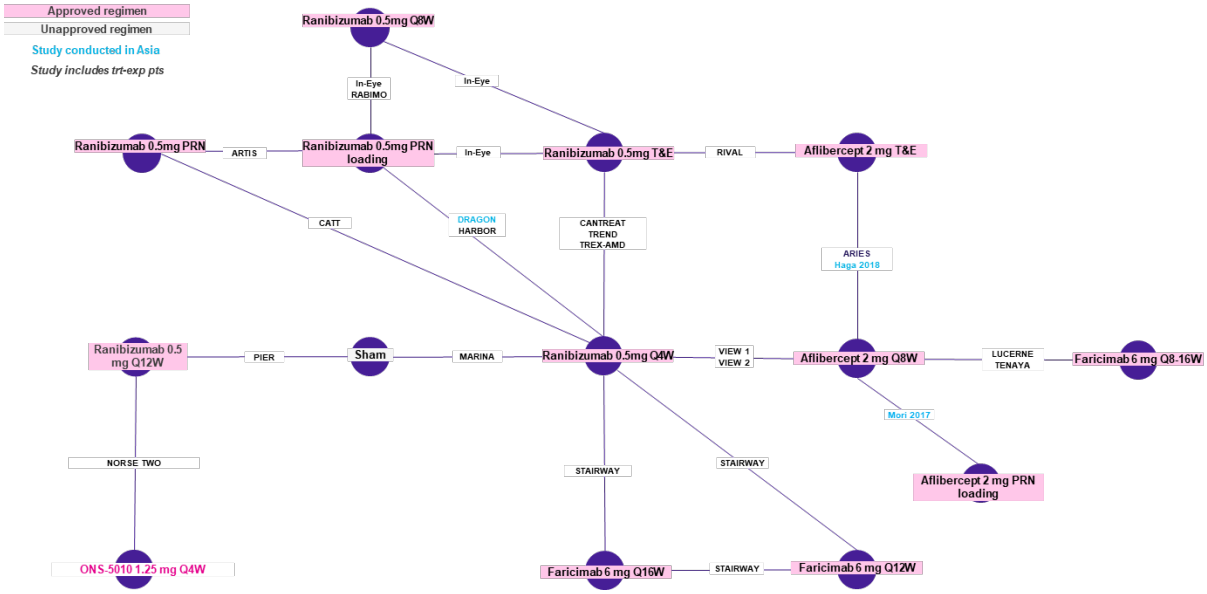
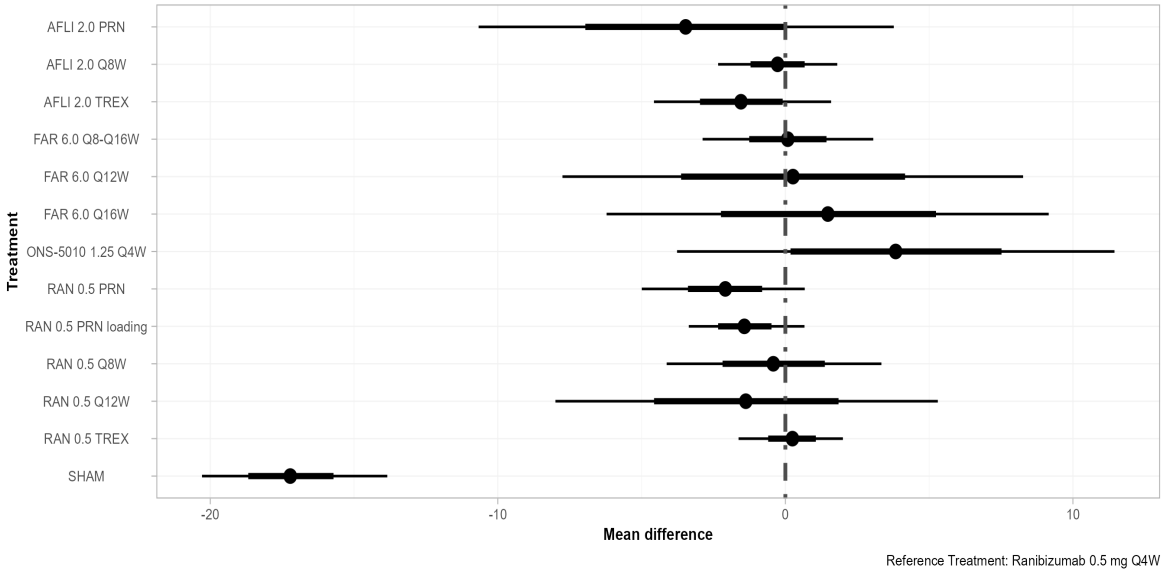


Figure 3-8 Forest plot – BCVA at 12 months (base case), all interventions vs ranibizumab 0.5 mg Q4W



Proportion of patients gaining at least 15 letters

The base case analysis included 20 trials that reported the proportion of patients gaining at least 15 letters at 12 months, as shown Figure 3-8. Under the random effects model, there was a statistically larger proportion of patents gaining at least 15 letters at 12 months in favour of bevacizumab gamma (ONS-5010) 1.25 Q4W patients compared to RAN 0.5 Q12W patients. This conclusion remained the same under the fixed effects model. The ORs relative to placebo for all interventions are shown in a forest plot (Figure 3-9). None of the evaluated

treatments were statistically superior to RAN 0.5 Q4W. Bevacizumab gamma (ONS-5010) 1.25 Q4W did not convey the greatest probability of being the most effective treatment.

Figure 3-9 Network of evidence – Proportion of patients gaining at least 15 letters at 12 months (base case)

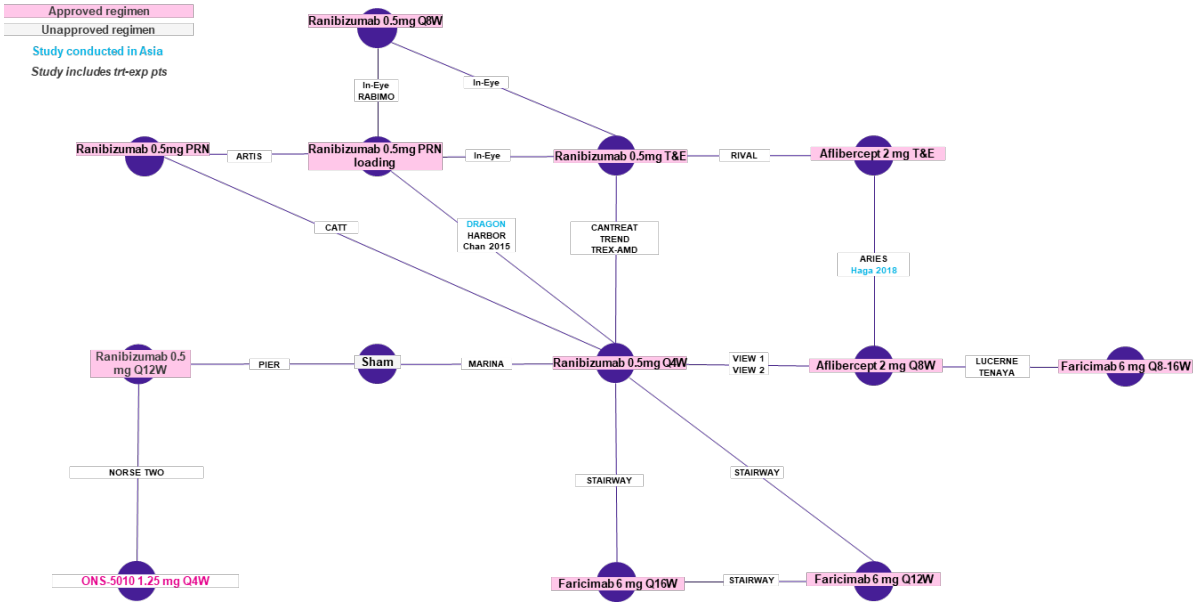
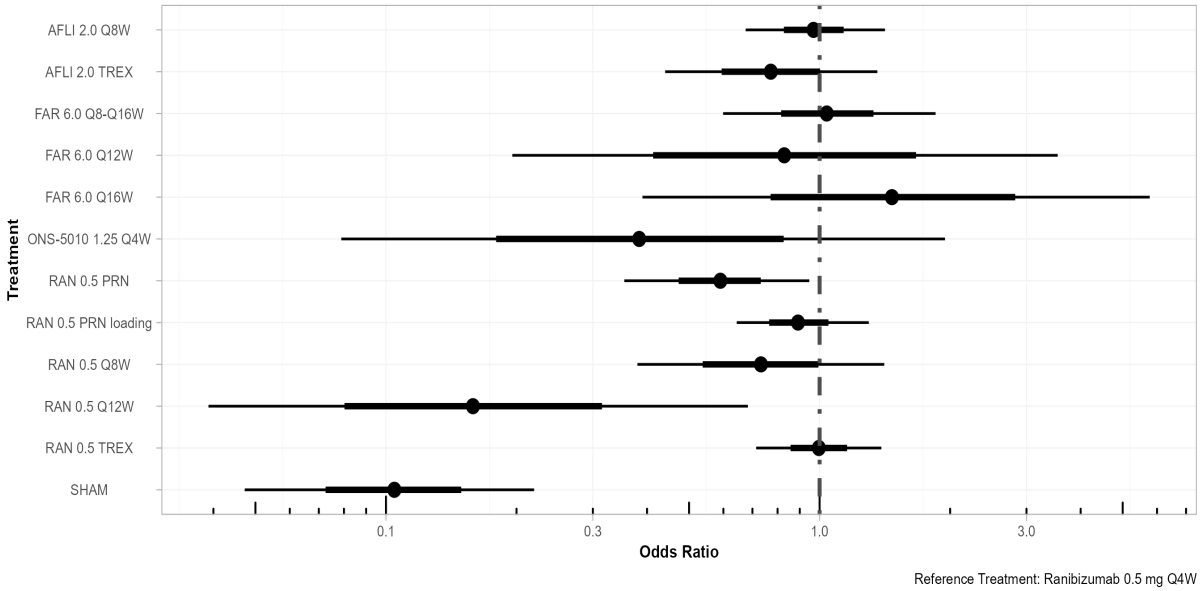


Figure 3-10 Forest plot – Proportion of patients gaining at least 15 letters at 12 months (base case), all interventions vs ranibizumab 0.5 mg Q4W



Proportion of patients losing less than 15 letters

The base case analysis included 16 trials that reported the proportion of patients losing less than 15 letters at 12 months, as shown in Figure 3-10**.** Under the random effects model, there was a statistically larger proportion of patents losing fewer than 15 letters at 12 months among bevacizumab gamma (ONS-5010) 1.25 Q4W patients compared to patients on sham patients. When considering the fixed effects model, ONS-5010 1.25 Q4W also showed a statistically larger proportion of patients losing fewer than 15 letters at 12 months when compared to RAN 0.5 Q12W. The ORs relative to RAN 0.5 mg Q4W for all interventions are shown in a forest plot (Figure 3-11). Bevacizumab gamma (ONS-5010) 1.25 Q4W has the highest SUCRA value, indicating a strong probability of being the best or among the best treatment options available.

Figure 3-11 Network of evidence – Proportion of patients losing less than 15 letters at 12 months (base case)

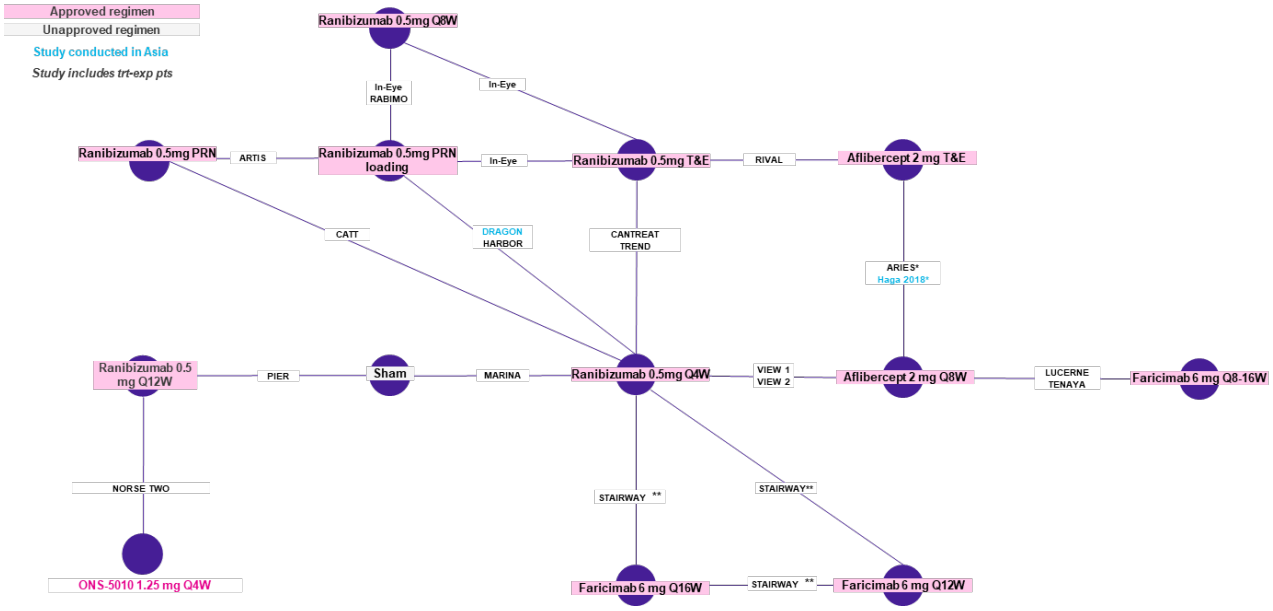
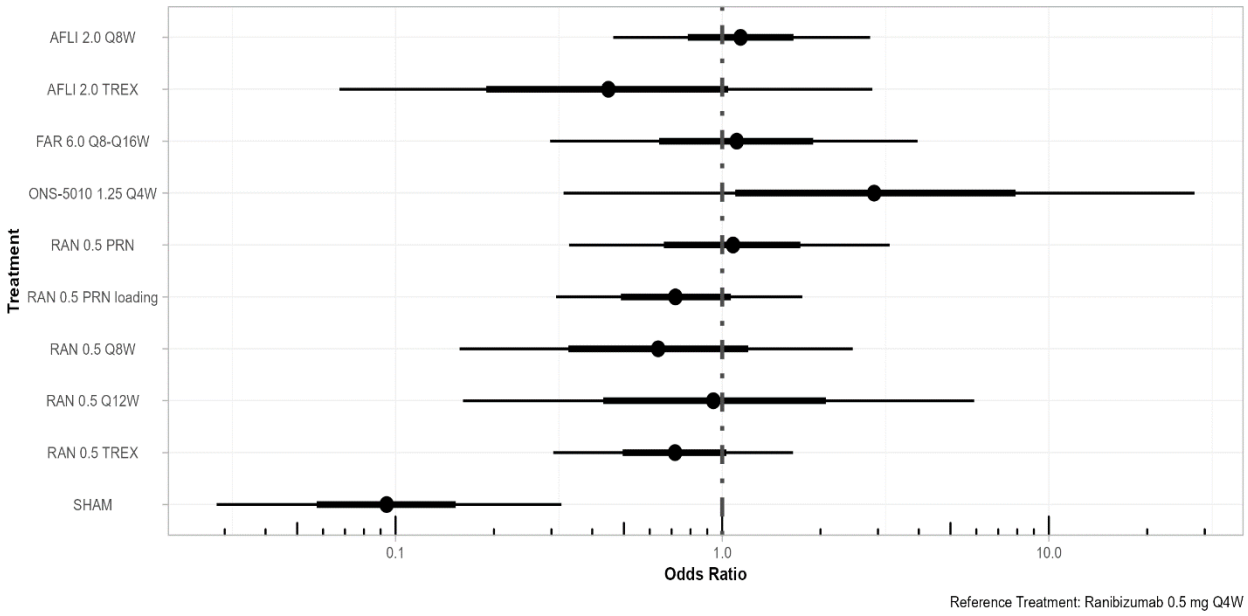


Figure 3-12 Forest plot – Proportion of patients losing less than 15 letters at 12 months (base case), all interventions vs ranibizumab 0.5 mg Q4W

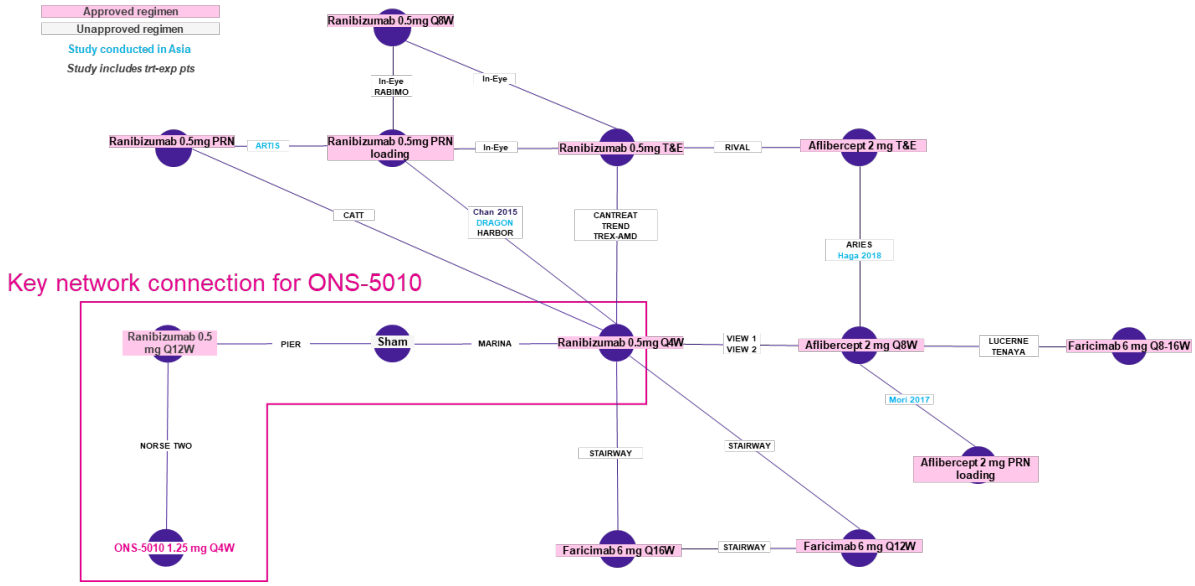


Matched Adjusted Indirect Comparison (MAIC)

The MAIC analysis aimed to compare the efficacy and safety profiles of bevacizumab gamma against various alternative treatments. This analysis was undertaken as an alternative and confirmatory analysis to the previously conducted network meta-analysis (NMA), driven by the potential limitations described below.

To construct the previously described NMA, and in line with TA800 (faricimab), a network of RCTs was constructed, with ranibizumab 0.5 mg as the central node this network is presented in Figure 3-12.[4] The studies were deemed to be reasonably homogeneous across the network, in line with TA800.[4] The current network notably adds NORSE TWO, which compares bevacizumab gamma to ranibizumab 0.5 mg Q12W, which was not a regimen of primary importance in prior submissions. However, for comparisons of bevacizumab gamma, the connection through ranibizumab 0.5 Q12W and sham to the remainder of the network is of critical importance.

Figure 3-13 Network of evidence for network meta-analysis



Any comparison of bevacizumab gamma to ranibizumab 0.5 Q4W (and thereby to any other active treatment in the network) relies on the appropriateness of the assumptions of comparability of study populations and regimens combined in each node. There were differences in observed outcomes in the sham arms of PIER and MARINA; in addition, there were differences in absolute outcomes in the ranibizumab 0.5 mg Q12W arms in PIER and

NORSE TWO. This suggests that these nodes may not be appropriate as “common comparators” for connection to the remainder of the network.

In addition, there were several outcomes of interest (ocular AEs, and gaining ≥10 or ≥5 letters) that were not reported in one or both of trials with a sham arm (PIER, MARINA); no NMA comparing bevacizumab gamma to the remainder of the network was possible for these outcomes.

MAIC methodology

For each comparison, a reference trial (or pooled set of trials) was selected. Where applicable, the primary trial used for previous NICE TAs were selected; if no such trial exists, a sufficiently large trial in a comparable population to that of NORSE TWO was selected. Where multiple trials were conducted to serve as replication (LUCERNE/TENAYA and VIEW 1/VIEW 2), these were treated as pooled single trials.[24, 49] Studies conducted in 100% Asian populations were excluded, as these are not representative of the UK population.

Comparison to ranibizumab 0.5 mg Q12W was not considered, as direct comparison to bevacizumab gamma is available through NORSE TWO. Finally, sham was not considered as a relevant comparator.

Table 3-16 Selected comparator trial for each intervention

Intervention	Selected comparator trial(s)	Other trials evaluating intervention
Afilbercept 2mg Q8W	VIEW 1/VIEW 2 [TA294][7]	ARIES LUCERNE/TENAYA
Aflibercept 2mg TREX	RIVAL	ARIES
Faricimab 6 mg Q12W	STAIRWAY	
Faricimab 6 mg Q16W	STAIRWAY	
Faricimab 6 mg Q8W-Q16W	LUCERNE/TENAYA[TA800] [4]	
Ranibizumab 0.5 mg Q4W	MARINA [TA155][6]	Asahi 2020 Chan 2015 CANTREAT HARBOR IVAN STAIRWAY TREND TREX-AMD VIEW 1/VIEW 2
Ranibizumab 0.5 TREX	TREND	CANTREAT RIVAL TREX-AMD

Ranibizumab 0.5 mg Q8W	In-EYE	RABIMO
Ranibizumab 0.5 PRN loading	HARBOR	Asahi 2020 Chan 2015 In-EYE
Ranibizumab 0.5 PRN	CATT	

Selection of matching variables, creation of an analytic dataset from IPD, further statistical methods, and matching scores are detailed in Appendix D.

MAIC Results

Aflibercept 2 mg Q8W (VIEW 1/VIEW 2)

After matching for BCVA, age, sex and race, bevacizumab gamma (ONS-5010) was not statistically different from aflibercept 2 mg Q8W in terms of proportion of patients gaining ≥15 letters at 11/12 months but was associated with higher odds of losing less than 15 letters from baseline (Table 3-17). Bevacizumab gamma did not differ from aflibercept 2 mg Q8W in terms of CFB in BCVA at 3, 9, or 12 months. Bevacizumab gamma was associated with statistically lower odds of ocular AEs than aflibercept 2 mg Q8W; for this analysis ocular AE was defined as ≥1 ocular TEAE in the study eye.

Table 3-17 Outcome Values and Relative Treatment Effects (VIEW 1/VIEW 2)

Outcome	Outcome value			Relative effect measure	Relative treatment effect estimates			
	Comparator	**Index – unweighted**	**Index - weighted**		**Unweighted GLM**	**Weighted GLM**	**Bootstrapped GLM**	**NMA results (RE model)**
Gain 15+ letters, %	30.97	44.55	38.09	OR	**1.79 (1.16, 2.75)**	1.37 (0.83, 2.24)	1.39 (0.73, 2.73)	2.44 (0.45, 12.95)
Lose < 15 letters, %	94.89	98.02	99.15	OR	2.66 (0.79, 16.62)	**6.27 (1.02, 341.72)**	**7.61 (2.39, ∞)**	2.57 (0.24, 28.90)
BCVA CFB at month 11/12	8.40 (14.7)	11.53 (12.19)	9.72 (11.38)	MD	**3.46 (0.52, 6.41)**	1.65 (-1.64, 4.93)	1.76 (-1.44, 6.75)	4.10 (-3.78, 11.96)
BCVA CFB at month 9	8.14 (13.29)	10.72 (12.05)	10.18 (10.52)	MD	**2.98 (0.24, 5.72)**	2.44 (-0.60, 5.47)	2.61 (-0.18, 7.03)	4.49 (-2.35, 11.40)
BCVA CFB at month 6	7.47 (12.87)	9.88 (12.70)	10.11 (10.44)	MD	**2.85 (0.15, 5.55)**	**3.09 (0.08, 6.09)**	**3.24 (0.97, 6.91)**	6.36 (-0.53, 13.09)
BCVA CFB at month 3	7.19 (7.71)	9.22 (10.67)	8.63 (9.43)	MD	**2.42 (0.71, 4.12)**	1.82 (-0.04, 3.68)	1.97 (-0.58, 5.47)	**5.23 (1.05, 9.33)**
Ocular AEs (Patients with ≥1 ocular TEAE in study eye), %	71.48	48.67	54.39	OR	**0.38 (0.25, 0.57)**	**0.48 (0.30, 0.77)**	**0.47 (0.32, 0.74)**	NA

Key: AE – adverse event; BCVA – best corrected visual acuity; CFB – change from baseline; GLM – generalized linear model; MD – mean difference; NA – not applicable; OR – odds ratio; RE – random effects; SD - standard deviation; TEAE – treatment-emergent adverse event

Aflibercept 2 mg TREX (T&E) (RIVAL)

After matching to the RIVAL study on baseline BCVA, bevacizumab gamma (ONS-5010) did not differ from aflibercept 2 mg TREX in terms of proportion of patients gaining more than 15 BCVA letters from baseline, and change from baseline in BCVA (Table 3-18). Bevacizumab gamma was associated with statistically higher odds of losing less than 15 letters from baseline, although this estimate was highly unstable due to comparing values above 95% in both groups.

Table 3-18 Outcome Values and Relative Treatment Effects (RIVAL)

Outcome	Outcome value			Relative effect measure	Relative treatment effect estimates			
	Comparator	Index – unweighted	Index - weighted		Unweighted GLM	Weighted GLM	Bootstrapped GLM	NMA results (RE model)
Gain 15+ letters, %	20.66	44.55	28.63	OR	3.09 (1.72, 5.63)	1.54 (0.55, 3.98)	1.49 (0.50, 4.68)	2.41 (0.39, 13.94)
Lose < 15 letters, %	95.04	98.02	99.87	OR	2.58 (0.58, 17.90)	38.77 (0.49, NA)	**50.05 (10.38, ∞)**	6.56 (0.37, 123.89)
BCVA CFB at month 11/12, mean (SD)	5.20 (12.83)	11.53 (12.19)	9.77 (6.33)	MD	5.34 (1.83, 8.84)	3.57 (-1.03, 8.17)	**3.64 (1.03, 6.67)**	3.83 (-3.77, 11.44)

Key: BCVA – best corrected visual acuity; CFB – change from baseline; GLM – generalized linear model; MD – mean difference; OR – odds ratio; RE – random effects; SD - standard deviation

Faricimab 6 mg Q12W (STAIRWAY)

After matching for BCVA, age, and race, bevacizumab gamma was not statistically different from faricimab 6 mg Q12W in terms of proportion of patients gaining ≥15 letters, ≥10 letters or ≥5 letters at 11/12 months; analyses of proportion of patients losing <15 letters did not converge due to comparison to an arm with 100%. Bevacizumab gamma did not differ from faricimab 6 mg Q12W in terms of CFB in BCVA at 3, 9, or 12 months; there was an association of bevacizumab gamma with greater CFB in BCVA at 6 months compared to faricimab 6 mg Q12W.

Table 3-19 Outcome Values and Relative Treatment Effects (STAIRWAY)

Outcome	Outcome value			Relative effect measure	Relative treatment effect estimates			
	Comparator	Index – unweighted	Index - weighted		Unweighted GLM	Weighted GLM	Bootstrapped GLM	NMA results (RE model)
Gain 15+ letters, %	33.33	44.55	35.72	OR	1.61 (0.61, 4.55)	1.11 (0.40, 3.29)	1.13 (0.62, 2.20)	2.16 (0.2, 19.42)
Gain 10+ letters, %	52.38	60.40	60.10	OR	1.39 (0.53, 3.59)	1.37 (0.50, 3.71)	1.41 (0.79, 2.66)	NA
Gain 5+ letters	66.67	73.27	70.28	OR	1.37 (0.48, 3.67)	1.18 (0.40, 3.33)	1.22 (0.66, 2.68)	NA
Lose < 15 letters	100.00	98.02	99.05	OR	0.00 (DNC)	0.00 (DNC)	0.00 (DNC)	DNC
BCVA CFB at month 11/12, mean (SD)	10.10 (13.93)	11.53 (12.19)	10.22 (9.26)	MD	-1.52 (-7.20, 4.17)	-2.84 (-7.22, 1.55)	-2.80 (-5.11, -0.69)	3.57 (-7.43, 14.62)
BCVA CFB at month 9, mean (SD)	9.30 (13.29)	10.72 (12.05)	10.40 (9.27)	MD	-1.38 (-7.10, 4.33)	-1.70 (-6.20, 2.81)	-1.75 (-3.85, 0.61)	5.72 (-3.01, 14.56)
BCVA CFB at month 6, mean (SD)	7.40 (12.87)	9.88 (12.70)	10.13 (9.35)	MD	5.56 (-0.14, 11.27)	**5.82 (1.78, 9.86)**	**5.93 (3.76, 8.01)**	7.36 (-2.80, 17.40)
BCVA CFB at month 3, mean (SD)	6.66 (7.71)	9.22 (10.67)	8.62 (8.39)	MD	1.88 (-2.75, 6.50)	1.27 (-2.04, 4.58)	1.31 (-0.88, 3.43)	7.18 (0.85, 13.45)

Key: AE – adverse event; BCVA – best corrected visual acuity; CFB – change from baseline; GLM – generalized linear model; MD – mean difference; NA – not applicable; OR – odds ratio; RE – random effects; SD - standard deviation; TEAE – treatment-emergent adverse event

Faricimab 6 mg Q16W (STAIRWAY)

After matching for BCVA, age, and race covariates, there were no statistical differences between bevacizumab gamma and faricimab 6 mg Q16W across all outcomes using the weighted GLM. When considering the bootstrapped GLM, bevacizumab gamma was associated with smaller increase in BCVA at 11/12 months compared to faricimab 6 mg Q16W, but larger increase in CFB in BCVA at 9 months; in addition, bevacizumab gamma was associated with higher odds of losing < 15 letters using the bootstrapped GLM, although the confidence interval was infinite.

Table 3-20 Outcome Values and Relative Treatment Effects (STAIRWAY)

Outcome	Outcome value			Relative effect measure	Relative treatment effect estimates			
	Comparator	Index – unweighted	Index - weighted		Unweighted GLM	Weighted GLM	Bootstrapped GLM	NMA results (RE model)
Gain 15+ letters, %	46.43	44.55	35.72	OR	0.93 (0.40, 2.17)	0.64 (0.26, 1.59)	0.65 (0.36, 1.27)	3.83 (0.46, 32.10)
Gain 10+ letters, %	60.71	60.40	60.10	OR	0.99 (0.41, 2.31)	0.97 (0.39, 2.40)	1.01 (0.56, 1.89)	NA
Gain 5+ letters, %	82.14	73.27	70.28	OR	0.60 (0.19, 1.62)	0.51 (0.15, 1.47)	0.53 (0.29, 1.17)	NA
Lose < 15 letters, %	96.43	98.02	99.05	OR	1.83 (0.08, 19.84)	3.86 (0.13, 312.56)	**4.31 (1.45, ∞)**	DNC
BCVA CFB at month 11/12, mean (SD)	11.40 (13.93)	11.53 (12.19)	10.22 (9.26)	MD	-1.81 (-6.90, 3.27)	-3.13 (-7.14, 0.88)	**-3.09 (-5.40, -0.85)**	2.34 (-8.41, 13.21)
BCVA CFB at month 9, mean (SD)	12.50 (13.29)	10.72 (12.05)	10.40 (9.27)	MD	3.35 (-1.42, 8.11)	3.03 (-0.59, 6.66)	**2.94 (0.87, 5.25)**	2.78 (-5.76, 11.41)
BCVA CFB at month 6, mean (SD)	9.37 (12.87)	9.88 (12.70)	10.13 (9.35)	MD	0.24 (-4.97, 5.44)	0.49 (-3.41, 4.39)	0.55 (-1.71, 2.74)	5.19 (-4.20, 14.56)
BCVA CFB at month 3, mean (SD)	9.21 (7.71)	9.22 (10.67)	8.62 (8.39)	MD	-0.87 (-5.00, 3.27)	-1.47 (-4.54, 1.59)	-1.48 (-3.68, 0.70)	4.70 (-1.48, 10.74)

Key: BCVA – best corrected visual acuity; CFB – change from baseline; GLM – generalized linear model; MD – mean difference; NA – not applicable; OR – odds ratio; RE – random effects; SD - standard deviation

Faricimab 6 mg Q8-Q16W (LUCERNE/TENAYA)

After matching for BCVA, age, sex and race, bevacizumab gamma was not statistically different from faricimab 6.0 mg Q8-16W in terms of proportion of patients gaining ≥15, ≥10, ≥5 letters at 11/12 months but was associated with higher odds of losing less than 15 letters from baseline. This conclusion remained consistent when analyzed with the bootstrapped GLM. Bevacizumab gamma did not differ from faricimab 6.0 mg Q8-16W in terms of change from baseline in BCVA at 3,6, 9, or 12 months.

Table 3-21 Outcome Values and Relative Treatment Effects (LUCERNE/TENAYA)

Outcome	Outcome value			Relative effect measure	Relative treatment effect estimates			
	Comparator	Index – unweighted	Index - weighted		Unweighted GLM	Weighted GLM	Bootstrapped GLM	NMA results (RE model)
Gain 15+ letters, %	20.03	44.55	28.44	OR	**3.21 (2.06, 4.98)**	1.59 (0.54, 4.11)	1.59 (0.25, 6.88)	0.35 (0.06, 1.96)
Gain 10+ letters, %	38.05	60.40	59.63	OR	**2.48 (1.62, 3.85)**	2.40 (0.97, 6.25)	2.60 (0.63, 14.65)	NA
Gain 5+ letters, %	59.93	73.27	61.55	OR	**1.83 (1.16, 2.98)**	1.07 (0.43, 2.82)	1.16 (0.32, 9.77)	NA
Lose < 15 letters, %	95.62	98.02	99.98	OR	2.27 (0.66, 14.20)	**230.79 (1.27, NA)**	**1234.99 (61.42, ∞)**	2.65 (0.21, 36.25)
BCVA CFB at month 11/12, mean (SD)	6.20 (13.93)	11.53 (12.19)	8.92 (8.14)	MD	**5.47 (2.53, 8.42**)	2.86 (-3.15, 8.87)	3.45 (-0.91, 7.84)	3.74 (-4.40, 11.89)
BCVA CFB at month 9, mean (SD)	6.70 (13.29)	10.72 (12.05)	10.29 (7.65)	MD	**5.05 (2.22, 7.89)**	4.63 (-1.09, 10.34)	**5.06 (0.67, 10.15)**	3.93 (-3.16, 11.06)
BCVA CFB at month 6, mean (SD)	6.73 (12.87)	9.88 (12.70)	9.43 (7.17)	MD	3.62 (0.99, 6.25)	3.17 (-2.24, 8.58)	3.57 (-0.35, 8.91)	5.43 (-1.72, 12.41)
BCVA CFB at month 3, mean (SD)	6.74 (7.71)	9.22 (10.67)	7.47 (7.56)	MD	2.63 (0.98, 4.28)	0.88 (-2.28, 4.03)	1.48 (-3.82, 6.49)	4.35 (-0.05, 8.61)

Key: AE – adverse event; BCVA – best corrected visual acuity; CFB – change from baseline; GLM – generalized linear model; MD – mean difference; NA – not applicable; OR – odds ratio; RE – random effects; SD - standard deviation; TEAE – treatment-emergent adverse event.

Ranibizumab 0.5 mg TREX (T&E) (TREND)

After matching for BCVA, age and race covariates, there were no statistical differences between bevacizumab gamma and ranibizumab 0.5 mg TREX across all outcomes using the weighted GLM. However, this conclusion was not consistent when analyzed using the unweighted GLM and the bootstrapped GLM. Specifically, the unweighted GLM yielded different results across BCVA letter gain categories, incidence of ocular AEs and change from baseline in BCVA at months 9 and 12, whereas the bootstrapped GLM showed disparity across the loss of less than 15 letters outcome and change from baseline in BCVA at month 9.

Table 3-22 Outcome Values and Relative Treatment Effects (TREND)

Outcome	Outcome value			Relative effect measure	Relative treatment effect estimates			
	Comparator	Index – unweighted	Index - weighted		Unweighted GLM	Weighted GLM	Bootstrapped GLM	NMA results (RE model)
Gain 15+ letters, %	25.77	44.55	28.54	OR	**2.31 (1.44, 3.71)**	1.15 (0.49, 2.49)	1.14 (0.50, 3.45)	2.68 (0.50, 14.04)
Gain 10+ letters, %	42.27	60.40	54.97	OR	**2.08 (1.32, 3.32)**	1.67 (0.81, 3.48)	1.69 (0.73, 7.48)	NA
Gain 5+ letters, %	61.17	73.27	61.33	OR	**1.74 (1.07, 2.91)**	1.01 (0.49, 2.16)	1.03 (0.44, 5.57)	NA
Lose < 15 letters, %	93.81	98.02	99.85	OR	3.26 (0.92, 20.77)	43.74 (0.94, NA)	**75.85 (14.85, ∞)**	4.09 (0.39, 45.93)
BCVA CFB at month 11/12, mean (SD)	6.74 (7.71)	11.53 (12.19)	9.23 (7.90)	MD	**5.16 (2.05, 8.27)**	2.86 (-1.65, 7.37)	2.97 (0.42, 6.69)	3.61 (-4.19, 11.39)
BCVA CFB at month 9, mean (SD)	6.74 (7.71)	10.72 (12.05)	10.45 (7.79)	MD	**5.11 (2.19, 8.02)**	4.84 (0.62, 9.06)	**4.94 (2.26, 8.42)**	4.35 (-2.69, 11.44)
BCVA CFB at month 6, mean (SD)	6.74 (7.71)	9.88 (12.70)	9.57 (7.84)	MD	3.25 (0.52, 5.97)	2.94 (-1.00, 6.87)	**3.23 (0.24, 7.35)**	6.37 (-0.61, 13.36)
BCVA CFB at month 3, mean (SD)	6.74 (7.71)	9.22 (10.67)	7.67 (7.64)	MD	2.14 (0.25, 4.02)	0.58 (-1.93, 3.09)	0.86 (-2.68, 5.02)	**4.85 (0.48, 9.03)**
Ocular AEs, (NR if treatment-related) , %	35.91	48.67	37.17	MD	**1.69 (1.10, 2.61)**	1.06 (0.50, 2.16)	1.00 (0.54, 2.78)	NA

Key: AE – adverse event; BCVA – best corrected visual acuity; CFB – change from baseline; GLM – generalized linear model; MD – mean difference; NA – not applicable; NR – not reported; OR – odds ratio; RE – random effects; SD - standard deviation.

Ranibizumab 0.5 mg PRN (CATT)

After matching for BCVA, age, sex and race, there were no statistical differences between bevacizumab gamma and ranibizumab 0.5 mg PRN across all outcomes using the weighted GLM (Table 3-23). This conclusion remained consistent when analyzed with the bootstrapped GLM. However, the unweighted GLM conveyed different results for the proportion of patients gaining ≥15 letters at 11/12 months and change from baseline in BCVA at months 3,6 and 12.

Table 3-23 Outcome Values and Relative Treatment Effects (CATT)

Outcome	Outcome value			Relative effect measure	Relative treatment effect estimates			
	Comparator	Index – unweighted	Index - weighted		Unweighted GLM	Weighted GLM	Bootstrapped GLM	NMA results (RE model)
Gain 15+ letters, %	24.91	44.55	30.38	OR	**2.42 (1.50, 3.90)**	1.32 (0.32, 4.37)	1.10 (0.08, 14.52)	1.54 (0.24, 8.30)
Lose < 15 letters, %	95.44	98.02	100.00	OR	2.37 (0.64, 15.30)	1904.06 (7.22, NA)	∞ (64.13, ∞)	2.70 (0.24, 35.36)
BCVA CFB at month 11/12, mean (SD)	6.80 (13.10)	11.53 (12.19)	10.91 (5.87)	MD	**5.04 (2.11, 7.97)**	4.41 (-2.16, 10.98)	**4.56 (0.08, 8.91)**	5.93 (-2.15, 14.06)
BCVA CFB at month 9, mean (SD)	7.20 (13.29)	10.72 (12.05)	11.61 (6.64)	MD	3.48 (0.74, 6.23)	4.37 (-1.53, 10.27)	**4.40 (0.36, 11.57)**	3.79 (-3.38, 11.00)
BCVA CFB at month 6, mean (SD)	5.80 (12.87)	9.88 (12.70)	9.36 (6.79)	MD	**5.25 (2.41, 8.09)**	4.73 (-1.61, 11.07)	**5.17 (0.50, 13.78)**	5.91 (-1.29, 12.94)
BCVA CFB at month 3, mean (SD)	5.60 (7.71)	9.22 (10.67)	7.91 (7.00)	MD	**3.45 (1.47, 5.44)**	2.14 (-1.78, 6.06)	2.45 (-4.07, 10.38)	**5.94 (1.50, 10.42)**

Key: BCVA – best corrected visual acuity; CFB – change from baseline; GLM – generalized linear model; MD – mean difference; NA – not applicable; OR – odds ratio; RE – random effects; SD - standard deviation

Ranibizumab 0.5 mg Q8W (In-EYE)

After matching for BCVA and age, bevacizumab gamma was not statistically different from ranibizumab 0.5 Q8W in terms of proportion of patients gaining ≥15, gaining ≥5 letters, and losing less than 15 letters at 11/12 months, respectively, but was associated with higher odds of gaining ≥10 letters (Table 3-24). Additionally, bevacizumab gamma differed statistically from ranibizumab 0.5 Q8W in terms of change from baseline in BCVA at 12 months. This conclusion remained consistent when analyzed under both the unweighted GLM and the bootstrapped GLM. Bevacizumab gamma was not associated with statistically lower odds of ocular AEs, defined as ≥1 ocular AE in the study eye.

Table 3-24 Outcome Values and Relative Treatment Effects (In-EYE)

Outcome	Outcome value			Relative effect measure	Relative treatment effect estimates			
	Comparator	Index – unweighted	Index - weighted		Unweighted GLM	Weighted GLM	Bootstrapped GLM	NMA results (RE model)
Gain 15+ letters, %	24.27	44.55	35.81	OR	**2.51 (1.39, 4.60)**	1.74 (0.83, 3.61)	1.76 (0.94, 4.00)	1.95 (0.32, 11.29)
Gain 10+ letters, %	42.72	60.40	61.69	OR	**2.04 (1.17, 3.59)**	**2.16 (1.09, 4.35)**	**2.16 (1.09, 5.62)**	NA
Gain 5+ letters, %	59.22	73.27	71.20	OR	**1.89 (1.05, 3.43)**	1.70 (0.84, 3.58)	1.72 (0.86, 6.98)	NA
Lose < 15 letters, %	94.17	98.02	99.59	OR	3.06 (0.69, 21.25)	14.87 (0.92, NA)	**19.71 (5.22, ∞)**	**4.58 (0.35, 67.15)**
BCVA CFB at month 11/12, mean (SD)	7.00 (13.93)	11.53 (12.19)	10.81 (8.08	MD	**5.58 (1.85, 9.31)**	**4.85 (1.05, 8.65)**	**4.90 (2.84, 7.32)**	4.25 (-4.21, 12.69)
Ocular AEs, %	46.60	52.21	40.26	OR	1.25 (0.73, 2.14)	0.77 (0.39, 1.50)	0.76 (0.46, 1.58)	NA

Key: AE – adverse event; BCVA – best corrected visual acuity; CFB – change from baseline; GLM – generalized linear model; MD – mean difference; NA – not applicable; OR – odds ratio; RE – random effects; SD - standard deviation; TEAE – treatment-emergent adverse event

Ranibizumab 0.5 mg PRN loading (HARBOR)

After matching for BCVA, age, sex and race, bevacizumab gamma was not statistically different from ranibizumab 0.5 mg PRN loading in terms of proportion of patients losing less than 15 letters at 11/12 months but was associated with higher odds of gaining ≥15 letters and statistically differed in terms of change from baseline in BCVA at 11/12 months (Table 3-25). These conclusions remained consistent when analyzed with both the unweighted GLM and the bootstrapped GLM. Bevacizumab gamma was associated with statistically lower odds of ocular AEs under both the weighted GLM and bootstrapped GLM.

Table 3-25 Outcome Values and Relative Treatment Effects (HARBOR)

Outcome	Outcome value			Relative effect measure	Relative treatment effect estimates			
	Comparator	Index – unweighted	Index - weighted		Unweighted GLM	Weighted GLM	Bootstrapped GLM	NMA results (RE model)
Gain 15+ letters, %	30.18	44.55	42.76	OR	**1.86 (1.16, 2.97)**	**1.72 (1.07, 2.77)**	**1.75 (1.15, 2.63)**	2.35 (0.44, 12.56)
Lose < 15 letters, %	94.55	98.02	98.22	OR	2.86 (0.79, 18.33)	3.19 (0.83, 23.94)	**3.34 (1.20, ∞)**	4.08 (0.37, 44.81)
BCVA CFB at month 11/12, mean (SD)	8.20 (13.30)	11.53 (12.19)	11.15 (11.38)	MD	**3.65 (0.67, 6.63)**	**3.27 (0.31, 6.23)**	**3.31 (1.05, 5.29)**	5.25 (-2.61, 13.09)
BCVA CFB at month 9, mean (SD)	8.61 (13.29)	10.72 (12.05)	10.55 (11.28)	MD	1.40 (-1.58, 4.39)	1.24 (-1.73, 4.20)	1.26 (-0.93, 3.49)	-5.12 (-12.09, 1.74)
BCVA CFB at month 6, mean (SD)	8.05 (12.87)	9.88 (12.70)	9.97 (11.82)	MD	**3.03 (0.19, 5.86)**	**3.12 (0.32, 5.93)**	**3.17 (1.00, 5.13)**	-6.88 (-13.66, 0.06)
BCVA CFB at month 3, mean (SD)	8.33 (7.71)	9.22 (10.67)	9.13 (10.00)	MD	0.73 (-1.25, 2.72)	0.64 (-1.31, 2.59)	0.68 (-1.28, 2.50)	-5.01 (-9.14. -0.71)
Ocular AEs, %	62.18	52.21	51.14	OR	0.66 (0.43, 1.03)	**0.64 (0.41, 1.00**	**0.65 (0.44, 0.93)**	NA

Key: AE – adverse event; BCVA – best corrected visual acuity; CFB – change from baseline; GLM – generalized linear model; MD – mean difference; NA – not applicable; OR – odds ratio; RE – random effects; SD - standard deviation

Ranibizumab 0.5 mg Q4W (MARINA)

After matching for BCVA, age, sex and race, bevacizumab gamma was not statistically different from ranibizumab 0.5 mg Q4W in terms of proportion of patients gaining ≥15 letters and losing less than 15 letters at 11/12 months, respectively, when analyzed with the weighted GM (Table 3-26). Bevacizumab gamma was associated with larger CFB in BCVA at 11/12, 9, and 3 months in the weighted GLM.

In the sensitivity analysis against HARBOR, bevacizumab gamma was not statistically different from ranibizumab 0.5 mg Q4W in terms of CFB in BCVA or in gain/loss outcomes; however, bevacizumab gamma was associated with a lower risk of ocular AEs.

Table 3-26 Outcome Values and Relative Treatment Effects (MARINA)

Outcome	Outcome value			Relative effect measure	Relative treatment effect estimates			
	Comparator	Index – unweighted	Index - weighted		Unweighted GLM	Weighted GLM	Bootstrapped GLM	NMA results (RE model)
Gain 15+ letters, %	33.75	44.55	44.09	OR	1.58 (0.98, 2.54)	1.55 (0.95, 2.51)	**1.58 (1.02, 2.41)**	0.38 (0.08, 2.00)
Lose < 15 letters, %	94.58	98.02	98.75	OR	2.83 (0.76, 18.35)	4.51 (0.97, 57.53)	**4.81 (1.73, ∞)**	2.92 (0.33, 27.92)
BCVA CFB at month 11/12, mean (SD)	7.30 (13.93)	11.53 (12.19)	11.54 (11.05)	MD	**4.88 (1.74, 8.02)**	**4.89 (1.78, 7.99)**	**4.93 (2.91, 6.97)**	3.83 (-3.77, 11.44)
BCVA CFB at month 9, mean (SD)	7.15 (13.93)	10.72 (12.05)	11.09 (11.00)	MD	**3.04 (0.28, 5.79)**	**3.41 (0.70, 6.13)**	**3.46 (1.36, 5.56)**	3.51 (-3.04, 10.12)
BCVA CFB at month 6, mean (SD)	7.15 (13.93)	9.88 (12.70)	10.45 (11.54)	MD	2.11 (-1.04, 5.27)	2.68 (-0.45, 5.82)	**2.74 (0.62, 4.69)**	5.11 (-1.40, 11.57)
BCVA CFB at month 3, mean (SD)	7.15 (13.93)	9.22 (10.67)	9.46 (9.79)	MD	**3.49 (1.43, 5.55)**	**3.73 (1.72, 5.74)**	**3.81 (1.83, 5.61)**	**4.95 (0.96, 8.83)**

Key: BCVA – best corrected visual acuity; CFB – change from baseline; GLM – generalized linear model; MD – mean difference; NA – not applicable; OR – odds ratio; RE – random effects; SD - standard deviation

B.3.9.5 Uncertainties in the indirect and mixed treatment comparisons

Network Meta Analysis

This NMA has several limitations. The network connection through sham treatment is not robust, as both included trials evaluating a sham arm (MARINA, PIER) with a large proportion of anti-VEGF-experienced patients, which may act as an effect modifier and influence the relative effect estimates. Additionally, low event proportions in sham arms contributed to unstable estimates of relative treatment effects of bevacizumab gamma to other competing interventions. Lastly, the substantial amount of missing data for measures of dispersion such as SDs, necessitated the use of imputation.

Matched Adjusted Indirect Comparison

The MAIC findings reveal several important insights but also highlight some limitations and disparities when compared to the network meta-analysis (NMA) results. The MAIC allows estimates of relative treatment effects where no connected network is available, and in the case where assumptions of a network meta-analysis are violated, allows for comparison between competing interventions that adjusts for differences in baseline patient populations.

The effective sample size post-matching varied, ranging from 8 to 105 patients out of a total of 113 patients receiving bevacizumab gamma in NORSE TWO. Notably, comparisons with aflibercept 2 mg TREX, faricimab 6 mg Q8-Q16W, and ranibizumab 0.5 mg PRN resulted in an effective sample size constituting less than 20% of NORSE TWO trial population, indicating poor overlap and reduced reliability of these comparisons. This limited overlap suggests that the patient populations in the comparator trials were quite dissimilar from NORSE TWO, making robust comparisons challenging.

Overall, the comparative analysis using MAIC revealed informative results regarding the efficacy and safety profiles of bevacizumab gamma relative to other treatments – despite some analyses relying on very small sample sizes. Bevacizumab gamma generally demonstrated similar efficacy in terms of proportion of patients gaining ≥15 letters when compared to most other treatments. Bevacizumab gamma was associated with higher odds of losing less than 15 letters than all included interventions except ranibizumab 0.5 mg PRN, faricimab 6 mg Q16W; these relative effect estimates should be viewed with caution, as nearly all studies reported >95% of patients losing < 15 letters, resulting in many infinite confidence intervals. Regarding safety, bevacizumab gamma often exhibited lower odds of

ocular adverse events compared to all competing interventions for which a comparison was possible except ranibizumab 0.5 Q8W, indicating a favourable safety profile.

Due to lack of data availability of many potentially relevant baseline characteristics in both the index and comparator trials, the ability to match on all prognostic factors or treatment effect modifiers was limited. Unanchored MAICs assume all possible prognostic and treatment effect modifiers are accounted for. This is a strong assumption that is not met in this evidence base, though the importance of prognostic factors that are missing from the model specification is unclear.

In summary, this analysis highlights the complexity of indirect treatment comparisons and the importance of considering baseline characteristic alignment when interpreting results. Bevacizumab gamma appeared comparable to other treatments in terms of visual acuity efficacy outcomes and was associated with similar or lower risk of ocular adverse events than other competing interventions. While the MAIC provides the ability to adjust for individual patient-level covariates which can account for differences in baseline characteristics more precisely than aggregate-level adjustments used in NMA, this can lead to disparities in estimates of treatment effects as found in this analysis. Additionally, there are intrinsic methodological differences between MAIC and NMA, such as the handling of heterogeneity and the different statistical approaches which may also lead to variation and underscores the need for cautious interpretation.

In NICE technology appraisals cost-comparison analyses assume that the intervention and comparator have similar clinical efficacy and safety.[50] Results from the NMA and MAIC analyses are used to support inferences about the clinical similarities of bevacizumab gamma and the comparators aflibercept, faricimab and ranibizumab but do not directly inform the economic model.

Finally, it is relevant to note that indirect comparison results presented here for Q4W bevacizumab gamma, should be interpreted in light of the previously described bridging studies, which consistently conclude that monthly dosing and extended interval dosing have been shown to produce similar outcomes.

B.3.10 Adverse reactions

NORSE TWO (bevacizumab gamma)

The primary objective of the NORSE TWO study was to evaluate the safety and tolerability of bevacizumab gamma when administered monthly from baseline to 12 months. Note that, while subjects in the bevacizumab gamma group had 12 months of safety follow-up (the first 11 months of which were masked), subjects in the ranibizumab group had 11 months of safety follow-up (all of which were masked). Regardless of treatment, all subjects had their assigned study drug administered at the study center. Overall, the mean (SD) duration of study drug exposure was 316.1 (49.63) days for subjects in the bevacizumab gamma group and 299.6 (77.34) days for subjects in the ranibizumab group.

Of the 228 subjects in the safety population, 170 (74.6%) experienced at least 1 TEAE each during the study, with a similar frequency of events occurring in the bevacizumab gamma and ranibizumab groups (75.2% and 73.9%, respectively). This similarity was despite the more than 2-fold increase in the number of injections given to subjects in the bevacizumab gamma group (12 injections expected) compared with subjects in the ranibizumab group (5 injections expected), and the fact that the follow-up period was 1 month longer in the bevacizumab gamma group.

Within the bevacizumab gamma group, the ocular events occurring in the study eye reported at the 3 highest frequencies were conjunctival haemorrhage (8.8%), IOP increased (6.2%), and cataract nuclear, corneal abrasion, retinal haemorrhage, visual acuity reduced, vitreous detachment, and vitreous floaters (3.5% each). Within the ranibizumab group, the ocular events occurring in the study eye reported at the 3 highest frequencies were visual acuity reduced (12.2%), retinal haemorrhage (5.2%), and dry eye (4.3%).

Table 3-27 Serious Adverse Events and Adverse Events of Increased Ocular Pressure, Ocular Inflammation and Arterial Thromboembolic Events Following Treatment with Bevacizumab gamma and approved anti-VEGF Therapies

System Organ Class Preferred Term	Ranibizumab[a] (N = 115)	Bevacicumab gamma[a] (N = 113)
	n (%)/m	n (%)/m
Eye disorders	46 (40.0)	47 (41.6)
Cataract	2 (1.7)	2 (1.8)
Cataract nuclear	0	4 (3.5)
Conjunctival haemorrhage	3 (2.6)	10 (8.8)
Conjunctival hyperaemia	2 (1.7)	0
Corneal abrasion	1 (0.9)	4 (3.5)
Dermatochalasis	2 (1.7)	2 (1.8)
Dry eye	5 (4.3)	2 (1.8)
Eye irritation	0	2 (1.8)

Eye pain	2 (1.7)	1 (0.9)
Hordeolum	2 (1.7)	0
Metamorphopsia	3 (2.6)	1 (0.9)
Neovascular age-related macular degeneration	4 (3.5)	0
Posterior capsule opacification	2 (1.7)	1 (0.9)
Punctate keratitis	2 (1.7)	3 (2.7)
Retinal degeneration	2 (1.7)	1 (0.9)
Retinal haemorrhage	6 (5.2)	4 (3.5)
Retinal oedema	3 (2.6)	0
Subretinal fibrosis	2 (1.7)	2 (1.8)
Subretinal fluid	4 (3.5)	3 (2.7)
Vision blurred	0	2 (1.8)
Visual acuity reduced	14 (12.2)	4 (3.5)
Vitreous detachment	2 (1.7)	4 (3.5)
Vitreous floaters	1 (0.9)	4 (3.5)
Vitreous haemorrhage	1 (0.9)	2 (1.8)
Injury, poisoning and procedural complications	2 (1.7)	0
Procedural pain	2 (1.7)	0
Investigations	1 (0.9)	7 (6.2)
Intraocular pressure increased	1 (0.9)	7 (6.2)

Adverse events were coded using Medical Dictionary for Regulatory Activities, Version 23.0.
Table only includes ocular events in the study eye experienced by at least 2 subjects in either study drug group.
System organ classes are presented only if at least 1 preferred term within that class was reported for 2 or more subjects in either study drug group.

a Includes data obtained through 11 months of safety follow-up for the ranibizumab group and 12 months of safety follow-up for the bevacizumab gamma group.

Of the related ocular TEAEs occurring in the study eye, the only individual events reported for more than 2 subjects each in the bevacizumab gamma group were conjunctival haemorrhage (9 subjects) and vitreous floaters (3 subjects). None of the individual related ocular TEAEs occurring in the study eye were reported for more than 2 subjects each in the ranibizumab group.

Overall, 27 subjects (11.8%), including 14 (12.4%) in the bevacizumab gamma group and 13 (11.3%) in the ranibizumab group, experienced at least 1 TEAE (ocular [regardless of study eye] and non-ocular combined) that was ≥ Grade 3 in severity. The only ocular events with a severity of Grade 3 or higher were iritis (occurring in 1 subject in the bevacizumab gamma group), and retinal detachment and retinal tear (both occurring in the same subject in the ranibizumab group); the event of iritis was considered to be related to the study drug/study procedure.

No meaningful differences between study drug groups were observed based on an analysis of vital signs, ophthalmic safety findings, or concomitant medication uses. Regarding the ophthalmic safety findings, a small, expected increase in the mean IOP for the study eye at 30 minutes postinjection was observed following each administration of study drug; the mean increase was comparable between study drug groups. Further, the IOP values measured in both study drug groups at each subsequent pre-injection time point had

reverted to screening or near screening levels, indicating the initial increase in IOP was transient. Separately, at most visits, no subject in either study drug group had subfoveal scarring present in the study eye; at the last study visit, 6.3% of the subjects in the bevacizumab gamma group and 9.6% of the subjects in the ranibizumab group had subfoveal scarring present in the study eye. There were no anterior chamber cells or flare, and no vitreous cells graded > 0 in the study eye in either study drug group at any time during the study.

Relevant adverse events following treatment with bevacizumab gamma and UK approved anti-VEGF Therapies

With respect to safety, following intravitreal administration of bevacizumab gamma in the pivotal study NORSE TWO, SAEs were generally observed less frequently than in the registration studies for the previously appraised anti-VEGF treatments (Table 3.27). Intravitreal injections have been associated with transient increases in ocular pressure, ocular inflammation, and a potential risk for ATEs. While these events were seen in NORSE TWO, the numbers were low and generally consistent with what was reported in the registration trials for the approved anti-VEGF treatments (TA155, TA294 and TA800) in (Table 3.27).[4, 6, 7] In NORSE TWO, increases in ocular pressure, ocular inflammation and ATEs were observed at or below what was seen in the ANCHOR, MARINA, PIER, and VIEW2 studies.[34-36, 49] In these studies, IOP were seen in 9.5-17.6%, ocular inflammation in 15.0%, and ATEs in 2.6-4.6% of subjects compared to 6.2%, 0.8%, and 1.5%, respectively, in NORSE TWO. Overall, these results indicate that bevacizumab gamma is a safe treatment in nAMD patients, similar to the previously appraised anti-VEGF therapies (TA155, TA294 and TA800), with no increased safety concern.[4, 6, 7]

Table 3-28 Relevant adverse events following treatment with bevacizumab gamma and UK approved anti-VEGF Therapies

	LYTENAVA Bevacizumab gamma	**LUCENTIS (TA155)** Ranibizumab			**EYLEA (TA294)** Aflibercept		**VABYSMO (TA800)** Faricimab	
Parameter	NORSE TWO N=113	ANCHOR (N = 140)[1]	MARINA (N = 240)[2]	PIER (N =61)[3]	VIEW 1 (N = 301)[4]	VIEW 2 (N=306)[4]	TENAYA (N = 334)[5]	LUCERNE (N = 331)[5]
SAEs, %	12.4	20.0	15.0	16.4	29.7	26.4	10.2	17.5
IOP TEAEs, %	6.2	8.6	17.6	8.2	5.0	9.5	<5.0	<5.0
Ocular inflammation TEAEs, %	0.8	15.0	NR	NR	NR	NR	NR	0.9
ATEs, %	1.5	4.3	4.6	0	2.0	2.6	NR	NR

ATE –arteriothrombotic event; IOP – intraocular pressure; NR – not reported; SAE – serious adverse effects; TEAE – treatment-emergent adverse effects
ATEs include: nonfatal stroke, nonfatal myocardial infarction, nonfatal haemorrhagic stroke, or vascular death (including deaths of unknown cause)
Ocular inflammation include: uveitis, iritis, iridocyclitis, vitritis, anterior-chamber inflammation
Source: NORSE TWO CSR; (Brown 2006, Heier 2012, Heier 2022, Regillo 2008, Rosenfeld 2006)

Overall, the safety results for bevacizumab gamma, as assessed across all 3 completed clinical studies, were consistent with those found in the peer-reviewed literature. No unexpected safety signals or adverse safety trends were observed for bevacizumab gamma relative to the safety profile for Avastin® (repackaged off-label bevacizumab) reported in the IVAN, CATT, and other peer-reviewed clinical studies.[30, 31, 38-43, 45] This was confirmed in the safety analysis conducted during the MAIC. Thus when considering the comparative safety analysis, these published studies provide additional support to the safety profile of bevacizumab gamma.

In appendix F, provide details of any studies that report additional adverse reactions to those reported in the studies in section 3.2.

B.3.11 Conclusions about comparable health benefits and safety

Data from NORSE TWO showed that bevacizumab gamma met the primary and key secondary endpoints for efficacy with clinically impactful change observed for treated patients.[39, 41] After one year of treatment with bevacizumab gamma in the pivotal, NORSE TWO, Phase 3 trial, the proportions of subjects gaining ≥ 15 letters, ≥ 10 letters and ≥ 5 letters in BCVA from baseline, and mean letter change from baseline, were higher compared to observations across the registration studies for the approved anti-VEGF therapies, which confirms the non-inferiority premise for bevacizumab gamma in this cost-comparison analysis, when compared to the comparators of previous appraisals for nAMD (TA155, TA294 and TA800).[4, 6, 7] The proportions of subjects who lost < 15 letters in BCVA from baseline in NORSE TWO was consistent with those reported in the other studies.

The safety results demonstrated in NORSE TWO are consistent with previously reported safety results from Outlook Therapeutics NORSE ONE and NORSE THREE clinical trials.[38-43] Following exposure to bevacizumab gamma, only one subject reported an adverse event of ocular inflammation in all three trials. In NORSE TWO, there was only a single related ocular serious adverse event reported in the bevacizumab gamma trial arm, which resolved, and no unanticipated safety signals were detected. The most common ocular adverse event was intravitreal injection-related haemorrhage in the tissues on the surface of the eye (conjunctival haemorrhage) that resolved without any sequela. The bevacizumab gamma safety database, now with 12 months of NORSE TWO data, continues to be consistent with previously published results for bevacizumab, such as in the 2011 CATT clinical trial.

Although bevacizumab gamma was administered Q4W in the pivotal NORSE TWO trial, the results have been reviewed by EMA in the context of a scientific bridge to previous studies of bevacizumab in nAMD (*based on physicochemical and biological-functional parameters, showing a high similarity between Avastin® and bevacizumab gamma and further confirmed from the human PK evaluations*) by which monthly dosing and extended dosing regimens were shown to deliver similar efficacy and safety. This evidence was accepted by the EMA via a mixed marketing authorisation approval, and subsequently by the MHRA. The Q4W data from NORSE TWO is therefore carried forward to the indirect treatment comparison and cost comparison model with the understanding that similar efficacy would be expected from an 'as needed' treatment schedule.

Following the identification of relevant studies from the clinical SLR, an NMA was performed to assess the efficacy and safety of bevacizumab gamma compared with the relevant comparators to this appraisal: aflibercept, faricimab and ranibizumab. The SLR and NMA were conducted in line with the NICE guide to the methods of technology appraisal.[48] Patient-level data available for NORSE TWO, with baseline characteristics and additional outcomes of ocular AEs supported development of a MAIC. The MAIC was also conducted in line with the NICE guide to the methods of technology appraisal and added further depth to the safety analysis of the indirect comparison.[51] The NMA and MAIC were conducted to provide a robust and current analysis of comparative efficacy between bevacizumab gamma and relevant comparators. Results of the NMA and MAIC demonstrated bevacizumab gamma to be associated with comparable visual outcomes in terms of BCVA and comparable anatomical outcomes in terms of decreasing retinal thickness with current standard of care. Adverse events were also found to be comparable for bevacizumab gamma and relevant comparators.

Despite the limitations and uncertainties outlined in B.3.9.5 the results of the NMA and MAIC are still considered to be robust and represent the most recent analysis of comparative efficacy between bevacizumab gamma and the relevant comparators aflibercept, faricimab and ranibizumab.

Conclusion

Bevacizumab, as a parenteral injection, has been marketed for over 10 years in the UK as Avastin®, and has been approved for several cancer indications for use in combination with other chemotherapy drugs. As a result, the active substance has been extensively studied in non-clinical and clinical settings. Bevacizumab, as Avastin®, has also been aseptically

repackaged and used in the UK off-label in the treatment of nAMD where the intravenous formulation is injected into the vitreous of the eye,[52] however, this formulation is not approved for ophthalmic use and does not meet multiple ophthalmic intravitreal injection compendial standards and in 2023, NHS England commissioning guidance for medical retinal vascular medicines stated aseptic compounding services should be avoided due to the ongoing constraint in capacity (commercial and NHS). [17]

Therefore, there is a clear unmet need for a licensed ophthalmic formulation of bevacizumab in the UK, following the marketing authorisation of Lytenava™ (bevacizumab gamma), valid throughout the EU on 27th May 2024, and subsequently approved by the MHRA on 5th July 2024.

Overall, the clinical evidence presented in this submission supports the non-inferiority of bevacizumab gamma versus aflibercept, faricimab and ranibizumab, for visual outcomes in terms of BCVA. The evidence also supports the clinical comparability of bevacizumab gamma at improving anatomical outcomes, with decreasing retinal thickness a key marker of disease activity. Additionally, evidence from the scientific bridge (and accepted by the EMA) allows the consideration of published intravitreal Avastin® data to inform expected bevacizumab gamma outcomes – supporting the use of bevacizumab gamma in an 'as needed' dosing schedule.

There remains a clear unmet need for the introduction of the new licensed intravitreal anti-VEGF treatment Lytenava™ (bevacizumab gamma), that can provide an alternative mode of action to current standard of care, without compromising efficacy and safety.

Bevacizumab gamma therefore offers an additional first-line solution to the current patient and healthcare system burdens associated with anti-VEGF therapies.

B.3.12 Ongoing studies

There are two ongoing phase 3 studies for Lytenava™ (bevacizumab gamma):

NORSE SEVEN - *A 3-month Study to Compare the Safety of bevacizumab gamma in Vials Versus Pre-filled Syringe in Subjects With Visual Impairment Due to Retinal Disorders* [53]

NORSE SEVEN (ONS-5010-007), is a phase 3, ongoing, prospective, multicenter, open-label, nonrandomized study (ClinicalTrials.gov Identifier NCT05112861) to compare the safety of ophthalmic bevacizumab gamma in vials versus pre-filled syringes (PFS) in subjects diagnosed with exudative age-related macular degeneration (nAMD), diabetic

macular oedema (DME), or branch retinal vein occlusion (BRVO) enrolled into two cohorts. The primary objective of the study is to compare descriptive statistical analysis of the frequency and incidence of treatment-emergent adverse events following intravitreal injections of bevacizumab gamma in vials (Cohort 1) or PFS (Cohort 2). The PFS bevacizumab gamma is currently being developed. NORSE SEVEN intends to enroll 120 patients for both cohorts.

Subjects enrolled into Cohort 1, received bevacizumab gamma manufactured using the proposed commercial process and packaged in glass vials. Subjects will be enrolled into Cohort 2 to receive bevacizumab gamma manufactured using the proposed commercial process and packaged in PFS.

As of 18 May 2022, all 60 subjects enrolled in Cohort 1 completed the study; no subject discontinued either study drug or the study. Completed safety report, as well as cumulative summary of demographic data from this Cohort 1 study was provided in Outlook Therapeutics 2023 Annual Report.

This study is to support future commercialisation of pre-filled syringes for bevacizumab gamma.

NORSE EIGHT - *A 3-month Study to Assess the Safety and Effectiveness of bevacizumab gamma in Subjects with Neovascular Age-related Macular Degeneration (AMD)*[54]

NORSE EIGHT (ONS-5010-008), is a phase 3 clinical study (ClinicalTrials.gov Identifier NCT06190093) of intravitreally administered bevacizumab gamma. This study is an ongoing, multicenter, randomized, masked, controlled study of the safety and effectiveness of intravitreally administered bevacizumab gamma. Approximately 400 subjects with primary subfoveal CNV with or without a classic CNV component secondary to age-related macular degeneration (AMD) will be enrolled. Eligible subjects will be randomized in a 1:1 ratio to receive 1.25 mg bevacizumab gamma or 0.5 mg ranibizumab intravitreal injections. Subjects will receive 3 injections at Day 0 (randomization), Week 4 and Week 8 visits.

Key inclusion criteria include male and non-pregnant female patients, ≥50 years old with newly diagnosed and previously untreated nAMD requiring treatment with an anti-VEGF therapy.

The primary and safety objectives of the study are as follows:

- To evaluate the effectiveness of intravitreal injections of bevacizumab gamma compared to ranibizumab in preventing vision loss, as measured by the mean change in baseline best correct visual acuity (BCVA) at Week 8 is a Phase 3, multicenter, randomized, masked, controlled study of the safety and effectiveness of intravitreally administered bevacizumab gamma.

- To evaluate the safety and tolerability of intravitreal injections of bevacizumab gamma administered monthly from baseline to Week 12

This study is a second registration trial. The FDA has acknowledged agreement with the study design through a Special Protocol Assessment (SPA).

B.4 Cost-comparison analysis

B.4.1 Changes in service provision and management

Bevacizumab gamma is anticipated to be used in the outpatient hospital setting, in line with currently licensed anti-VEGF therapies used for nAMD, namely faricimab, aflibercept and ranibizumab.

Eyecare is the highest volume outpatient specialty within the NHS, and the medicines used for medical retinal vascular conditions account for some of the highest cost and volume treatments used within secondary care.[16, 17]

Differences in resource use are expected to be driven primarily by the required injection frequency of each treatment option. Although bevacizumab gamma was administered Q4W in the pivotal NORSE TWO trial (in line with FDA preference), the results have been reviewed by EMA in the context of a scientific bridge to previous studies of bevacizumab in nAMD (namely, CATT, IVAN, and LUCAS) by which monthly dosing and extended dosing regimens were shown to deliver similar efficacy and safety. The scientific bridge was based on physicochemical and biological-functional parameters, showing a high similarity between Avastin® and bevacizumab gamma and further confirmed from the human PK evaluations. This evidence was accepted by the EMA via a mixed marketing authorisation approval, and subsequently by the MHRA. Clinical similarities were further tested in an indirect treatment comparison and a series of MAIC analyses, to demonstrate that bevacizumab gamma has a similar efficacy and safety profile to other licensed treatment options when all products are used according to their licensed treatment intervals.

Although not evaluated in clinical trials, physician-driven dosing of bevacizumab gamma, following initial loading doses, is expected to maintain visual acuity at a level not clinically or statistically different from that achieved with continuous monthly dosing. The majority of BCVA gain was achieved after the initial 3 treatments in NORSE TWO, which is consistent with other intravitreally dosed anti-VEGFs. Accordingly, in alignment with the approved anti-VEGFs, bevacizumab gamma would be dosed initially every 4 weeks (monthly) for at least the first three doses, after which the treating physician can individualise treatment intervals based on disease activity as assessed by visual acuity and/or anatomical parameters. A statement regarding less frequent dosing has been included in the SmPC section 5.1.

As such, minimal additional requirements are anticipated in terms of service provision or disease management with the inclusion of bevacizumab gamma in the treatment pathway.

Details of the resource consumption associated with the use of bevacizumab gamma are provided in Section B.4.2 below.

B.4.2 Cost-comparison analysis inputs and assumptions

The objective of this analysis was to evaluate the costs associated with bevacizumab gamma versus faricimab, aflibercept and ranibizumab for the treatment of nAMD, using a healthcare system perspective in the UK (England and Wales).

B.4.2.1 Features of the cost-comparison analysis

An overview of the features of the cost-comparison analysis are presented in Table 4-1 below:

Table 4-1 Features of the cost-comparison analysis

Perspective	United Kingdom (UK) National Health Service and Personal Social Services
Time Horizon	Lifetime: 21 Years (assuming maximum age of 100 Years), entering the model at 79 years old which is the mean and median of the bevacizumab gamma treated patient (n = 113) population
Population	Adults (aged >18 years) eligible for first-line treatment of neovascular age-related macular degeneration
Comparators	Bevacizumab gamma, faricimab, aflibercept and ranibizumab
Costs	Diagnostic testing costs, pharmacy costs, administration costs, and monitoring costs
Currency	British pounds 2024 (GBP)
Outcomes	Total per-patient costs and incremental per-patient costs
Sensitivity Analysis	One-way sensitivity analysis

To better understand the economic implications of bevacizumab gamma, a cost-comparison model was developed to evaluate the costs of bevacizumab gamma treatment versus other approved therapies for patients with nAMD. The model adopts a United Kingdom (UK) National Health Service (NHS) and Personal Social Services (PSS) perspective over a lifetime time horizon.

A lifetime time horizon assumes a maximum age of 100 years - equivalent to 21 years modelled, given the average baseline age of 79 for patients in NORSE TWO (n = 113).[41]The time horizon was in line with the previous NICE appraisal TA800 for faricimab in this indication (25 years) and considered to be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.[4]

Following guidance from NICE methods, and previous appraisals in the same indication, costs have been discounted by 3.5%.[46, 50]

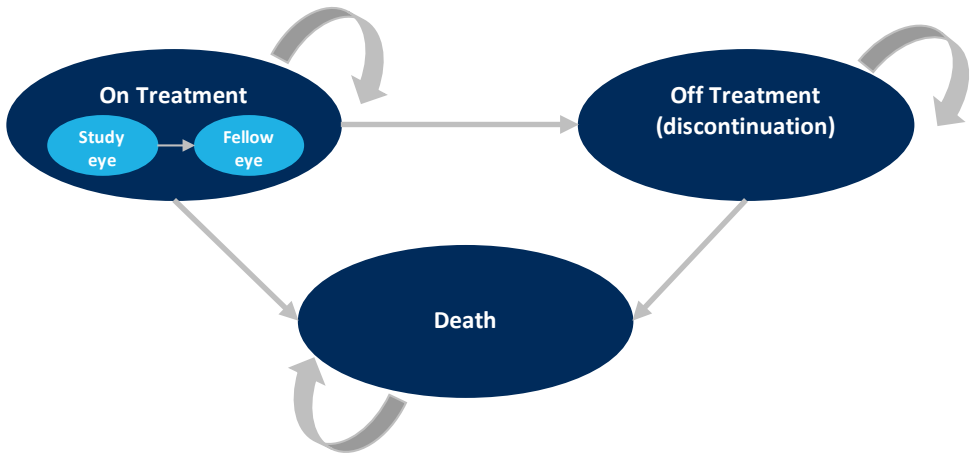
B.4.2.2 Model structure

The cost-comparison model was consistent with recent NICE appraisals in the same indication.[4, 5] The model is built on the premise that all available anti-VEGF options provides similar clinical outcomes, supported by both expert clinical insights, and the outcomes of the clinical trials, NMA and MAIC presented earlier in this document.[10, 11]

The model estimates the cost of bevacizumab gamma, faricimab, aflibercept, and ranibizumab for the treatment of wet AMD from the UK NHS and PSS perspective. Costs are compared over a lifetime time horizon to provide a complete picture of the economic implications. The total costs per-patients are calculated as the sum of diagnostic testing costs, pharmacy costs, administrations costs, and monitoring costs. Incremental costs per-patient are calculated as the difference between bevacizumab gamma, faricimab, aflibercept, and ranibizumab.

Figure 4-1 provides a schematic presentation of the model structure.

Figure 4-1 Cost-comparison model structure



The cost-comparison model was developed in Microsoft Excel® using a Markov model cohort approach to calculate the proportion of patients across three health states with a cycle length of one year:

- On treatment (unilateral “study eye” or bilateral “fellow eye” treatment);
- Discontinued treatment (off treatment)
- Death.

Patients could enter the model with either unilateral or bilateral disease. Patients with unilateral disease could develop bilateral disease over time according to an annual probability of neovascularisation. Once patients developed bilateral disease, they are unable to revert to having unilateral disease.

A cycle length of one year was adopted, reflecting the relative rate of visual decline in this population. The 21-year time horizon was considered to be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. (See section B.4.2.1.) An overview of the perspective and parameters of the cost-comparison analysis are presented in Table 4-2 below:

Table 4-2 Model parameters

Parameter	Perspective	Rationale
Model perspective	The model was developed from a UK NHS and PSS perspective.	Method consistent with previous cost-comparisons in the same indication[4, 5].
Time horizon	A lifetime time horizon of 21 years was used	Explanation above (B.4.2.1)
Model comparators	The model comparators include faricimab, aflibercept, and ranibizumab	Commercially available, UK licensed anti-VEGFs for treatment of nAMD and consistent with previous cost-comparisons in the same indication[4, 5, 8]
Costs	Costs in the model include diagnostic testing costs, pharmacy costs, administrations costs, and monitoring costs	Methods are consistent with previous cost-comparisons in the same indication. [4, 5]

Model outcomes	The cost comparison analysis used the estimated costs over the time horizon to calculate the total per-patient costs and incremental per-patient costs	Consistent with previous cost-comparisons in the same indication. [4, 5]

A similar model structure was used and accepted in the previous cost-comparison submissions to NICE for the treatment of nAMD, namely TA672[5] and TA800[4]. Clinical experts also agreed the model structure appropriately reflected the disease pathway for nAMD patients.[10]

Model inputs

Data sources include published studies, previous NICE appraisals for the same indication, publicly available cost data, product prescribing information, and where necessary, clinically supported assumptions aligning with previous appraisals. The following sections describe the inputs and data sources used in the model.

B.4.2.3 Patient Population

Aside from the starting age which was defined based on the clinical trial (79 years in NORSE-2, compared to a range of 75 – 80 years in a majority of comparator trials) , the model includes population parameters related to gender, increased relative risk of mortality due to nAMD, percentage with bilateral disease at baseline and annual probability of developing bilateral disease.

The key population characteristics are reflective of both the marketing authorisations for bevacizumab gamma and of the populations evaluated in the clinical trial NORSE TWO. [39]

Other clinical parameters are sourced from literature or recent NICE appraisals, where cost-comparison was appraised for equivalent comparator treatments for nAMD.[4, 5] The population model parameters are shown in Table 4-3.

Table 4-3 Population model parameters

Parameter	Value	Source
Age, mean at baseline	79	Outlook Therapeutics, NORSE TWO Clinical Study Report synopsis 2022[41]

Percentage male	40.70%	Outlook Therapeutics, NORSE TWO Clinical Study Report synopsis 2022[41]
Increased RR of mortality due to AMD	1.09	Wang 2017 [55]
Percentage with bilateral disease at baseline	7.3%	Consistent with previous cost-comparisons in the same indication. [4, 5]
Annual probability of developing bilateral disease	1.39%	Consistent with previous cost-comparisons in the same indication. [4, 5]

Key: RR – relative risk; AMD – age-related macular degeneration

B.4.2.4 Mortality

The rate of mortality is assumed to be equal across all treatment arms to reflect equivalent efficacy between the intervention and all comparators. The results of the network meta-analysis and consultation with UK clinical experts supported the view that bevacizumab gamma was similar in efficacy and safety to faricimab, aflibercept and ranibizumab, and as such, there is no evidence to suggest that mortality rates would differ across treatments. Increased RR of mortality (1.09) due to nAMD was applied to the general population mortality. [55]

B.4.2.5 Resource utilisation inputs

The healthcare resource utilisation inputs are shown in Table 4.4. Inputs are predominantly based on the ERG and NICE Committee critique of the faricimab appraisal (TA800), and reflect their preferences from June 2022. [4]

Given the similarities in clinical effectiveness (as described in prior NICE appraisals, and supported by the NMA presented in section B.3) and in disease monitoring (as described in prior NICE appraisals), the key clinical model driver is likely to be injection frequency.

The previously described scientific bridge, accepted by the EMA, allows the evidence generated in NORSE TWO to be evaluated in light of previously published trials of repackaged, off-label Avastin® (bevacizumab). Both bevacizumab (Avastin®) and ranibizumab (Lucentis®) have been shown to have comparable outcomes with respect to visual acuity regardless of monthly or as-needed dosing.[30-33]

This demonstrates that patients are likely to be successfully controlled with an ‘as needed’ injection frequency after the initial loading phase. The model has assumed the same number of doses as proposed for [redacted], to establish a base case scenario.[4] A statement regarding less frequent dosing has been included in the SmPC section 5.1, where

the treating physician can individualise treatment intervals based on disease activity as assessed by visual acuity and/or anatomical parameters.[1]

The Evidence Review Group (ERG) comments on the faricimab approach in TA800, recommended long term (year 3 onwards) dosing frequencies are assumed to be the same across all treatments.[4] The frequency of injection administration visits for Year 3 onwards has been informed by the Committee's preferred assumptions from both TA672 and TA294, assuming that all patients will receive 4 injections from Year 3 and beyond. [5, 7]

Accurate quantification of 'real-world' monitoring visits was highlighted as an uncertainty in prior NICE appraisals, with experts preferring to de-link the monitoring of patients from their injection visit. As such this model proposes an annual monitoring frequency of three per year, with associated costs applied separately from the administration visit.

Treatment discontinuation rates are assumed to be 8.9% annually for all treatments based on the discontinuation rate of year 3 onwards in the faricimab appraisal TA800.[4]

Table 4-4 Resource utilisation inputs

Parameter	Value	Source
Dosing frequency per year		
Bevacizumab gamma Year 1	[redacted]	[redacted]
Bevacizumab gamma Year 2	[redacted]	
Bevacizumab gamma Year ≥ 3	[redacted]	
Faricimab Year 1	6.79	Commercially available, UK licensed anti-VEGFs for treatment of nAMD consistent with TA672 and TA800 [4, 5]
Faricimab Year 2	4.69	
Faricimab Year ≥ 3	4.00	
Aflibercept Year 1	8.00	
Aflibercept Year 2	5.63	
Aflibercept Year ≥ 3	4.00	
Ranibizumab Year 1	9.13	
Ranibizumab Year 2	7.14	
Ranibizumab Year ≥ 3	4.00	
Monitoring frequency per year		
All interventions	3.00	Assumption based on clinical expert input [10]
Annual treatment discontinuation rate		
Bevacizumab gamma	8.9%	Commercially available, UK licensed anti-VEGFs for
Faricimab	8.9%	

Aflibercept	8.9%	treatment of nAMD consistent with TA672 and TA800 [4, 5]
Ranibizumab	8.9%	

B.4.2.6 Intervention and comparators' acquisition costs

Faricimab, aflibercept and ranibizumab are licensed treatments for patients with nAMD with associated NICE guidance (TA800, TA294 and TA155).[4, 6, 7] These technologies are part of the treatment pathway for this patient population and are highlighted in this appraisal scope.

The drug acquisition costs for faricimab, aflibercept, and ranibizumab are based on the list price stated in the British National Formulary.[56] Confidential Patient Access Schemes (PAS) have been arranged with the Department of Health for these comparators, however the values are unknown to Outlook Therapeutics. As such, list prices were used for comparators in the base case cost-comparison analysis.

The confidential discounted net prices for biosimilar ranibizumab comparators are also unknown to Outlook Therapeutics and therefore a weighted average of the list prices was used in the base case cost-comparison analysis.

Bevacizumab gamma is available with a confidential simple PAS discount, reducing the net price to [redacted]. This net price has been used in the base case cost-comparison analysis. Hereafter the bevacizumab gamma price used within the cost-comparison analysis will be referred to as net price.

Total costs are calculated as the sum of diagnostic testing costs, pharmacy costs, administration costs, and monitoring costs. Pharmacy costs (drug costs) are taken from the British National Formulary (BNF) list prices.[56] The ranibizumab drug cost is calculated as the average cost of the branded product Lucentis®, and the biosimilars (Ongavia, Byooviz, Ranivisio, and Ximluci).

Discounting of costs is not normally required in a cost-comparison analysis, however, for consistency, costs have been discounted by 3.5% in line with the most recent TA800 faricimab for nAMD. [4] All costs are inflated to 2024 Great British Pounds (GBP) sterling.

A summary of the acquisition costs for faricimab, aflibercept and ranibizumab is presented in Table 4-5 below. Treatment is assumed to be lifelong until considered clinically inappropriate. Discontinuation rates have previously been estimated at 8.9% per year.

Table 4-5 Acquisition costs of the intervention and comparator technologies

	Bevacizumab gamma (Lytenava™)	**Faricimab (Vabysmo®)**	**Aflibercept (Eylea®)**	**Ranibizumab (Lucentis®)**	**Ranibizumab (Ongavia®) (Byooviz®) (Ranivisio®) (Ximluci®)**
Pharmaceutical formulation	25mg/ml vial	28.8mg /0.24ml vial	40mg/1ml pre-filled syringe or vial	25mg/ml vial	28.8mg /0.24ml vial
(Anticipated) care setting	Outpatient ophthalmology clinic	Outpatient ophthalmology clinic	Outpatient ophthalmology clinic	Outpatient ophthalmology clinic	Outpatient ophthalmology clinic
Acquisition cost (excluding VAT) *	£470	£857	£816	£551	Ongavia: £523.45 Byooviz: £523.45 Ranivisio: £523.45 Ximluci: £495.90
Unit price after PAS (or biosimilar tender discounts)	[redacted]	N/A confidential	N/A confidential	N/A confidential	N/A confidential
Method of administration	Intravitreal injection	Intravitreal injection	Intravitreal injection	Intravitreal injection	Intravitreal injection
Doses	1.25mg	6mg	2mg	0.5mg	0.5mg
Dosing frequency	Initially monthly for three months followed by individualised treatment intervals	Initially monthly for four months followed by extended treatment intervals up to 4 months	Initially monthly for three months followed by individualised treatment intervals	Initially monthly for three months followed by individualised treatment intervals	Initially monthly for three months followed by individualised treatment intervals
* NHS List price (Source: BNF June 2024)					

B.4.2.7 Intervention and comparators' healthcare resource use and associated costs

NHS costs used within the model were obtained from 2023/25 NHS Payment Scheme (amended).[28] The methods used for the model design, were in line with TA800 and the ERG feedback on the cost-comparison model.[4]

Table 4-6 Diagnostic, administration and monitoring costs

Parameter	**NHS cost**	**Source**	**Codes**
Diagnostic testing cost	£126.55 (Unbundled weighted average cost)	2023/25 NHS Payment Scheme (amended) [29] [28]	HRG codes: RD30Z, RD31Z & RD32Z

Administration cost	£69 (unit price)	2023/25 NHS Payment Scheme (amended) [28, 29]	Treatment function code: 130.
Administration costs multiplier for bilateral treatment	1.5	Assumption based on the NICE brolucizumab appraisal (TA672) [5]	
Monitoring visits	3	Assumption based on the NICE faricimab appraisal (TA800) [4]	
Monitoring cost	£110	2023/25 NHS Payment Scheme (amended) [28, 29]	HRG code: BZ88A
Monitoring cost multiplier for bilateral treatment	1	Assumption based on the NICE brolucizumab appraisal (TA672) [5]	

Cost of diagnostic testing

In current UK clinical practice, fundus fluorescein angiography (FFA) is commonly used to diagnose nAMD, although optical coherence tomography (OCT) can also be used to diagnose the condition. The NHS cost of FFA uses a weighted average of the HRG codes RD30Z, RD31Z & RD32Z. This weighted average was calculated from the percentage activity from National Health Service. National schedule of NHS costs - Year 2021/22 and applied to the costs from the 2023/25 NHS Payment Scheme (amended). [28, 57]

Table 4-7 Cost of diagnosis

HRG	HRG Description	Cost [a]	Total Activity [b]	Percentage	Weighted average cost
RD30Z	Contrast Fluoroscopy Procedures with duration of less than 20 minutes	£116.00	106,401	70.65%	**£126.55**
RD31Z	Contrast Fluoroscopy Procedures with duration of 20 to 40 minutes	£140.00	30,282	20.11%	
RD32Z	Contrast Fluoroscopy Procedures with duration of more than 40 minutes	£178.00	13,912	9.24%	

Source:

[a] HRG costs: 2023/25 NHS Payment Scheme (amended), available from https://www.england.nhs.uk/publication/2023-25-nhs-payment-scheme/ 2023/25 NHS Payment Scheme: 2024/25 prices workbook. Accessed June 21 2024

[b] Activity costs: National schedule of NHS costs - Year 2021/22 - all NHS trusts and NHS foundation trusts - HRG data. https://www.england.nhs.uk/costing-in-the-nhs/national-cost-collection/. Accessed June 21, 2024.

A one-off cost for FFA of £126.55 was assumed to be applied at the time of new diagnosis of nAMD in an eye prior to commencement of treatment. Table 4-7 above provides the methods used to calculate a weighted average cost of diagnosis. In the model the cost of an FFA is applied across all patients at baseline, irrespective of treatment; it is also applied a second time, in the first model cycle for patients that develop nAMD in their second (fellow) eye. The cost of an FFA was not applied at subsequent monitoring visits.

The methods outlined above for diagnostic costs within the model, are in-line with previous cost-comparisons assessed for nAMD (TA672 & TA800) and based on the approach used in the economic evaluation of NG82.[4, 5, 27]

Administration costs

Administration cost is based on outpatient attendances to ophthalmology service, using the Treatment Function Code (TFC) 130.[4, 5, 28] In UK clinical practice, most intravitreal injections are administered by specialist nurses and optometrists, therefore, the scrutiny panel for TA800, preferred to remove OCT from the injection visit and use a non-consultant led appointment for the administration cost as their preferred method (Committee Papers TA800).[4] In line with this recommendation, the model uses the following code; WF01A – Follow-up attendance – single professional (£69). The same cost of £69 applies to follow-up outpatient attendance at single professional clinics for both consultant-led or non-consultant-led ophthalmology service, based on NHS unit prices 2024/25.[28]

Monitoring costs

The following guidance from related NICE quality standards: Serious eye disorders (2019) QS180, indicates there is no specific interval for each of the comparators relating to monitoring advice for adults with nAMD in the UK.[58]

Adults with late AMD (wet active) have both their eyes monitored regularly so that treatment can be planned to preserve their sight and quality of life. The time between appointments is determined by the healthcare professional responsible for planning their care.[58]

The model makes the assumption that all patients will be treated with anti-VEGFs have equal monitoring, which was specified by the scrutiny panel in TA800, with a preference to set monitoring visits equal across treatment arms.[4] The monitoring costs are based on the 2023/25 NHS Payment Scheme (amended), HRG code for optical coherence tomography (OCT): BZ88A (£110),[29] and assumed to occur three times per year. This assumption was based on expert clinical opinion, as frequency of monitoring is not reported in the UK AMD audit.

B.4.2.8 Adverse reaction unit costs and resource use

Given that there were no statistically significant or clinically significant differences in safety observed between bevacizumab gamma and ranibizumab in the NORSE ONE, NORSE TWO, CATT and IVAN trials, adverse reaction costs were not incorporated in the base case analysis. [31, 38-45]

The model assumes the safety of bevacizumab gamma, faricimab, aflibercept and ranibizumab is equivalent. As such, cost and resource use related to adverse events have not been included in the base case analysis. The omission of these costs from the base case analysis is not anticipated to have a significant impact on the overall results, as previously proposed in TA800.[4, 14]

B.4.2.9 Miscellaneous unit costs and resource use

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

B.4.2.10 Clinical expert validation

Both TA672 and TA800 provide information on accepted precedents of cost-comparison analysis, most of the assumptions adopted in the base case analysis have been informed by existing appraisals. [4, 5]

Eight practising NHS clinicians, with experience managing nAMD patients administered intravitreal anti-VEGFs, and experience of health technology appraisal in nAMD, were consulted for opinion, from across England, Wales & Scotland.[10] Validation, including any adjustment, was sought on the applicability of prior resource consumption estimates, specifically those used in TA800 faricimab for the treatment of nAMD.[4, 10] Feedback from structured interviews was used for the determination of NHS resources in routine clinical management. [10]

B.4.2.11 Uncertainties in the inputs and assumptions

A summary of the assumptions adopted in the base case cost-comparison analysis is listed below.

Model assumptions

- All patients with unilateral vision impairment are assumed to require treatment.
- All patients with bilateral vision impairment are assumed to require treatment for both eyes.
- Patients with neovascular age-related macular degeneration in the fellow eye are assumed to follow a standard dosing schedule.
- Model assumes that administration costs would only double in 50% of the cases with bilateral disease.
- Model assumes 3 monitoring visits per year based on clinical expert opinion.[10] Monitoring visits are set equal across treatment arms as preferred by the TA800 scrutiny panel.
- Model assumes continuous treatment without gaps in therapy.
- Model assumes no mortality impact on based on treatment.
- For ranibizumab pharmacy costs, an average of available ranibizumab drugs is used.
- Half-cycle correction is not applied to diagnostic testing in the study eye as it is a one-time cost.

B.4.3 Base-case results

B.4.3.1 Cost-comparison

The total per-patient costs and incremental per-patient costs are shown in Table 4-8 and Table 4-9. The graphic presentation of total per-patient costs is shown in Figure 4-2, ordered from the least, to most costly treatment.

The total lifetime per-patient cost of bevacizumab-gamma (based on net price) is [redacted] which is lower than faricimab [redacted], aflibercept [redacted], and ranibizumab [redacted] (based on list prices). The total cost savings per patient with bevacizumab-gamma treatment versus faricimab, aflibercept, and ranibizumab are [redacted], [redacted], and [redacted], respectively, (again based on bevacizumab gamma net price versus comparator list prices).

Table 4-8 Total per-patient costs

Total per-patient costs	Bevacizumab gamma	Faricimab	Aflibercept	Ranibizumab
Diagnostic Testing Costs	[redacted]	£142	£142	£142
Pharmacy Costs	[redacted]	£22,280	£23,300	£16,460
Administration Costs	[redacted]	£1,702	£1,875	£2,070
Monitoring Costs	[redacted]	£1,553	£1,553	£1,553
Total Costs	[redacted]	**£25,678**	**£26,870**	**£20,224**

Table 4-9 Incremental per-patient costs

Total per-patient costs	Δ Aflibercept	Δ Ranibizumab	Δ Faricimab
Diagnostic Testing Costs	[redacted]	[redacted]	[redacted]
Pharmacy Costs	[redacted]	[redacted]	[redacted]
Administration Costs	[redacted]	[redacted]	[redacted]
Monitoring Costs	[redacted]	[redacted]	[redacted]
Total Costs	[redacted]	[redacted]	[redacted]

Figure 4-2 Total per-patient costs

Bevaizumab gamma (net price) is shown to be a cost saving treatment option versus all relevant comparators (all at list price).

B.4.4 Sensitivity and scenario analyses

B.4.4.1 Sensitivity analysis inputs

The model incorporates a one-way sensitivity analysis for key model parameters. The one-way sensitivity analysis allows the user to assess the impact of parameter values on the model output. The default ranges are set at ±10% of the base case value, with the flexibility for the user to customize alternative low and high values. Sensitivity analysis inputs are shown in Table 4-10

Table 4-10 Sensitivity analysis inputs

Parameter	Base Case	Model Low Input	Model High Input
Discount rate for costs	3.5%	3.2%	3.9%
Patient sex % (male)	40.70%	36.63%	44.77%
Increased relative risk (RR) of mortality due to AMD	1.09	0.981	1.199
Percentage with bilateral disease at baseline	7.30%	6.57%	8.03%
Yearly probability of developing bilateral disease	1.39%	1.25%	1.53%
Dosing bevacizumab-gamma Year 1	[redacted]	[redacted]	[redacted]
Dosing bevacizumab-gamma Year 2	[redacted]	[redacted]	[redacted]
Dosing bevacizumab-gamma Year ≥ 3	[redacted]	[redacted]	[redacted]
Dosing Faricimab Year 1	6.79	6.11	7.47
Dosing Faricimab Year 2	4.69	4.22	5.16
Dosing Faricimab Year ≥ 3	4.00	3.60	4.40
Dosing Aflibercept Year 1	8.00	7.20	8.80
Dosing Aflibercept Year 2	5.63	5.07	6.19
Dosing Aflibercept Year ≥ 3	4.00	3.60	4.40
Dosing Ranibizumab Year 1	9.13	8.22	10.04
Dosing Ranibizumab Year 2	7.14	6.43	7.85
Dosing Ranibizumab Year ≥ 3	4.00	3.60	4.40
Monitoring visits	3.00	2.70	3.30
Treatment discontinuation rate Bevacizumab-gamma	8.9%	8.0%	9.8%
Treatment discontinuation rate Faricimab	8.9%	8.0%	9.8%
Treatment discontinuation rate Aflibercept	8.9%	8.0%	9.8%
Treatment discontinuation rate Ranibizumab	8.9%	8.0%	9.8%
Pharmacy costs - Bevacizumab-gamma	[redacted]	[redacted]	[redacted]
Pharmacy costs - Faricimab	£857.00	£771.30	£942.70
Pharmacy costs - Aflibercept	£816.00	£734.40	£897.60
Pharmacy costs - Ranibizumab	£523.45	£471.11	£575.80
Administration costs	£69.00	£62.10	£75.90

Diagnostic testing costs	£126.55	£113.90	£139.21
Monitoring cost	£110.00	£99.00	£121.00
Multiplier bilateral treatment - administration costs	1.5	1.4	1.7
Multiplier bilateral treatment - monitoring costs	1.0	0.9	1.1

Sensitivity analysis

One-way sensitivity analyses were conducted to test the sensitivity of the model results to variation in the input parameters by varying the key model parameters over a range of ±10% of the base case value.

The output for the one-way sensitivity analysis is the difference in total per-patient costs between bevacizumab gamma and the selected comparator. The results of the 15 most impactful parameters are shown are shown in Figure 4-3, Figure 4-4, and Figure 4-5. The width of the bars represents the variation in the cost difference over the range of tested parameter values.

Using faricimab as comparator, the model results were most sensitive to pharmacy costs of faricimab, bevacizumab gamma, and the dosing frequency of faricimab in year 3 and onwards.

Using aflibercept as comparator, the model results were most sensitive to pharmacy costs of aflibercept, bevacizumab gamma, and the dosing frequency of aflibercept in year 1.

Using ranibizumab as comparator, the model results were most sensitive to pharmacy costs of bevacizumab gamma, ranibizumab, and the dosing frequency of ranibizumab in year 1.

In all cases, bevacizumab gamma remained cost saving versus relevant comparators.

Figure 4-3 Tornado diagram – bevacizumab gamma versus faricimab

Figure 4-4 Tornado diagram – bevacizumab gamma versus aflibercept

Figure 4-5 Tornado diagram – bevacizumab gamma versus ranibizumab

Scenario analysis

Scenario One: Estimation of comparator PAS discounts

To provide a closer estimate of real-world net prices for comparators in the UK, scenario one seeks to over-estimate the net PAS discount rates of comparator options, in order to present a highly conservative estimate of likely savings associated with bevacizumab gamma: PAS (or tender discounts) of 50% (£428.50) for faricimab, 40% (£489.60) for aflibercept, 20% (£440.80) for ranibizumab (Lucentis) and 40% (£297.54 and £314.07) for ranibizumab (biosimilars), were applied.

The total lifetime per-patient cost of bevacizumab-gamma is [redacted] which remains lower than the discounted scenario for faricimab [redacted], aflibercept [redacted], and ranibizumab [redacted]. Total cost savings per patient with bevacizumab-gamma treatment vs discounted faricimab, aflibercept, and ranibizumab are [redacted], [redacted], and [redacted], respectively.

Figure 4-6 Scenario One - Total costs

Scenario Two: Discount rate at 0%

Given that discounting of costs is not normally required in a cost-comparison analysis, scenario four explores the impact of a 0% discount rate:

Figure 4-7 Scenario two - total costs

Bevacizumab gamma remained highly cost saving versus all comparators in this scenario, presenting savings of [redacted] versus ranibizumab, [redacted] versus faricimab, and [redacted] versus aflibercept.

Scenario Three: Alternative monitoring frequency

Linking monitoring and administration visits has been identified as a source of uncertainty in prior NICE appraisals of nAMD. Scenario three continues to de-link monitoring from administration (as in the base case) but explores the impact of receiving six monitoring visits in year one, five in year two, and four in year three onwards (versus three/ year in the base case).

Figure 4-8 Scenario three - total costs

Bevacizumab gamma remained highly cost saving versus all comparators in this scenario, presenting savings of [redacted] versus ranibizumab, [redacted] versus faricimab, and [redacted] versus aflibercept.

Scenario Four: Alternative starting age

Scenario four explores the impact of patients starting treatment at a younger age (75 years versus 79 years in the base case). This starting age replicates population estimates from TA800.[4]

Figure 4-9 Scenario four - total costs

Bevacizumab gamma remained highly cost saving versus all comparators in this scenario, presenting savings of [redacted] versus ranibizumab, [redacted] versus faricimab, and [redacted] versus aflibercept.

Scenario Five: Increased injection frequency for bevacizumab gamma

Scenario five explores the impact of increasing the injection frequency of bevacizumab gamma [redacted]

Figure 4-10 - Scenario five: Injection Frequency

[redacted]

Bevacizumab gamma remained highly cost saving versus all comparators in this scenario, presenting savings of [redacted] versus ranibizumab, [redacted] versus faricimab, and [redacted] versus aflibercept.

Scenario Six: Threshold analysis of varied comparator discounts

Scenario six explores the total modelled costs of bevacizumab gamma (at net price) versus each comparator at a range of discounts.

Table 4-11 Scenario Six – Varied comparator discounts

Bevacizumab gamma			Faricimab			Aflibercept			Ranibizumab (average of Lucentis® and biosimilars)		
net price	Total modelled costs	Comparator discount	estimated net price	Total modelled costs	Δ vs bevacizumab gamma	estimated net price	Total modelled costs	Δ vs bevacizumab gamma	estimated net price	Total modelled costs	Δ vs bevacizumab gamma
[redacted]											

This scenario shows bevacizumab gamma to continue to be cost-saving/ cost-neutral versus faricimab (with a discount of between 50% and 60%), versus aflibercept (with a discount of between 50% and 60%), and versus ranibizumab (with a discount of between 40% and 50%).

B.4.5 Subgroup analysis

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

B.4.6 Interpretation and conclusions of economic evidence

The anti-VEGF therapies aflibercept, faricimab and ranibizumab are the current standard of care for nAMD, and most publications suggest that between these therapies, equal efficacy and similar safety profiles are demonstrable.[27, 58] All three therapies have been assessed and recommended for reimbursement for the treatment of nAMD by NICE.[6, 7, 14]

Bevacizumab gamma is anticipated to be used in clinical practice in accordance with its full licensed indication, for the treatment of nAMD – the same population currently receiving aflibercept, faricimab and ranibizumab. The efficacy of bevacizumab gamma as a treatment for nAMD has been demonstrated in a pivotal Phase 3 multi-center, randomised, double-masked, active controlled trial versus ranibizumab, NORSE TWO, and further supported by indirect comparison, and bridging evidence to prior trials of off-label Avastin® investigating ophthalmic use.

The key strength of evidence supporting this submission is that consistently, bevacizumab gamma clinical trial data, the scientific bridge to pre-existing off-label bevacizumab clinical trials, indirect analyses, and clinical opinion, all support the non-inferiority of clinical outcomes associated with all anti-VEGF treatment options. This justifies the use of a cost-comparison methodology, and simplifies the analysis by highlighting drug acquisition cost and injection intervals as the key model inputs.

Given the similarities in clinical effectiveness and monitoring, and the (assumed) similarities in pricing, the key model driver is further prioritised to be injection frequency. The majority of BCVA gain was achieved after the initial 3 treatments in NORSE TWO, which is consistent with other intravitreally dosed anti-VEGFs. Accordingly, in alignment with the approved anti-VEGFs, the European Medicines Agency (EMA) have supported a treat and extend dosing schedule for bevacizumab gamma, based on scientifically bridging to repackaged, off-label Avastin® (bevacizumab) within strictly controlled clinical trial protocols.

The model has assumed the same number of doses as proposed for [redacted], to establish a base-case scenario. [4]A statement regarding less frequent dosing has been included in the SmPC section 5.1, where the treating physician can individualise treatment intervals based on disease activity as assessed by visual acuity and/or anatomical parameters.[1]

The results of this cost comparison analysis suggest that, compared to currently approved anti-VEGF treatments, bevacizumab gamma is associated with cost savings for patients with nAMD over a lifetime from a UK NHS and PSS perspective – based on both the required net price versus comparator list price analysis, and the scenario analysis in which net prices for all comparators are estimated.

The assumptions adopted within the base case cost-comparison analysis were further explored in scenario analyses; the results of which demonstrated bevacizumab gamma remains cost saving across all scenarios versus both aflibercept, faricimab and ranibizumab, even when the key model input of injection frequency was adjusted to a highly conservative scenario for bevacizumab gamma.

There remains a clear unmet need for the new licensed formulation bevacizumab gamma (Lytenava™), as an additional first-line treatment option for treating clinicians and patients with nAMD in the UK.

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Sage Vancouver has been used for referencing with EndNote™ 21 reference manager.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Cost Comparison appraisal

Bevacizumab gamma for treating wet age-related macular degeneration [ID6320]

Summary of Information for Patients (SIP)

July 2024

File name	Version	Contains confidential information	Date
SIP Document – ID6320 (no conf.)	V1.0	Yes/no	17 July 2024

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Response:
Bevacizumab gamma (LYTENAVA™)

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

Response:
Adults with wet age-related macular degeneration (nAMD)

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

Response:
LYTENAVA™ is indicated in adults for treatment of neovascular (wet) age-related macular degeneration (nAMD). EU Marketing authorisation issued: 27th May 2024 EMA product number: EMEA/H/C/005723 [1, 2] MHRA Marketing Authorisation issued: 5th July 2024 Marketing authorisation number: PL 59162/0001 [3]

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

Response:

None

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

Response:

Neovascular (exudative/wet) age-related macular degeneration (nAMD) is a progressive chronic disease of the central retina and a leading cause of vision loss. The development of new blood vessels in the eye, unlike normal blood vessels, bleed or leak blood constituents, resulting in distortion and scarring of the retina.[4, 5]

Generally, early and intermediate AMD are not associated with disturbances of central visual function, but advanced nAMD can cause severe visual impairment. Untreated nAMD can progress within weeks or months to cause severe visual loss.[4, 5]

The prevalence of late AMD in the UK among people aged 50 years or over was reported by NICE (NG82) to be 2.4%.[6] The Office for National Statistics population estimate of over 50-year-olds in England and Wales in mid-2022 was 23,048,972, meaning a prevalent population of nAMD patients of approximately 550,000.[7]

There is also a well-documented link between sight loss and poor mental health outcomes. LYTENAVA™ (bevacizumab gamma), if successful, could reduce the burden on mental health services.[8] - *Royal National Institute of the Blind*

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

Response:

A person with nAMD may be asymptomatic, with retinal signs detected incidentally by an optometrist during a routine eye test. If nAMD is suspected, the person should be referred urgently for ophthalmology assessment and investigations.[4, 5]

Investigations are performed in secondary care to confirm the diagnosis. Optical coherence tomography (OCT) is a non-invasive imaging investigation. Fluorescein angiography (FA) is used if nAMD is suspected, in order to confirm the diagnosis and assess the type, extent, size, and location of lesions.[4, 5]

There are no additional diagnostic tests required prior to using LYTENAVA™ (bevacizumab gamma).

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

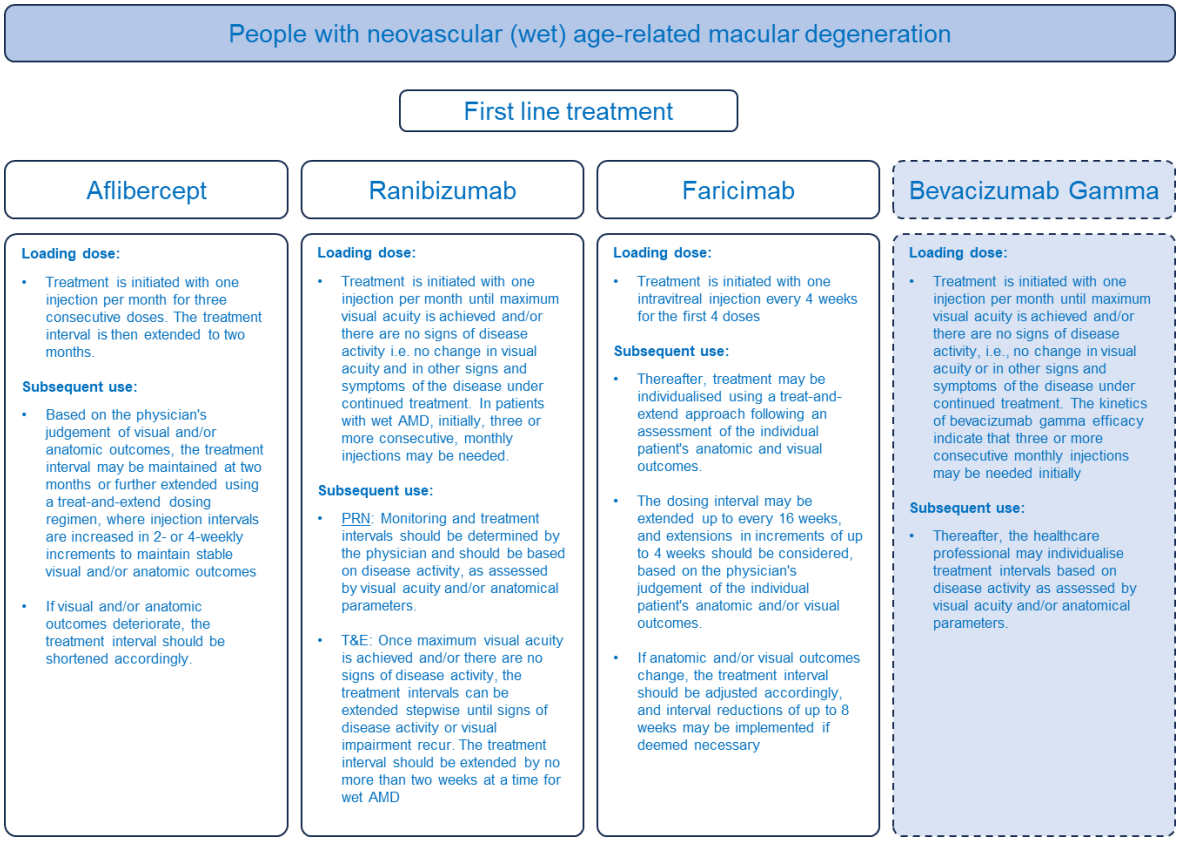
- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
    - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
    - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

Response:

For people who receive timely treatment for nAMD, the prognosis has greatly improved in recent years. With treatment, about a third of people will gain some improvement in vision. The majority will maintain vision at their current level, but about 10% will not respond to therapy. Anti-VEGF drugs could theoretically reduce the rate of blindness by up to 70% over 2 years, however, long-term follow-up over 7 years showed these gains in visual acuity were lost in two-thirds of people. Factors that affect the effectiveness of anti-VEGF therapy include visual acuity and lesion size at diagnosis, and the number of injections received. [4]

LYTENAVA™ (bevacizumab gamma) is positioned as an alternative option to currently available anti-VEGF treatment options (aflibercept, faricimab and ranibizumab), covering an identical population of adults with neovascular (nAMD), as presented in Figure 1, below.

Figure 1: Proposed Treatment Pathway



LYTENAVA™ (bevacizumab gamma) is an ophthalmic-grade formulation of the anti-VEGF treatment bevacizumab, and has been approved as a new active substance by the EMA and MHRA. [2, 3]

Despite a significant number of clinical studies in the UK and worldwide, off-label, re-packaged Avastin® (bevacizumab) is no longer routinely available to UK clinicians for the treatment of newly diagnosed nAMD patients due to specific commissioning restrictions.[9-12 13-15] This off-label, repackaged Avastin® (bevacizumab) produced at UK compounding pharmacies is not manufactured to the same EU ophthalmic quality standards as LYTENAVA™ (bevacizumab gamma) and intravitreal use of Avastin® is out-with both EU and MHRA marketing authorisation.[16, 17] Studies have shown reduced potency with one study demonstrating that 81% of samples had lower protein concentrations than required, with statistically significant variations in protein concentration among samples leading to increased probability of adverse events.[17]

The introduction of LYTENAVA™ (bevacizumab gamma) will provide the first opportunity to use a formulation of bevacizumab which is licensed for ophthalmic use, and which conforms to the stringent EU standards required for the manufacture of ophthalmic solutions. [16, 18, 19]

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden

and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

Response:

A systematic review of quality-of-life evidence was conducted by Taylor and colleagues and published in 2016, in the BMJ. A range of approaches were identified, including performance-based methods, quantitative and qualitative patient-reported outcome measures (PROMs).

This systematic review concluded that nAMD can significantly impact a person's quality of life.

1. **Visual Ability and Real-World Tasks:**
   - AMD affects various tasks, including mobility, face recognition, scene perception, computer use, meal preparation, shopping, cleaning, watching TV, reading, and driving.
   - Some individuals with wet AMD may experience difficulties with self-care.[20]
2. **Depression Rates:**
   - Research indicates higher rates of depression among people with AMD compared to community-dwelling elderly individuals.[20]
   - The link between sight loss and poor mental health increases the burden on mental health services, as highlighted by the Royal National Institute of the Blind in their comments during the consultation phase of the scope for this NICE appraisal.[8]
3. **Adaptation Strategies:**
   - People with AMD often develop adaptation strategies to cope with the condition.
   - However, much of the research lacks information on the specific type of AMD studied or the duration of the disease in participants.[20]

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

Response:

LYTENAVA™ (bevacizumab gamma) blocks vascular endothelial growth factor (VEGF) which is a protein that can cause the development of abnormal blood vessels. Bevacizumab gamma targets VEGF, helping to stop the growth of abnormal blood vessels in the back of the eye, and therefore classified as an anti-VEGF treatment.

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes / No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

Response:

No

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

Response:

LYTENAVA™ (bevacizumab gamma) is a solution that is injected into the patient's eye and the frequency of injection will depend on the condition of the eye, such as quality of vision and the health of the eye. Monitoring and treatment intervals should be determined by the healthcare professional and should be based on disease activity, including clinical examination, functional testing or imaging techniques.

The recommended dose is 1.25 mg administered by intravitreal injection[2, 3]

Treatment is initiated with one injection per month until maximum visual acuity is achieved and/or there are no signs of disease activity. Bevacizumab gamma treatment begins with three or more consecutive monthly injections – as seen with all other anti-VEGF options. Thereafter, the healthcare professional may individualise treatment intervals based on disease activity as assessed by visual acuity and/or anatomical parameters – likely leading to the need for less frequent injections.[2, 3]

The clinician will numb the eye and put the injection into the corner of the eye, so the patient should not see it. The injection is given in a small volume and is usually painless; patients should only feel a little pressure during the procedure.

This method of administration is similar for LYTENAVA™ (bevacizumab gamma) as existing anti-VEGF treatments.

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

There are 3 completed clinical trials for LYTENAVA™ (bevacizumab gamma), NORSE ONE, NORSE TWO and NORSE THREE.[21-23] NORSE ONE was used to help with the design of larger, pivotal NORSE TWO study, and NORSE THREE was a short-term study of safety.

The key study of significance is NORSE TWO, which was the pivotal phase 3 trial comparing LYTENAVA™ (bevacizumab gamma) with Lucentis® (ranibizumab).

NORSE TWO

A Clinical Effectiveness Study Examining the Efficacy and Safety of ONS-5010 in Subjects with Neovascular Age-related Macular Degeneration (AMD) [NCT03834753]

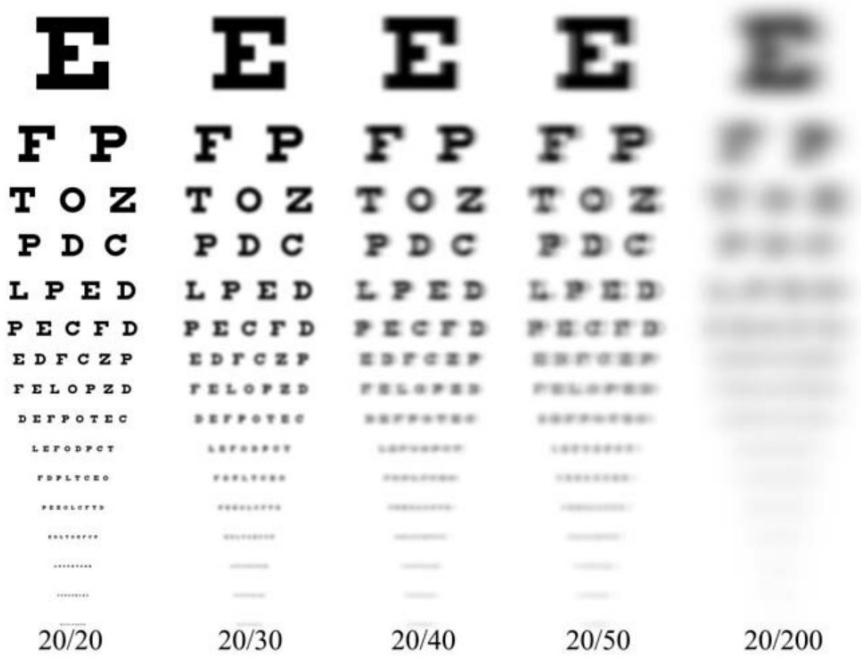
A total of 228 patients with nAMD were entered into the trial.

Inclusion criteria:

- Active primary Subfoveal Choroidal Neovascularization lesions secondary to (AMD) in the study eye.
- Best corrected visual acuity of 25-67 letters read (20/50 to 20/320 Snellen equivalent)
- Only treatment naïve patients
- 50 Years and older

Visual acuity is a measurement of the sharpness of vision over distance and represented in fractional score. A visual acuity chart (most commonly the Snellen chart) is set up 20 feet away from the patient. The visual acuity score is a ratio which compares vision to that of someone with “normal” vision. 20/20 vision is considered “normal” visual acuity. The top number is the distance in feet from the chart, and the bottom number of the score representing the distance at which someone with “normal” vision would be able to clearly read the letters in that row. As illustrated in **Figure 2** , the higher the lower number of the visual acuity score, the poorer the vision.

Figure 2: Illustration of 20/50 to 20/200 Snellen equivalent vision



Source: https://www.illustratedverdict.com/template-eye-eye-exams

Exclusion criteria:

- Previous subfoveal focal laser photocoagulation in the study eye
- Any concurrent intraocular condition in the study eye that may require medical or surgical intervention or contribute to vision loss within 1 year

The trial was multi-centre, with 39 study sites across the US.

The study was a well-designed, randomised, double-masked, active controlled trial. Patients were assigned randomly to different treatment groups, to help eliminate bias and ensure that the groups were comparable at the start of the study. Both the participants and the researchers involved in the trial are unaware of which treatment each participant is receiving, to prevent any unintentional influence or bias during the study. The active-controlled design also allowed researchers to assess the effectiveness of LYTENAVA™ (bevacizumab gamma) relative to an established treatment - ranibizumab Lucentis® (ranibizumab).

The patients were given monthly intravitreal injections. Subjects in the Lucentis® (ranibizumab) group underwent sham procedures at visits when they did not receive an active Lucentis® ranibizumab injection. The sham procedure was an injection with placebo to simulate the active drug, this ensures that the results of the trial are not influenced by the placebo effect.

LYTENAVA™ (bevacizumab gamma):

- 1.25 mg by intravitreal injection monthly in the study eye
    - Duration 12 months

Lucentis® (ranibizumab):

- 0.5 mg by intravitreal injection in the study eye, every month for 3 months (ie, on Days 0, 30, and 60) followed by 2 additional injections on Days 150 and 240
    - Duration 11 months

Primary Outcome Measures:

- The difference in proportion of subjects who gain ≥ 15 letters from baseline in best-corrected visual acuity (BCVA) at 11 months
- To evaluate the safety and tolerability of intravitreal injections of bevacizumab gamma administered monthly from baseline to 12 months

Method of assessment:

- BCVA to be assessed as letters read using the Early Treatment Diabetic Retinopathy Study (ETDRS) charts.

  A positive change represents an improvement in visual acuity.

Secondary Outcome Measures:

To evaluate the efficacy of intravitreal injections of bevacizumab gamma as compared with ranibizumab in preventing vision loss, as measured by the following:

1. The mean change in BCVA from baseline to 11 months
2. The proportion of subjects who gain ≥ 5 or ≥ 10 letters in visual acuity at 11 months compared with baseline.

3. The proportion of subjects who lose fewer than 15 letters in visual acuity at 11 months compared with baseline.
4. The proportion of subjects with a visual acuity Snellen equivalent of 20/200 or worse at 11 months
5. The mean change from baseline in visual acuity over time up to 11 months

Method of assessment: (1-4 above)

BCVA to be assessed as letters read using the ETDRS charts.

- A positive change represents an improvement in visual acuity. (1-3,5)
- A negative change represents a decrease in visual acuity. (4)

The dosing administration for ranibizumab in this study is in a manner consistent with the PIER study dosing regimen used in the company's marketing authorisation submission.[24]

A scientific bridge was demonstrated, which included physicochemical and biological-functional parameters, showing a high similarity between bevacizumab and bevacizumab gamma. This information therefore allows the consideration of published intravitreal bevacizumab data (given less frequently than monthly) to inform expected bevacizumab gamma outcomes (based on a monthly administration frequency used in the pivotal NORSE TWO trial).[23]

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

Response:

NORSE TWO met its primary efficacy endpoint, demonstrating that bevacizumab gamma was superior to ranibizumab, when ranibizumab was administered in a manner consistent with the PIER study dosing regimen.[23, 24] (**Table 1**) The proportion of subjects who achieved an increase of ≥15 letters in BCVA from baseline to 11 months was 41.7% and 23.1% respectively, in the bevacizumab gamma and ranibizumab groups. The primary efficacy analysis was statistically significant, in favour of bevacizumab gamma.

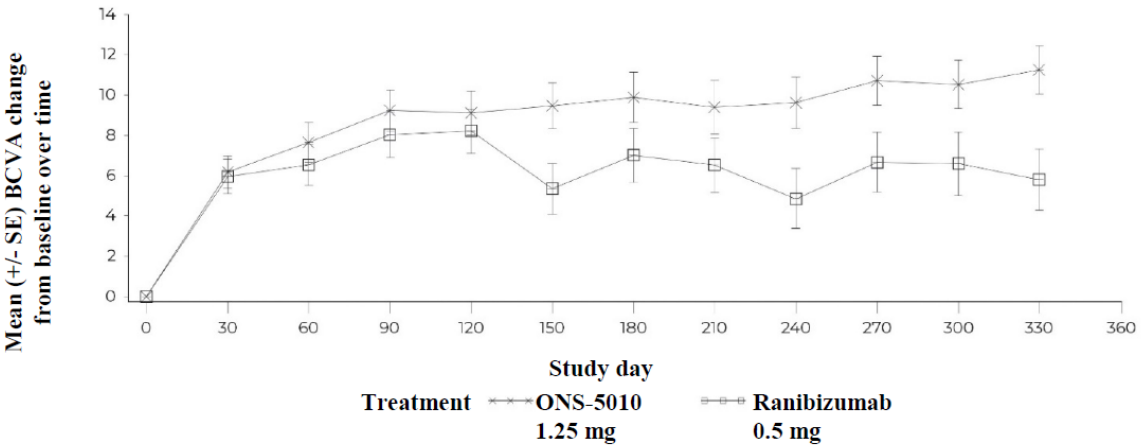
Table 1: NORSE TWO results

	Ranibizumab (N = 115)	**Bevacizumab gamma** (N = 113)
Primary Endpoint		
Subjects gaining ≥15 letters from baseline at 11 months, n/N (%)	24/104 (23.1%)	45/108 (41.7%)
Secondary Endpoint		
BCVA mean change from baseline to 11 months, mean (SD)	5.8 (14.80%)	11.2 (12.19%)
Subjects gaining ≥10 letters from baseline at 11 months, n/N (%)	36/104 (34.6%)	61/108 (56.5%)
Subjects gaining ≥5 letters from baseline at 11 months, n/N (%)	53/104 (51.0%)	74/108 (68.5%)

Subjects losing <15 letters from baseline at 11 months, n/N (%)	86/104 (82.7%)	101/108 (93.5%)

Bevacizumab gamma (ONS-5010) was dosed monthly for 12 months; ranibizumab was dosed every month for 3 months (i.e. on Days 0, 30, and 60) followed by every 90 days (i.e. on Days 150 and 240). In total, 5 injections in the ranibizumab arm were compared to 11 injections in the bevacizumab gamma arm for the assessment of the efficacy endpoints. The dosing administration for ranibizumab is consistent with the PIER study dosing regimen used in the company's marketing authorisation submission.[24] The 'scientific bridge' between bevacizumab gamma and bevcizumab, was used to inform regulators that the effect of monthly bevavcizumab gamma is likely to be reflected in a less frequent dosing regimen, i.e. bevacizumab gamma dosed at the same frequency to ranbizumab is likely to provide similar outcomes.

Figure 3: Best-corrected visual acuity change from baseline over time



3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

Response:

Formal quality-of-life measures were not specifically evaluated during the clinical development of bevacizumab gamma, however, the consensus that all anti-VEGF options work in a similar way, implies that benefits (or loss of deterioration) to vision, are likely to realise quality-of-life benefits for patients with nAMD.

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Response:

Summary of the safety profile:

The majority of adverse reactions reported following administration of bevacizumab gamma are related to the intravitreal injection procedure. The most frequently reported adverse reactions were conjunctival haemorrhage (5.0%), vitreous floaters (1.5%), eye pain (1.2%), and intraocular pressure increased (1.2%). Less frequently reported, but more serious adverse reactions were intraocular pressure increases (0.6%), blindness transient (0.3%), endophthalmitis (0.3%), intraocular inflammation (0.3%).

A total of 341 patients from two randomised and one open-label clinical studies were treated with the recommended dose of 1.25 mg. The adverse reactions reported in clinical studies of bevacizumab gamma are listed in **Table 2** below.

Frequency categories for each adverse reaction are based on the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1 000 to <1/100), rare (≥1/10 000 to <1/1 000), very rare (<1/10 000), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 2: Frequencies of adverse reactions

System organ class	Common	Uncommon
Infections and infestations		Endophthalmitis
Immune system disorders		Iodine allergy

Eye disorders	Vitreous floaters Eye pain Conjunctival haemorrhage	Retinal pigment epithelial tear, Vitreous haemorrhage, Iritis, Corneal scar, Keratopathy, Punctate keratitis, Blindness transient, Vitreous detachment, Photopsia, Ocular discomfort, Corneal abrasion, Eye irritation, Eye pruritus, Dry eye, Ocular hyperaemia
Investigations	Intraocular pressure increased	

As previously outlined in 2c) the manufacture of LYTENAVA™ (bevacizumab gamma) conforms to strict manufacturing guidelines for ophthalmology use which should allay previous safety concerns related to off-label, repackaged Avastin®.[17]

Overall, no difference was seen in the adverse events associated with bevacizumab gamma versus other anti-VEGF treatments.

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration
-

Response:

LYTENAVA™ (bevacizumab gamma) is an ophthalmic-grade formulation of the anti-VEGF treatment bevacizumab, and has been approved as a new active substance by the EMA and MHRA [2, 3]. This is the first new active substance for the treatment of nAMD since faricimab in 2022, as recent additions have either consisted of biosimilars or modification in strength or dosage of existing treatments used in current clinical practice.

The introduction of LYTENAVA™ (bevacizumab gamma) will provide the first opportunity to use a formulation of bevacizumab which is licensed for ophthalmic use, and which conforms to the stringent EU standards required for the manufacture of ophthalmic solutions. [16, 18, 19]

LYTENAVA™ (bevacizumab gamma) provides the lowest NHS list price, (cost per treatment), of the branded anti-VEGFs currently available in the UK.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

Response:

LYTENAVA™ (bevacizumab gamma) is likely to provide similar health benefits at similar or lower cost when compared to technologies recommended in published NICE technology appraisal guidance for the same indication.

The real-world frequency of injections for patients is not yet proven.

3i) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

Response:

How the model reflects the condition

To better understand the economic implications of bevacizumab gamma, a cost-comparison model was developed to evaluate the costs of bevacizumab gamma treatment versus other approved therapies for patients with nAMD. The model adopts a United Kingdom (UK) National Health Service (NHS) and Personal Social Services (PSS) perspective over a lifetime time horizon.

The model is based on the premise that all anti-VEGF treatments deliver similar efficacy and safety – demonstrated in clinical trials as well as via a systematic literature review (SLR), and statistical analyses called network meta-analyses (NMA) and match-adjusted indirect comparisons (MAIC), which support comparison of comparators not directly

included in clinical trials. Results consistently demonstrate that bevacizumab gamma is likely to provide similar health benefits when compared to technologies recommended in published NICE technology appraisal guidance for the same indication.

This fulfilled NICE criteria, for the development of a simple cost comparison model for bevacizumab gamma using the comparators faricimab, aflibercept and ranibizumab.

Modelling how the costs of treatment differ with the new treatment

Bevacizumab gamma is anticipated to be used in the outpatient hospital setting, in line with currently licensed anti-VEGF therapies used for nAMD, namely faricimab, aflibercept and ranibizumab.

Eyecare is the highest volume outpatient specialty within the NHS, and the medicines used for medical retinal vascular conditions account for some of the highest cost and volume treatments used within secondary care.[13, 14]

Differences in resource use are expected to be driven primarily by the required injection frequency of each treatment option and the unit cost of each anti-VEGF treatment.

Injection frequency

Injection frequency for anti-VEGF treatments follow a treat-and-extend model, where treatment is initiated with one injection per month until maximum visual acuity is achieved and/or there are no signs of disease activity. Thereafter, the healthcare professional may individualise treatment intervals based on disease activity as assessed by visual acuity and/or anatomical parameters. Injection frequency will therefore vary from patient to patient.

Unit cost of anti-VEGF treatment

The NHS list price for one treatment of LYTENAVA™ (bevacizumab gamma) is £470. This means that LYTENAVA™ (bevacizumab gamma) has the lowest NHS list price of the branded comparators. A confidential simple Patient Access Scheme (PAS) discount further reduces the net price of LYTENAVA™ (bevacizumab gamma) to the UK NHS. Comparators also are subject to confidential PAS discounts, which are not publicly available. The model therefore applied the PAS net price for LYTENAVA™ (bevacizumab gamma) to the known NHS list price for the comparators, with sensitivity and scenario analyses exploring the impact of estimated comparator discounts and varied injection frequencies.

Uncertainties and Model assumptions

- All patients with unilateral vision impairment are assumed to require treatment. (One eye)
- All patients with bilateral vision impairment are assumed to require treatment for both eyes. (Both eyes)
- Patients with neovascular age-related macular degeneration in the fellow eye are assumed to follow a standard dosing schedule.
- Model assumes that administration costs would only double in 50% of the cases with bilateral disease. (Both eyes)

- Model assumes 3 monitoring visits per year based on clinical expert opinion.[25] Monitoring visits are set equal across treatment arms as preferred by the TA800 scrutiny panel.[26]
- Model assumes continuous treatment without gaps in therapy.
- Model assumes no mortality impact on based on treatment.
- For ranibizumab pharmacy costs, an average of available ranibizumab drugs is used.
- Half-cycle correction is not applied to diagnostic testing in the study eye as it is a one-time cost.

The assumptions adopted within the base case cost-comparison analysis allowed these inputs to be changed. The model had the flexibility to analyse different scenarios; the results of which demonstrated bevacizumab gamma remains cost saving across all scenarios versus aflibercept, faricimab and ranibizumab, even when the key model input of injection frequency was adjusted to a highly conservative scenario for LYTENAVA™ (bevacizumab gamma).

Results

The results of the cost comparison analysis suggest that, compared to currently approved anti-VEGF treatments, bevacizumab gamma is associated with cost savings for patients with nAMD over a lifetime from a UK NHS and PSS perspective – based on both the required net price versus comparator list price analysis, and the scenario analysis in which net prices for all comparators are estimated.

Conclusion

There remains a clear unmet need for the new licensed formulation LYTENAVA™ (bevacizumab gamma), as an additional first-line treatment option for treating clinicians and patients with nAMD in the UK.

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations.
If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Response:

LYTENAVA™ (bevacizumab gamma) is an ophthalmic-grade formulation of the anti-VEGF treatment bevacizumab, and has been approved as a new active substance by the EMA and MHRA [2, 3]

The introduction of LYTENAVA™ (bevacizumab gamma) will provide the first opportunity to use a formulation of bevacizumab which is licensed for ophthalmic use, and which conforms to the stringent EU standards required for the manufacture of ophthalmic solutions. [16, 18, 19]

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here
Response: Outlook Therapeutics does not foresee any specific equity issues to be considered as part of this appraisal but would reiterate that visual impairment resulting from wet AMD is recognised as a disability in the UK (as highlighted in prior NICE appraisals in wet AMD). No clinically relevant groups can be identified who are expected to have a differential outcome. This appraisal would not exclude people with protected characteristics or should have adverse impact of their health.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc. Where possible, please provide open access materials or provide copies that patients can access.
Response: Further information on NICE and the role of patients**:** • Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE • NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE • EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/ • EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf • National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/ • INAHTA: http://www.inahta.org/ • European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

Response:

AMD	Age-related macular degeneration
nAMD	(Neovascular) age-related macular degeneration
Anti-VEGF	Anti-vascular endothelial growth factor
BCVA	Best-corrected visual acuity
CNV	Choroidal neovascularisation
CSFT	Central subfield retinal thickness
FA	Fluorescein angiography
ITT	Intention to treat
LP	Loading phase
MAIC	Matching-adjusted indirect comparison
NI	Non-inferiority
NMA	Network meta-analysis
OCT	Optical coherence tomography
ONS-5010	Bevacizumab gamma (LYTENAVA™)
PAS	Patient Access Scheme
PPS	Per protocol analysis set
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
SRF	Sub-retinal fluid
T&E	Treat-and-extend dosing regimen
VA	Visual acuity
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

Response:

References

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12. Berg K, Pedersen TR, Sandvik L, et al. Comparison of Ranibizumab and Bevacizumab for Neovascular Age-Related Macular Degeneration According to LUCAS Treat-and-Extend Protocol. *Ophthalmology* 2015; 122: 146-152. DOI: 10.1016/j.ophtha.2014.07.041.

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22. Outlook Therapeutics Inc. NORSE ONE - A Clinical Effectiveness, Multicenter, Randomized, Double-masked, Controlled Study of the Efficacy and Safety of ONS-5010 in Subjects With Subfoveal Choroidal Neovascularization (CNV) Secondary to Age-related Macular Degeneration [NCT03844074], https://classic.clinicaltrials.gov/ct2/show/NCT03844074 (2021, accessed 14th June 2024).

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25. Outlook Therapeutics Data on file. *Data on file - OTLK-DoF-UK-LYT-001*. 2024.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Cost Comparison Appraisal

Bevacizumab gamma for treating wet age-related macular degeneration [ID6320]

Clarification questions

July 2024

File name	Version	Contains confidential information	Date
Response_ID6320 bevacizumab Clarification letter v2.0 (conf visible)	V1.0	Yes	14 Aug 2024

Section A: Clarification on effectiveness data

Systematic literature review

A1. Please provide the complete reference list of excluded studies at the title/abstract and full-text screening levels as mentioned in company submission (CS) Appendix D section 1.1 (page 33).

Thank you for your comment. The complete reference list of excluded studies mentioned in company submission (CS) Appendix D section 1.1 (page 33) is provided via NICEdocs in Excel format. F*ile name: Outlook Therapeutics_Clinical SLR in nAMD_Study update listing_07August2024_v4.0*

NORSE trial programme

A2. PRIORITY QUESTION Please provide the full clinical study reports (CSRs), Protocols and Statistical Analysis Plans for NORSE ONE and NORSE TWO

Thank you for your request. The full clinical study reports (CSRs), Protocols and Statistical Analysis Plans for NORSE ONE and NORSE TWO are provided via NICEdocs in confidence, in PDF format.

NORSE ONE

- *ons-5010-001-protocol.pdf*
- *ons-5010-001-report-body.pdf*
- *ons-5010-001-sap.pdf*

NORSE TWO

- *ons-5010-002-protocol.pdf*
- *ons-5010-002-report-body.pdf*
- *ons-5010-002-sap.pdf*

A3. Please provide citations to any peer-reviewed journal publications for NORSE ONE, TWO and THREE. If none are yet available, please indicate what plans you have for publishing them.

Thank you for your comment. None of the studies have been published yet. The NORSE TWO manuscript is under review at OSLIRetina, with an expected publication date of late 2024.

A4. The CS refers to completed studies NORSE ONE, TWO and THREE and to ongoing studies NORSE SEVEN and EIGHT. Please confirm if there were studies NORSE FOUR, FIVE and SIX? If so, please provide details of these studies.

Thank you for your comment.

- NORSE FOUR is a planned registration clinical trial evaluating ONS-5010 (bevacizumab gamma) to treat Branch Retinal Vein Occlusion (BRVO).
- NORSE FIVE and NORSE SIX are two planned registration clinical trials evaluating ONS-5010 to treat Diabetic Macular Edema (DME).

None of these studies have been initiated.

A5. The design characteristics of NORSE ONE and NORSE TWO in Table 3-1 are near identical: both are described as phase 3 multicentre randomised double-masked controlled studies, with identical patient populations and study outcome measures. However, on CS page 30 NORSE ONE is described as a small “clinical experience trial” which was not intended to be assessed statistically. This seems at odds with Table 3-1. Please can you check that descriptive information on these two trials is correct in the submission.

Thank you for your comment. Additional descriptive information on the overall study design is provided below, as the information provided in Table 3-1 of the CS was too broad in relation to the study population and inclusion criteria.

NORSE ONE included a different sub-patient population than NORSE TWO, with both pre-treated and treatment-naïve subjects enrolled in this smaller trial. Patients

in NORSE ONE also differed from NORSE TWO in their visual acuity inclusion criteria. NORSE ONE patients were also allowed to have better vision (~20/40) than was allowed in NORSE TWO (~20/50).

NORSE ONE was designed as a smaller, proof of biological activity study from its inception. Likewise, NORSE TWO was always designed as the larger, pivotal trial that was powered to have the opportunity to achieve statistical significance and demonstrate a difference between the two study arms.

Data from published literature was used to calculate the sample size needed to support a superiority trial in the ONS-5010 development program. The change in visual acuity over time measured in patients with nAMD and dosed with monthly intravitreal Avastin was known from the IVAN [1, 2] and CATT [3] trials. Lucentis administered in a fixed dosing regimen, ie, as in the PIER trial,[4] was considered to provide the most reliable numbers for calculating a sample size. The calculated sample size was then incorporated into the pivotal NORSE TWO trial and the power was reduced to design a smaller, proof-of-effect and safety trial, NORSE ONE. Essentially, NORSE ONE had the purpose of providing initial information on the effects and safety of ONS-5010 as well as informing the final study population to be enrolled in NORSE TWO.

For NORSE TWO, overall demographic data from the NORSE ONE study helped inform the selection of the most appropriate patient population to maximize the likelihood that the study would demonstrate a treatment effect for both the ONS-5010 and ranibizumab treatment arms. An evaluation of the treatment population demographics of NORSE ONE was conducted along with consulting the literature for visual acuity outcomes based upon baseline characteristics. The resulting consensus was that a treatment-naïve population would have the best opportunity to demonstrate effectiveness in NORSE TWO. The use of baseline characteristics to enroll a population in which efficacy is more likely to be demonstrated, i.e., enriched to show an effect, is commonly applied in clinical study design. [5, 6]

Notably, the use of bevacizumab gamma in a treatment naïve population is likely to be a more accurate reflection of real-world use in the UK and aligns to the population validated by UK clinical experts informing the company budget impact estimate

(where treatment switching was regarded as uncommon unless significant economic benefits were expected).

Please note: ONS-5010 is Lytenava™ (bevacizumab gamma).

A6. In Table 3-1 NORSE ONE is described as a phase 3 proof-of-concept trial. Please can you clarify if this was the intended description of the study and if so, explain how proof of concept was assessed within the context of a phase 3 trial.

Thank you for your comment. As described in response A5, NORSE ONE was designed as a smaller, proof of biological activity study from its inception. Likewise, NORSE TWO was always designed as the larger, pivotal trial that was powered to have the opportunity to achieve statistical significance and demonstrate a difference between the two study arms.

The purpose of both NORSE ONE and NORSE TWO was to demonstrate the effectiveness and safety of ONS-5010. Given the large body of available literature for off-label use of bevacizumab (branded Avastin), both dose and posology were already known prior to the initiation of the ONS-5010 development program; thus, a Phase 2 program was unnecessary.

As a proof of biological activity study, NORSE ONE was not powered to show a significant difference in subjects gaining 3 lines of BCVA, ie, the proportion of subjects achieving an increase of ≥ 15 letters in BCVA from baseline to 11 months, in a mixed treatment-naïve and previously treated nAMD population.

Although NORSE ONE did not meet its primary efficacy statistical endpoint, a treatment effect in terms of visual gains was observed for subjects in the ONS-5010 group. Following treatment with ONS-5010, positive trends across all outcome measures were reported: 7% subjects gaining ≥15 letters, 8.33 letters mean BCVA gain, 42.3% subjects gaining ≥5 letters, 11.5% subjects gaining ≥10 letters, 88.5% subjects losing <15 letters, and 15.4% subjects with Snellen equivalent of 20/200 or worse. When compared to sham control arms, e.g., from the ANCHOR [7] and MARINA [8] studies, that are indicative of the natural course of the disease that reported negative values of -10.5 letters or even -16.5 letters mean BCVA gain and

only 62.2% or even 49.9% subjects losing <15 letters, it is obvious that ONS-5010 had a beneficial treatment effect in NORSE ONE.

These robust efficacy signals are further strengthened when only taking the subgroup of treatment naïve subjects (n=6) into account: 33.3% subjects gaining ≥15 letters, 7.3 [SD 10.58] letters mean BCVA gain, 50.0% subjects gaining ≥5 letters, 33.3% subjects gaining ≥10 letters, 100% subjects losing <15 letters, and 0% subjects with Snellen equivalent of 20/200 or worse.

Overall, NORSE ONE provided proof of biological activity for ONS-5010 consistent with the anti-VEGF class and evidence of effectiveness consistent with the treatment effects observed in the NORSE TWO study population.

Please note: ONS-5010 is Lytenava™ (bevacizumab gamma).

A7. Please describe the sham procedures in the ranibizumab arms of the NORSE ONE and TWO trials. Furthermore, please state whether those blinded to study allocation were asked if they could distinguish between sham and real injections.

Thank you for your comment. In NORSE ONE and NORSE TWO, subjects in the ranibizumab group were administered monthly intravitreal injections of study treatment for the first 3 months (Days 0, 30 and 60) followed by 2 additional injections, 90-days apart, on Days 150 and 240. Subjects in the ranibizumab group underwent sham procedures at visits when active treatment was not administered. Per protocol, these subjects were prepped as though they would receive an intravitreal injection but a syringe with no needle was used to touch the eye to simulate the injection in order to maintain the subject's masking.

Physicians were instructed to carry out the procedure under controlled aseptic conditions, which included surgical hand disinfection. A minimum of five minutes prior to the procedure, a thorough cleansing of the lid, lashes, and periorbital area with 5% povidone iodine for ophthalmic use was completed and local anesthesia was administered. Immediately prior to the procedure, a sterile lid speculum was inserted and 5% povidone iodine for ophthalmic use was applied to the procedure site. The provided 1 mL syringe was removed from its sterile pouch and the tip of the syringe (the hub with no needle) was placed on the entry site for the approximate

amount of time it would take to perform an IVT injection without penetrating the eye. Post-procedure assessments matched that of the post-injection assessments.

As the patient's eye was anesthetized and held open via cannula, the patient would not have been able to feel the difference between live injection and sham procedure. The question was not explicitly asked if patients could distinguish between sham and real injections.

Additionally, the primary endpoint, BCVA, was assessed by a masked, certified technician on qualified equipment.

Please note: ONS-5010 is Lytenava™ (bevacizumab gamma).

Indirect treatment comparison (ITC)

A8. PRIORITY QUESTION. CS Document B section 3.9.4 page 60 states "*Full results for all outcomes/timepoints as well as the sensitivity analyses can be seen within the NMA report*". The NMA report was not provided to the EAG. Please provide this document as soon as possible.

Thank you for your comment. The full NMA report has been uploaded to NICEdocs together with this response (confidential please). *File name: Outlook wet AMD_Clinical SLR-NMA Final report_13AUG2024*

A9. Please describe the decision to undertake a series of MAICs in preference to potential alternatives, such as multilevel network meta-regression (ML-NMR).

Thank you for your comment. The primary reasons for conducting a MAIC were:

> Firstly, 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 ML-NMR would be possible), and
>
> Secondly, 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. [4, 8]

Analysis via a ML-NMR addresses imbalances in study populations but does not accommodate these structural issues.

A10. Please add references to all studies cited in CS Appendix D, Section D1.3 (Appendix D, p92)

Thank you for your comment. The full list of citations identified via the SLR for each of the referenced trials can be found on the table below.

Trial name	Full citation
ARIES	Anonymous,. Erratum: Efficacy and safety of intravitreal aflibercept using a treat-and-extend regimen for neovascular age-related macular degeneration - The aries study: A randomized clinical trial (Retina (2021) (1911-1920) DOI: 10.1097/IAE.0000000000003128). Retina. 2022. 42:E43
ARIES	Mitchell, P.,Holz, F. G.,Hykin, P.,Midena, E.,Souied, E.,Allmeier, H.,Lambrou, G.,Schmelter, T.,Wolf, S.. EFFICACY AND SAFETY OF INTRAVITREAL AFLIBERCEPT USING A TREAT-AND-EXTEND REGIMEN FOR NEOVASCULAR AGE-RELATED MACULAR DEGENERATION: The ARIES Study: A Randomized Clinical Trial. Retina (Philadelphia, Pa.). 2021. 41:1911-1920
Asahi 2020	Asahi, M. G.,Wallsh, J.,Onishi, S. M.,Kuroyama, S.,Gallemore, R. P.. Multifocal erg and microperimetry changes in response to ranibizumab treatment of neovascular amd: Randomized phase 2 open-label study. Clinical Ophthalmology. 2020. 14:3599-3610
CANTREAT	Kertes, P. J.,Galic, I. J.,Greve, M.,Williams, R. G.,Rampakakis, E.,Scarino, A.,Sheidow, T.. Canadian Treat-and-Extend Analysis Trial with Ranibizumab in Patients with Neovascular Age-Related Macular Disease: One-Year Results of the Randomized Canadian Treat-and-Extend Analysis Trial with Ranibizumab Study. Ophthalmology. 2019. 126:841-848
CANTREAT	Kertes, P. J.,Galic, I. J.,Greve, M.,Williams, G.,Baker, J.,Lahaie, M.,Sheidow, T.. Efficacy of a Treat-and-Extend Regimen with Ranibizumab in Patients with Neovascular Age-Related Macular Disease: A Randomized Clinical Trial. JAMA Ophthalmology. 2020. 138:244-250
CATT	Comparison of Age-related Macular Degeneration Treatments Trials Research, Group,Writing, Committee,Martin, Daniel F.,Maguire, Maureen G.,Fine, Stuart L.,Ying, Gui-Shuang,Jaffe, Glenn J.,Grunwald, Juan E.,Toth, Cynthia,Redford, Maryann,Ferris, Frederick L., 3rd. Ranibizumab and Bevacizumab for Treatment of Neovascular Age-related Macular Degeneration: Two-Year Results. Ophthalmology. 2020. 127:S135-S145

Trial name	Full citation
CATT	Martin, D. F.,Maguire, M. G.,Fine, S. L.,Ying, G. S.,Jaffe, G. J.,Grunwald, J. E.,Toth, C.,Redford, M.,Ferris, Iii F. L.. Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: Two-year results. Ophthalmology. 2012. 119:1388-1398
CATT	Maguire, M. G.,Martin, D. F.,Ying, G. S.,Jaffe, G. J.,Daniel, E.,Grunwald, J. E.,Toth, C. A.,Ferris, F. L.,Fine, S. L.. Five-Year Outcomes with Anti-Vascular Endothelial Growth Factor Treatment of Neovascular Age-Related Macular Degeneration: The Comparison of Age-Related Macular Degeneration Treatments Trials. Ophthalmology. 2016. 123:1751-1761
CATT	Daniel, E.,Toth, C. A.,Grunwald, J. E.,Jaffe, G. J.,Martin, D. F.,Fine, S. L.,Huang, J.,Ying, G. S.,Hagstrom, S. A.,Winter, K.,Maguire, M. G.. Risk of scar in the comparison of Age-related Macular Degeneration Treatments Trials. Ophthalmology. 2014. 121:656-666
CATT	Grunwald, J. E.,Pistilli, M.,Ying, G. S.,Maguire, M. G.,Daniel, E.,Martin, D. F.. Growth of geographic atrophy in the comparison of age-related macular degeneration treatments trials. Ophthalmology. 2015. 122:809-816
CATT	Meredith, T. A.,McCannel, C. A.,Barr, C.,Doft, B. H.,Peskin, E.,Maguire, M. G.,Martin, D. F.,Prenner, J. L.. Postinjection endophthalmitis in the comparison of Age-Related Macular Degeneration Treatments Trials (CATT). Ophthalmology. 2015. 122:817-821
CATT	Ying, G. S.,Maguire, M. G.,Daniel, E.,Ferris, F. L.,Jaffe, G. J.,Grunwald, J. E.,Toth, C. A.,Huang, J.,Martin, D. F.. Association of baseline characteristics and early vision response with 2-year vision outcomes in the comparison of AMD Treatments Trials (CATT). Ophthalmology. 2015. 122:2523-2531
CATT	Martin, D. F.,Maguire, M. G.,Ying, G. S.,Grunwald, J. E.,Fine, S. L.,Jaffe, G. J.. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. New England Journal of Medicine. 2011. 364:1897-1908
CATT	Martin, D. F.,Maguire, M. G.,Fine, S. L.,Ying, G. S.,Jaffe, G. J.,Grunwald, J. E.,Toth, C.,Redford, M.,Ferris, F. L.. Ranibizumab and Bevacizumab for Treatment of Neovascular Age-related Macular Degeneration: Two-Year Results. Ophthalmology. 2020. 127:S135-S145
Chan 2015	Chan, C. K.,Abraham, P.,Sarraf, D.,Nuthi, A. S. D.,Lin, S. G.,McCannel, C. A.. Earlier therapeutic effects associated with high dose (2.0 mg) ranibizumab for treatment of vascularized pigment epithelial detachments in age-related macular degeneration. Eye (Basingstoke). 2015. 29:80-87
HARBOR	Frenkel, R. E. P.,Shapiro, H.,Stoilov, I.. Predicting vision gains with anti-VEGF therapy in neovascular age-related macular degeneration patients by using low-luminance vision. British Journal of Ophthalmology. 2016. 100:1052-1057
HARBOR	Freund, K. B.,Staurenghi, G.,Jung, J. J.,Zweifel, S. A.,Cozzi, M.,Hill, L.,Blotner, S.,Tsuboi, M.,Gune, S.. Macular neovascularization lesion type and vision outcomes in

Trial name	Full citation
	neovascular age-related macular degeneration: post hoc analysis of HARBOR. Graefe's Archive for Clinical and Experimental Ophthalmology. 2022. 260:2437-2447
HARBOR	Ho, A. C.,Busbee, B. G.,Regillo, C. D.,Wieland, M. R.,Van Everen, S. A.,Li, Z.,Rubio, R. G.,Lai, P.. Twenty-four-month efficacy and safety of 0.5 mg or 2.0 mg ranibizumab in patients with subfoveal neovascular age-related macular degeneration. Ophthalmology. 2014. 121:2181-2192
HARBOR	Sadda, S. R.,Tuomi, L. L.,Ding, B.,Fung, A. E.,Hopkins, J. J.. Macular Atrophy in the HARBOR Study for Neovascular Age-Related Macular Degeneration. Ophthalmology. 2018. 125:878-886
HARBOR	Sarraf, D.,London, N. J. S.,Khurana, R. N.,Dugel, P. U.,Gune, S.,Hill, L.,Tuomi, L.. Ranibizumab Treatment for Pigment Epithelial Detachment Secondary to Neovascular Age-Related Macular Degeneration: Post Hoc Analysis of the HARBOR Study. Ophthalmology. 2016. 123:2213-2224
HARBOR	Stoller, G. L.,Kokame, G. T.,Dreyer, R. F.,Shapiro, H.,Tuomi, L. L.. Patterns of early and delayed visual response to ranibizumab treatment for neovascular age-related macular degeneration. JAMA Ophthalmology. 2016. 134:545-553
HARBOR	Khurana, R. N.,Chang, L.,Day, B. M.,Ghanekar, A.,Stoilov, I.. Timing of Peak Vision Gains in Patients with Neovascular Age-Related Macular Degeneration Treated with Ranibizumab. Ophthalmology Retina. 2020. 4:760-766
HARBOR	Busbee, B. G.,Ho, A. C.,Brown, D. M.,Heier, J. S.,Suner, I. J.,Li, Z.,Rubio, R. G.,Lai, P.. Twelve-month efficacy and safety of 0.5 mg or 2.0 mg ranibizumab in patients with subfoveal neovascular age-related macular degeneration. Ophthalmology. 2013. 120:1046-1056
In-Eye	Lopez Galvez, M. I.,Arias Barquet, L.,S. Figueroa M,Garcia-Layana, A.,Ruiz Moreno, J. M.,Fernandez Rodriguez, M.,Garcia Arumi, J.,Amat Peral, P.,Ascaso Puyuelo, J.,Armada Maresca, F.,Cervera Taulet, E.,Torres Imaz, R.,Gutierrez Sanchez, E.,Cordoves Dorta, L. M.,Esteban Gonzalez, E.,Velilla Oses, S.,Abengoechea Hernandez, S.,Ruiz Miguel, M.,Basauri Rementeria, E.,Caballos Castilla, R.,Villavilla Castillo, J.,Lopez Guajardo, L.,Gallego Pinazo, R.,Araiz Iribarren, J. J.,Rodriguez Garcia, L.,Cabrera Lopez, F.,Lopez Garrido, J. A.,Lopez-Herrera, M. L.,Alforja Castiella, M. S.,Ruiz Moreno, O.,Martinez Alday, N.,Fernandez-Vega Sanz, A.,Garcia Campos, J.. Bimonthly, treat-and-extend and as-needed ranibizumab in naive neovascular age-related macular degeneration patients: 12-month outcomes of a randomized study. Acta Ophthalmologica. 2020. 98:e820-e829
In-Eye	Saenz-de-Viteri, M.,Recalde, S.,Fernandez-Robredo, P.,Lopez Galvez, M. I.,Arias Barquet, L.,Garcia-Arumi, J.,Figueroa, M. S.,Rodriguez, M. F.,Arumi, J. G.,Amat, P.,Alicante, V.,Garcia-Layana, A.,Barquet, L. A.,Moreno, J. M. R.,Puyuelo, J. A.,Maresca, F. A.,Taulet, E. C.,Galvez, M. I. L.,Imaz, R. T.,Sanchez, E. G.,Dorta, L. M. C.,Gonzalez, E. E.,Oses, S. V.,Hernandez, S. A.,Miguel, M. R.,Rementeria, E.

Trial name	Full citation
	B.,Castilla, R. C.,Castillo, J. V.,Guajardo, L. L.,Pinazo, R. G.,Iribarren, J. J. A.,Garcia, L. R.,Lopez, F. C.,Garrido, J. A. L.,Lopez-Herrera, M. L.,Castiella, M. S. A.,Moreno, O. R.,Alday, N. M.,Sanz, A. F. V.,Campos, J. G.,Hernandez, M.,Llorente, S.,Sayar, O.,Iriarte, E. O.. Role of intraretinal and subretinal fluid on clinical and anatomical outcomes in patients with neovascular age-related macular degeneration treated with bimonthly, treat-and-extend and as-needed ranibizumab in the In-Eye study. Acta Ophthalmologica. 2021. 99:861-870
IVAN	Chakravarthy, U.,Harding, S. P.,Rogers, C. A.,Downes, S.,Lotery, A. J.,Dakin, H. A.,Culliford, L.,Scott, L. J.,Nash, R. L.,Taylor, J.,Muldrew, A.,Sahni, J.,Wordsworth, S.,Raftery, J.,Peto, T.,Reeves, B. C.. A randomised controlled trial to assess the clinical effectiveness and cost-effectiveness of alternative treatments to Inhibit VEGF in Age-related choroidal Neovascularisation (IVAN). Health Technology Assessment. 2015. 19:1-298
IVAN	Chakravarthy, U.,Harding, S. P.,Rogers, C. A.,Downes, S. M.,Lotery, A. J.,Culliford, L. A.,Reeves, B. C.,Ivan study investigators. Alternative treatments to inhibit VEGF in age-related choroidal neovascularisation: 2-year findings of the IVAN randomised controlled trial. Lancet. 2013. 382:1258-1267
IVAN	Chakravarthy, U.,Harding, S. P.,Rogers, C. A.,Downes, S. M.,Lotery, A. J.,Wordsworth, S.,Reeves, B. C.. Ranibizumab versus bevacizumab to treat neovascular age-related macular degeneration: One-year findings from the IVAN randomized trial. Ophthalmology. 2012. 119:1399-1411
LUCERNE	Heier, Jeffrey S.,Khanani, Arshad M.,Quezada Ruiz, Carlos,Basu, Karen,Ferrone, Philip J.,Brittain, Christopher,Figueroa, Marta S.,Lin, Hugh,Holz, Frank G.,Patel, Vaibhavi,Lai, Timothy Y. Y.,Silverman, David,Regillo, Carl,Swaminathan, Balakumar,Viola, Francesco,Cheung, Chui Ming Gemmy,Wong, Tien Y.,Tenaya,,Lucerne Investigators. Efficacy, durability, and safety of intravitreal faricimab up to every 16 weeks for neovascular age-related macular degeneration (TENAYA and LUCERNE): two randomised, double-masked, phase 3, non-inferiority trials. Lancet (London, England). 2022. 399:729-740
MARINA	Rosenfeld, P. J.,Brown, D. M.,Heier, J. S.,Boyer, D. S.,Kaiser, P. K.,Chung, C. Y.,Kim, R. Y.. Ranibizumab for neovascular age-related macular degeneration. New England Journal of Medicine. 2006. 355:1419-1431
MARINA	Boyer, D. S.,Antoszyk, A. N.,Awh, C. C.,Bhisitkul, R. B.,Shapiro, H.,Acharya, N. R.. Subgroup Analysis of the MARINA Study of Ranibizumab in Neovascular Age-Related Macular Degeneration. Ophthalmology. 2007. 114:246-252
MARINA	Blodi, B. A.,Domalpally, A.,Corkery, E.,Osborne, A.,Blotner, S.,Grzeschik, S. M.,Gune, S.. Prevalence of Macular Atrophy in the MARINA Study of Ranibizumab versus Sham for Neovascular Age-Related Macular Degeneration. Ophthalmology Retina. 2023. 7:661-671

Trial name	Full citation
RABIMO	Feltgen, N.,Bertelmann, T.,Bretag, M.,Pfeiffer, S.,Hilgers, R.,Callizo, J.,Goldammer, L.,Bemme, S.,Hoerauf, H.. Efficacy and safety of a fixed bimonthly ranibizumab treatment regimen in eyes with neovascular age-related macular degeneration: results from the RABIMO trial. Graefe's Archive for Clinical and Experimental Ophthalmology. 2017. 255:923-934
RIVAL	Gillies, M. C.,Hunyor, A. P.,Arnold, J. J.,Guymer, R. H.,Wolf, S.,Pecheur, F. L.,Munk, M. R.,McAllister, I. L.. Macular Atrophy in Neovascular Age-Related Macular Degeneration: A Randomized Clinical Trial Comparing Ranibizumab and Aflibercept (RIVAL Study). Ophthalmology. 2020. 127:198-210
RIVAL	Gillies, M. C.,Hunyor, A. P.,Arnold, J. J.,Guymer, R. H.,Wolf, S.,Ng, P.,Pecheur, F. L.,McAllister, I. L.. Effect of Ranibizumab and Aflibercept on Best-Corrected Visual Acuity in Treat-and-Extend for Neovascular Age-Related Macular Degeneration: A Randomized Clinical Trial. JAMA Ophthalmology. 2019. 137:372-379
STAIRWAY	Khanani, A. M.,Patel, S. S.,Ferrone, P. J.,Osborne, A.,Sahni, J.,Grzeschik, S.,Basu, K.,Ehrlich, J. S.,Haskova, Z.,Dugel, P. U.. Efficacy of Every Four Monthly and Quarterly Dosing of Faricimab vs Ranibizumab in Neovascular Age-Related Macular Degeneration: The STAIRWAY Phase 2 Randomized Clinical Trial. JAMA Ophthalmology. 2020. 138:964-972
TENAYA	Heier, Jeffrey S.,Khanani, Arshad M.,Quezada Ruiz, Carlos,Basu, Karen,Ferrone, Philip J.,Brittain, Christopher,Figueroa, Marta S.,Lin, Hugh,Holz, Frank G.,Patel, Vaibhavi,Lai, Timothy Y. Y.,Silverman, David,Regillo, Carl,Swaminathan, Balakumar,Viola, Francesco,Cheung, Chui Ming Gemmy,Wong, Tien Y.,Tenaya,,Lucerne Investigators. Efficacy, durability, and safety of intravitreal faricimab up to every 16 weeks for neovascular age-related macular degeneration (TENAYA and LUCERNE): two randomised, double-masked, phase 3, non-inferiority trials. Lancet (London, England). 2022. 399:729-740
TENAYA	Mori, R.,Honda, S.,Gomi, F.,Tsujikawa, A.,Koizumi, H.,Ochi, H.,Ohsawa, S.,Okada, A. A.. Efficacy, durability, and safety of faricimab up to every 16 weeks in patients with neovascular age-related macular degeneration: 1-year results from the Japan subgroup of the phase 3 TENAYA trial. Japanese Journal of Ophthalmology. 2023. 67:301-310
TENAYA; LUCERNE	Chaudhary, V.,Kotecha, A.,Willis, J.,Souverain, A.,Shildkrot, E.,Swaminathan, B.,Margaron, P.. Individualized faricimab dosing up to every 16 weeks maintains robust anatomic and vision outcomes through 2 years in nAMD. Investigative Ophthalmology and Visual Science. 2023. 64:5056
TENAYA; LUCERNE	Takahashi, K.,Cheung, C. M. G.,Iida, T.,Lai, T. Y. Y.,Ohji, M.,Yanagi, Y.,Kawano, M.,Ohsawa, S.,Suzuki, T.,Kotecha, A.,Lin, H.,Patel, V.,Swaminathan, B.,Lee, W. K.. Efficacy, durability, and safety of faricimab in patients from Asian countries with neovascular age-related macular degeneration: 1-Year subgroup analysis of the

Trial name	Full citation
	TENAYA and LUCERNE trials. Graefe's Archive for Clinical and Experimental Ophthalmology. 2023. 261:3125-3137
TENAYA; LUCERNE	Heier, Jeffrey S.,Khanani, Arshad M.,Quezada Ruiz, Carlos,Basu, Karen,Ferrone, Philip J.,Brittain, Christopher,Figueroa, Marta S.,Lin, Hugh,Holz, Frank G.,Patel, Vaibhavi,Lai, Timothy Y. Y.,Silverman, David,Regillo, Carl,Swaminathan, Balakumar,Viola, Francesco,Cheung, Chui Ming Gemmy,Wong, Tien Y.,Tenaya,,Lucerne Investigators. Efficacy, durability, and safety of intravitreal faricimab up to every 16 weeks for neovascular age-related macular degeneration (TENAYA and LUCERNE): two randomised, double-masked, phase 3, non-inferiority trials. Lancet (London, England). 2022. 399:729-740
TENAYA; LUCERNE	Guymer, R. H.,Holz, F. G.,Lin, H.,Basu, K.,Ruiz, C. Q.,Wong, T. Y.. Faricimab in neovascular age-related macular degeneration: Week 48 results from the phase 3 TENAYA and LUCERNE trials. Clinical and Experimental Ophthalmology. 2022. 49:835
TENAYA; LUCERNE	Querques, G.,London, N.,Kotecha, A.,Willis, J.,Souverain, A.,Shildkrot, E.,Margaron, P.. Faricimab rapidly improves fluid parameters in patients with nAMD. Investigative Ophthalmology and Visual Science. 2023. 64:2185
TREND	Waldstein, S. M.,Coulibaly, L.,Riedl, S.,Sadeghipour, A.,Gerendas, B. S.,Schmidt-Erfurth, U. M.. Effect of posterior vitreous detachment on treat-and-extend versus monthly ranibizumab for neovascular age-related macular degeneration. British Journal of Ophthalmology. 2020. 104:899-903
TREND	Silva, R.,Berta, A.,Larsen, M.,Macfadden, W.,Feller, C.,Mones, J.. Treat-and-Extend versus Monthly Regimen in Neovascular Age-Related Macular Degeneration: Results with Ranibizumab from the TREND Study. Ophthalmology. 2018. 125:57-65
TREX-AMD	Wykoff, Charles C.,Ou, William C.,Brown, David M.,Croft, Daniel E.,Wang, Rui,Payne, John F.,Clark, W. Lloyd,Abdelfattah, Nizar Saleh,Sadda, SriniVas R.,Trex-Amd Study Group. Randomized Trial of Treat-and-Extend versus Monthly Dosing for Neovascular Age-Related Macular Degeneration: 2-Year Results of the TREX-AMD Study. Ophthalmology. Retina. 2017. 1:314-321
TREX-AMD	Wykoff, Charles C.,Ou, William C.,Croft, Daniel E.,Payne, John F.,Brown, David M.,Clark, W. Lloyd,Abdelfattah, Nizar Saleh,Sadda, SriniVas R.,Trex-Amd Study Group. Neovascular age-related macular degeneration management in the third year: final results from the TREX-AMD randomised trial. The British journal of ophthalmology. 2018. 102:460-464
TREX-AMD	Wykoff, C. C.,Croft, D. E.,Brown, D. M.,Wang, R.,Payne, J. F.,Clark, L.,Abdelfattah, N. S.,Sadda, S. R.. Prospective trial of treat-and-extend versus monthly dosing for neovascular age-related macular degeneration: TREX-AMD 1-year results. Ophthalmology. 2015. 122:2514-2522
VIEW 1	Heier, J. S.,Brown, D. M.,Chong, V.,Korobelnik, J. F.,Kaiser, P. K.,Nguyen, Q. D.,Kirchhof, B.,Ho, A.,Ogura, Y.,Yancopoulos, G. D.,Stahl, N.,Vitti, R.,Berliner, A.

Trial name	Full citation
	J.,Soo, Y.,Anderesi, M.,Groetzbach, G.,Sommerauer, B.,Sandbrink, R.,Simader, C.,Schmidt-Erfurth, U.. Intravitreal aflibercept (VEGF trap-eye) in wet age-related macular degeneration. Ophthalmology. 2012. 119:2537-2548
VIEW 1; VIEW 2	Schmidt-Erfurth, U.,Kaiser, P. K.,Korobelnik, J. F.,Brown, D. M.,Chong, V.,Nguyen, Q. D.,Ho, A. C.,Ogura, Y.,Simader, C.,Jaffe, G. J.,Slakter, J. S.,Yancopoulos, G. D.,Stahl, N.,Vitti, R.,Berliner, A. J.,Soo, Y.,Anderesi, M.,Sowade, O.,Zeitz, O.,Norenberg, C.,Sandbrink, R.,Heier, J. S.. Intravitreal aflibercept injection for neovascular age-related macular degeneration: Ninety-six-week results of the VIEW studies. Ophthalmology. 2014. 121:193-201
VIEW 1; VIEW 2	Ho, A. C.,Saroj, N.,Baker, K.,Vitti, R.,Berliner, A. J.,Thompson, D.,Roth, D. B.. Impact of Baseline Characteristics on Treatment Response to Intravitreal Aflibercept Injection for Wet Age-Related Macular Degeneration. Ophthalmology Retina. 2018. 2:676-683
VIEW 1; VIEW 2	Jaffe, G. J.,Kaiser, P. K.,Thompson, D.,Gibson, A.,Saroj, N.,Vitti, R.,Berliner, A. J.,Heier, J. S.. Differential Response to Anti-VEGF Regimens in Age-Related Macular Degeneration Patients with Early Persistent Retinal Fluid. Ophthalmology. 2016. 123:1856-1864
VIEW 1; VIEW 2	Khurana, R. N.,Rahimy, E.,Joseph, W. A.,Saroj, N.,Gibson, A.,Vitti, R.,Berliner, A. J.,Chu, K.,Cheng, Y.,Boyer, D. S.. Extended (Every 12 Weeks or Longer) Dosing Interval With Intravitreal Aflibercept and Ranibizumab in Neovascular Age-Related Macular Degeneration: Post Hoc Analysis of VIEW Trials. American Journal of Ophthalmology. 2019. 200:161-168
VIEW 1; VIEW 2	Moshfeghi, D. M.,Hariprasad, S. M.,Marx, J. L.,Thompson, D.,Soo, Y.,Gibson, A.,Saroj, N.,Vitti, R.,Heier, J. S.. Effect of fluid status at week 12 on visual and anatomic outcomes at week 52 in the VIEW 1 and 2 trials. Ophthalmic Surgery Lasers and Imaging Retina. 2016. 47:238-244
VIEW 1; VIEW 2	Richard, G.,Mones, J.,Wolf, S.,Korobelnik, J. F.,Guymer, R.,Goldstein, M.,Norenberg, C.,Sandbrink, R.,Zeitz, O.. Scheduled versus Pro Re Nata dosing in the VIEW trials. Ophthalmology. 2015. 122:2497-2503
VIEW 1; VIEW 2	Yuzawa, M.,Fujita, K.,Wittrup-Jensen, K. U.,Norenberg, C.,Zeitz, O.,Adachi, K.,Wang, E. C. Y.,Heier, J.,Kaiser, P.,Chong, V.,Korobelnik, J. F.. Improvement in vision-related function with intravitreal aflibercept: Data from phase 3 studies in wet age-related macular degeneration. Ophthalmology. 2015. 122:571-578
VIEW 1; VIEW 2	Heier, J. S.,Brown, D. M.,Chong, V.,Korobelnik, J. F.,Kaiser, P. K.,Nguyen, Q. D.,Kirchhof, B.,Ho, A.,Ogura, Y.,Yancopoulos, G. D.,Stahl, N.,Vitti, R.,Berliner, A. J.,Soo, Y.,Anderesi, M.,Groetzbach, G.,Sommerauer, B.,Sandbrink, R.,Simader, C.,Schmidt-Erfurth, U.. Intravitreal aflibercept (VEGF trap-eye) in wet age-related macular degeneration. Ophthalmology. 2012. 119:2537-2548
VIEW 2	Heier, J. S.,Brown, D. M.,Chong, V.,Korobelnik, J. F.,Kaiser, P. K.,Nguyen, Q. D.,Kirchhof, B.,Ho, A.,Ogura, Y.,Yancopoulos, G. D.,Stahl, N.,Vitti, R.,Berliner, A.

Trial name	Full citation
	J.,Soo, Y.,Anderesi, M.,Groetzbach, G.,Sommerauer, B.,Sandbrink, R.,Simader, C.,Schmidt-Erfurth, U.. Intravitreal aflibercept (VEGF trap-eye) in wet age-related macular degeneration. Ophthalmology. 2012. 119:2537-2548
VIEW 2	Kaiser, Peter K.,Kodjikian, Laurent,Korobelnik, Jean-Francois,Winkler, Julia,Torri, Albert,Zeitz, Oliver,Vitti, Robert,Ahlers, Cristiane,Zimmermann, Torsten,Dicioccio, A. Thomas,Hochel, Joachim. Systemic pharmacokinetic/pharmacodynamic analysis of intravitreal aflibercept injection in patients with retinal diseases. BMJ open ophthalmology. 2019. 4:e000185
VIEW 2	Ogura, Y.,Terasaki, H.,Gomi, F.,Yuzawa, M.,Iida, T.,Honda, M.,Nishijo, K.,Sowade, O.,Komori, T.,Schmidt-Erfurth, U.,Simader, C.,Chong, V.. Efficacy and safety of intravitreal aflibercept injection in wet age-related macular degeneration: Outcomes in the Japanese subgroup of the VIEW 2 study. British Journal of Ophthalmology. 2015. 99:92-97
VIEW 2	Lukacs, R.,Schneider, M.,Nagy, Z. Z.,Sandor, G. L.,Kaan, K.,Asztalos, A.,Enyedi, L.,Pek, G.,Barcsay, G.,Szabo, A.,Borbandy, A.,Kovacs, I.,Resch, M. D.,Papp, A.. Seven-year outcomes following intensive anti-vascular endothelial growth factor therapy in patients with exudative age-related macular degeneration. BMC ophthalmology. 2023. 23:110

A11. Please provide the R programming code and study input data for the MAIC and NMA, including priors.

Thank you for your comment. The programming code and study input data for the NMA & MAIC are provided below, including priors.

Programming language for the indirect or mixed treatment comparison

All NMA analyses were conducted in R (v 4.4.0) using the `multinma` package.

Dichotomous outcomes

```
## set up network ##
net_bin_gain15 <- set_agd_arm(
  data = dat_bin_UK_gain15,
  study = study.id,
  trt = trt.short,
  r = outcome.r,
  n = n.assessed,
  trt_ref = 'RAN 0.5 Q4W'
)

thin <- 2L
nma_fe_bin_gain15 <- nma (# fixed effect NMA
  network = net_bin_gain15,
  trt_effects = 'fixed',
  likelihood = 'binomial',
  link = 'logit',
```

```
  chains = 4L,
  warmup = thin*2e4,
  seed = 42,
  iter = thin*5e4,
  cores = 4L,
  thin = thin,
  prior_intercept = normal (scale = 10),
  prior_trt = normal (scale = 10)
); rm(thin)

nma_re_bin_gain15 <- nma(#random effect NMA
  network = net_bin_gain15,
  trt_effects = 'random',
  likelihood = 'binomial',
  link = 'logit',
  chains = 4L,
  warmup = thin*2e4,
  seed = 42,
  iter = thin*5e4,
  cores = 4L,
  thin = thin,
  prior_intercept = normal (scale = 10),
  prior_trt = normal (scale = 15)
  prior het = half normal (scale = 5)
); rm(thin)
```

Continuous outcomes

```
## set up network ##
net_con_bcva_12 <- set_agd_arm(
  data = dat_cfb_bcva_12,
  study = study.id,
  trt = trt.short,
  y = cfb.mean,
  se = cfb.se,
  sample_size = n.cfb,
  trt_ref = 'RAN 0.5 Q4W'
)

nma_fe_con_bcva_12 <- nma(# fixed effect NMA
  network = net_con_bcva_12,
  trt_effects = 'fixed',
  likelihood = 'normal',
  link = 'identity',
  chains = 4L,
  warmup = thin*2e4,
  seed = 42,
  iter = thin*5e4,
  thin = thin,
  cores = 4L,
  prior_intercept = normal (scale = 10),
  prior_trt = normal (scale = 10)
); rm(thin)



thin <- 2L
nma_re_con_bcva_12 <- nma( #random effect NMA
  network = net_con_bcva_12,
  trt_effects = 'random',
  likelihood = 'normal',
  link = 'identity',
  chains = 4L,
  warmup = thin*2e4,
  seed = 42,
  iter = thin*5e4,
  thin = thin,
  cores = 4L,
  prior_intercept = normal (scale = 100),
  prior_trt = normal (scale = 10),
  prior_het = half_normal(scale = 3),
  adapt_delta = 0.99
```

```
); rm(thin)
```

All MAIC analyses were conducted in R version 4.4.0. Weights were calculated using version 0.1.4 of the MAIC package, which, in turn, leverages the weight generation code present in NICE TSD 18.[9] A sample of the code used for dichotomous and continuous outcomes is provided below:

Dichotomous outcomes

```
maic.boot.bin <- function(
  index.bl.data,
  resample.test,
  i,
  outcome,
  index.outcome.data,
  comparator.data,
  target,
  dictionary,
  matching.vars
) {

  resample.subjid <- data.frame(resample.test[[i]])
  names(resample.subjid) <- "subjid"

  index.bl.data.resample <- merge(x = resample.subjid, y = index.bl.data, by.x = "subjid", by.y = "subjid",
all.x = TRUE)

  maic_mat_full <- createMAICInput(
    index = index.bl.data.resample,
    target = target,
    dictionary = dictionary,
    matching.variables = matching.vars
  )

  wts_full <- maicWeight(maic_mat_full)
  index.bl.data.aug.resample <- as.data.frame(cbind(index.bl.data.resample, wts_full)) # add weights to
bl data

  # merge IPD outcomes with IPD baseline/weights
  index.data <- merge(x = index.bl.data.aug.resample, y = index.outcome.data, by = 'subjid', all.x = T)
  index.data$study.id <- rep('Index', nrow(index.data))

  # combine IPD and pseudo IPD into a single dataset for glm
  dt_glm <- rbind(index.data[,c("subjid", "study.id", outcome, "wts_full")], comparator.data)
  dt_glm$study.id <- relevel(as.factor(dt_glm$study.id), ref = "Comparator")

  names(dt_glm)[names(dt_glm) == outcome] <- 'outcome'

  fit.weighted <- glm(
    formula = outcome ~ study.id,
    data = dt_glm,
    weights = wts_full,
    family = quasibinomial
  )

  or <- exp(coef(fit.weighted))[2]

  return(or)

}

boot.summary <- function(boot.vector) {
  median <- quantile(boot.vector, 0.5, na.rm = TRUE)
  lower.ci <- quantile(boot.vector, 0.025, na.rm = TRUE)
  upper.ci <- quantile(boot.vector, 0.975, na.rm = TRUE)
```

```
  return(c(median, lower.ci, upper.ci))
}

bootstrap.ci.bin <- function(
  index.bl.data = dt_sl_maic,
  index.outcome.data = index_outcome,
  outcome = outcome,
  comparator.data = comp.pseudo,
  target = target,
  dictionary=dict,
  matching.vars=matching.vars,
  R = 1000
) {

  resample.test <- lapply(1:R, function(i) sample(index.bl.data$subjid, replace = TRUE))
  bootstrapped.ors <- numeric(length = R)

  for (i in 1:R) {
    bootstrapped.ors[i] <- maic.boot.bin(
      index.bl.data = index.bl.data,
      resample.test = resample.test,
      i,
      outcome = outcome,
      index.outcome.data = index.outcome.data,
      comparator.data = comparator.data,
      target = target,
      dictionary = dict,
      matching.vars = matching.vars
    )
  }

  summary.btstrap <- boot.summary(bootstrapped.ors)
  names(summary.btstrap) <- c("median", "lci", "uci")
  return(summary.btstrap)

}

fit.unweighted <- glm(
  formula = gain_ge15 ~ study.id,
  data = dt_outcome,
  family = binomial
)

fit.weighted <- glm(
  formula = gain_ge15 ~ study.id,
  data = dt_outcome,
  weights = wts_full,
  family = quasibinomial
)

summary.bootstrap <- bootstrap.ci.bin(
  index.bl.data = dt_sl_maic,
  index.outcome.data = index_outcome,
  outcome = outcome,
  comparator.data = comp.pseudo,
  target = target,
  dictionary = dict,
  matching.vars = matching.vars,
  R = 1e4
)
```

Continuous outcomes

```
maic.boot.cfb <- function(
  index.bl.data,
  resample.test,
  i,
  index.outcome.data,
  comparator.data,
  target,
  dictionary,
```

```
  matching.vars
) {

  resample.subjid <- data.frame(resample.test[[i]])
  names(resample.subjid) <- "subjid"

  index.bl.data.resample <- merge(x = resample.subjid, y = index.bl.data, by.x = "subjid", by.y = "subjid",
all.x = TRUE)

  maic_mat_full <- createMAICInput(
    index = index.bl.data.resample,
    target = target,
    dictionary = dictionary,
    matching.variables = matching.vars
  )

  wts_full <- maicWeight(maic_mat_full)
  index.bl.data.aug.resample <- as.data.frame(cbind(index.bl.data.resample, wts_full)) # add weights to
bl data

  # merge IPD outcomes with IPD baseline/weights
  index.data <- merge(x = index.bl.data.aug.resample, y = index.outcome.data, by = 'subjid', all.x = T)
  index.data$study.id <- rep('Index', nrow(index.data))
  index.data[is.na(index.data[2]), 2] <- 0

  # combine IPD and pseudo IPD into a single dataset for glm
  dt_glm <- rbind(index.data[,c("subjid", "study.id", "chg", "wts_full")], comparator.data)
  dt_glm$study.id <- relevel(as.factor(dt_glm$study.id), ref = "Comparator")

  fit.weighted <- glm(
    formula = chg ~ study.id,
    data = dt_glm,
    weights = wts_full,
    family = gaussian
  )

  md <- coef(fit.weighted)[2]

  return(md)

}

boot.summary <- function(boot.vector) {
  median <- quantile(boot.vector, 0.5, na.rm = TRUE)
  lower.ci <- quantile(boot.vector, 0.025, na.rm = TRUE)
  upper.ci <- quantile(boot.vector, 0.975, na.rm = TRUE)
  return(c(median, lower.ci, upper.ci))
}

bootstrap.ci.cfb <- function(
  index.bl.data = dt_sl_maic,
  index.outcome.data = index_outcome,
  outcome = outcome,
  comparator.data = comp.pseudo,
  target = target,
  dictionary = dict,
  matching.vars = matching.vars,
  R = 1000
) {

  resample.test <- lapply(1:R, function(i) sample(index.bl.data$subjid, replace = TRUE))
  bootstrapped.mds <- numeric(length = R)

  ##### need to rewrite from here
  for (i in 1:R) {
    bootstrapped.mds[i] <- maic.boot.cfb(
      index.bl.data = dt_sl_maic,
      resample.test = resample.test,
      i,
      index.outcome.data = index_outcome,
      comparator.data = comp.pseudo,
      target = target,
      dictionary = dict,
      matching.vars = matching.vars
```

```
    )
  }

  summary.btstrap <- boot.summary(bootstrapped.mds)
  names(summary.btstrap) <- c("median", "lci", "uci")
  summary.btstrap

}

fit.unweighted <- glm(
  formula = chg ~ study.id,
  data = dt_outcome,
  family = gaussian
)

fit.weighted <- glm(
  formula = chg ~ study.id,
  data = dt_outcome,
  weights = wts_full,
  family = gaussian
)

summary.bootstrap <- bootstrap.ci.cfb(
  index.bl.data = dt_sl_maic,
  index.outcome.data = index_outcome,
  outcome = outcome,
  comparator.data = comp.pseudo,
  target = target,
  dictionary = dict,
  matching.vars = matching.vars,
  R = boot.R
)
```

A12. Please indicate where variance data used in the NMA has been imputed.

Thank you for your comment. In the analysis of change from baseline in BCVA. SDs were imputed for the following studies at the following timepoints:

3 months:

- CATT
- DRAGON
- Haga 2018
- HARBOR
- LUCERNE
- MARINA
- Mori 2017
- STAIRWAY
- TENAYA
- TREND
- TREX-AMD
- VIEW 1
- VIEW 2

6 months:

- CATT
- DRAGON
- HARBOR
- LUCERNE
- MARINA
- Mori 2017
- PIER
- STAIRWAY
- TENAYA
- TREND
- TREX-AMD
- VIEW 1
- VIEW 2

9 months:

- CATT
- DRAGON
- HARBOR
- LUCERNE
- MARINA
- Mori 2017
- PIER
- STAIRWAY
- TENAYA
- TREND
- TREX-AMD
- VIEW 1
- VIEW 2

12 months

- ARIES
- DRAGON
- Haga 2018
- In-Eye

- LUCERNE
- MARINA
- Mori 2017
- RABIMO
- STAIRWAY
- TENAYA
- TREND
- TREX-AMD

In the analysis of change from baseline in CVT at 12 months, SDs were imputed for the following studies:

- CATT
- Chan 2015
- DRAGON
- HARBOR
- In-Eye
- LUCERNE
- Mori 2017
- PIER
- STAIRWAY
- TENAYA
- TREND
- TREX-AMD

A13. The CS (section B.3.3) gives reasons why the NORSE ONE study was not used to inform the indirect comparison or economic model, including: lack of statistical power, the mixed patient population and the small sample size. Please update the NMA and MAICs to include the NORSE ONE study, to enable any differences in the NMA/MAIC results associated with this study to be explored.

Thank you for your comments. The company maintains that the best use of available data is to use NORSE TWO alone in indirect evidence synthesis, however, to explore the robustness of the original analyses, we have provided an updated NMA and MAIC to include NORSE ONE, as requested. This analysis is available in

sections 9 and 10 of the NMA report attached via NICEdocs. *File name: "Outlook wet AMD_Clinical SLR-NMA Final report_13AUG2024".*

As described in response A5, NORSE ONE included a different patient population than NORSE TWO, with both pre-treated and treatment-naïve subjects enrolled in this smaller trial. Patients in NORSE ONE also differed from NORSE TWO in their visual acuity inclusion criteria. NORSE ONE patients were also allowed to have better vision (~20/40) than was allowed in NORSE TWO (~20/50).

It is known from the literature that pre-treated nAMD patients have lower effect sizes than treatment-naïve patients,[13, 14] as was seen in NORSE ONE, that included a mixed patient population. However, as the disease process is the same both in pivotal trial populations and the broader nAMD population, patients who continue to have neovascularization and resulting leakage of those new vessels, will continue to have a need for anti-VEGF therapy to treat or prevent vision loss. As such, while a difference in effect between treatment-naïve and previously treated subjects may exist, patients with prior therapy still benefit from anti-VEGF treatment with considerable improvements in visual outcomes. [13-15]

Updated NMA and MAIC results:

Detailed methodology and results can be found in the attached file "*Outlook wet AMD_Clinical SLR-NMA Final report_13AUG2024*". Results across all endpoints and timeframes are consistent with those presented in the original indirect comparison.

The inclusion of NORSE ONE data (whether the full or treatment naïve population) drives a small numerical reduction in the comparative effectiveness of bevacizumab gamma versus comparators (as expected due to a reduced scope for treatment effect in previously treated patients), but all products remain statistically non-inferior to one another, confirming the cost-comparison approach.

The updated MAIC analysis is further confirms this conclusion, and is available in the *'Outlook MAIC Report August 2024'.*

The company believes that the best available data to inform an indirect comparison is to use NORSE TWO alone, given the high number of confounding factors associated with the inclusion of NORSE ONE data.

Section B: Clarification on cost-effectiveness data

Drug acquisition costs

B1. CS Table 4-5 reports acquisition costs and vial sizes for comparators in the economic model, using information from the British National Formulary (BNF). However, there are differences between the vial sizes reported in the CS and in the current BNF (as of July 2024). Please explain these discrepancies (in red font in the table below).

Table 1 Discrepancies in vial sizes for drug acquisition costs

Source		Bevacizumab gamma (Lytenava™)	Faricimab (Vabysmo®)	Aflibercept (Eylea®)	Ranibizumab (Lucentis®)	Ranibizumab (Ongavia®) (Byooviz®) (Ranivisio®) (Ximluci®)
CS	Pharmaceutical formulation	25mg/ml vial	28.8mg /0.24ml vial	40mg/1ml pre-filled syringe or vial	25mg/ml vial	28.8mg /0.24ml vial
	Acquisition cost (excluding VAT)	£470	£857	£816	£551	Ongavia: £523.45 Byooviz: £523.45 Ranivisio: £523.45 Ximluci: £495.90
BNF	Pharmaceutical formulation	25mg/ml vial	28.8mg /0.24ml vial	4mg/100 microlitres or 3.6mg per 90 microlitres pre-filled syringe or vial	2.3mg/0.23ml vial	2.3mg/0.23ml vial
	Acquisition cost (excluding VAT)	£470	£857	£816	£551	Ongavia: £523.45 Byooviz: £523.45 Ranivisio: £523.45 Ximluci: £495.90

Thank you for your comments. The discrepancies highlighted in red font by NICE in Table 1 have been checked against the most recent BNF and have now been amended accordingly below.

CS Table 4-5: Acquisition costs of the intervention and comparator technologies

Source		Bevacizumab gamma (Lytenava™)	Faricimab (Vabysmo®)	Aflibercept (Eylea®)	Ranibizumab (Lucentis®)	Ranibizumab (Ongavia®) (Byooviz®) (Ranivisio®) (Ximluci®)
BNF	Pharmaceutical formulation	25mg/ml vial	28.8mg /0.24ml vial	4mg/100 microlitres or 3.6mg per 90 microlitres pre-filled syringe or vial	2.3mg/0.23ml vial	2.3mg/0.23ml vial
	Acquisition cost (excluding VAT)	£470	£857	£816	£551	Ongavia: £523.45 Byooviz: £523.45 Ranivisio: £523.45 Ximluci: £495.90

These discrepancies should also be amended in CS Table 4-5 Acquisition costs of the intervention and comparator technologies.

Healthcare resource costs

B2. The economic model uses information from the '2023/25 NHS Payment Scheme (amended)' (which has replaced the NHS National Tariff) to calculate administration, diagnostic and monitoring costs (CS B.4.2.7). However, the NICE health technology evaluations manual (paragraph 4.4.9) indicates that healthcare resources should be costed using 'reference costs' - national average unit costs collected from NHS organisations. Please revise the economic model to use the most recent National Cost Collection data: National schedule of NHS costs 2022/23 (available from (https://www.england.nhs.uk/costing-in-the-nhs/national-cost-collection).

Thank you for your comment. The company have updated the healthcare resource costs by using the most recent National Cost Collection data: National schedule of NHS costs 2022/23.

Table details the specific updates made.

Table 2 Updated costs used in the cost-comparison model

Variable	Model label	**Costs used to address clarification letter**	Costs previously used in the company submission
Administration Costs	c_admin	**£141.00**	£69.00
Diagnostic Testing Costs	c_diag	**£218.99**	£126.55
Monitoring Costs	c_monitoring	**£158.00**	£110.00

The impact of the above updates is negligible in terms of relative cost differences between comparators. While an overall increase in costs for all treatment options is demonstrated (driven by the higher reference costs), the lifetime cost differences between comparators is only ~£200 versus faricimab and ranibizumab, with no change versus aflibercept (see Table 3).

Table 3 Base case results of updated versus original cost comparison model

Total Per-Patient Costs	**ONS-5010**	**Faricimab**	**Aflibercept**	**Ranibizumab**
Diagnostic Testing Costs	[redacted]	[redacted]	[redacted]	[redacted]
Pharmacy Costs	[redacted]	[redacted]	[redacted]	[redacted]
Administration Costs	[redacted]	[redacted]	[redacted]	[redacted]
Monitoring Costs	[redacted]	[redacted]	[redacted]	[redacted]
Total Costs	[redacted]	[redacted]	[redacted]	[redacted]
Total costs in original submission	[redacted]	[redacted]	[redacted]	[redacted]
Difference in total costs	[redacted]	[redacted]	[redacted]	[redacted]
Incremental Per-Patient Costs		**Δ Faricimab**	**Δ Aflibercept**	**Δ Ranibizumab**
Diagnostic Testing Costs		[redacted]	[redacted]	[redacted]
Pharmacy Costs		[redacted]	[redacted]	[redacted]
Administration Costs		[redacted]	[redacted]	[redacted]
Monitoring Costs		[redacted]	[redacted]	[redacted]
Incremental Costs		[redacted]	[redacted]	[redacted]
Inc. costs in original submission		[redacted]	[redacted]	[redacted]
Difference in incremental costs		[redacted]	[redacted]	[redacted]

The use of more expensive reference costs is therefore shown to increase overall costs for all comparators; however, these are largely cancelled out when applied to all comparators.

Figures below show the updated one-way sensitivity analysis for each comparator, with results again showing negligible differences to the original company submission.

Figure 1 - Updated one-way sensitivity analysis versus faricimab

Figure 2 - Updated one-way sensitivity analysis versus aflibercept

Figure 3 - Updated one-way sensitivity analysis versus ranibizumab

Given the similarity in results between the original company submission and the ERG preferred cost inputs, updates to the scenario analysis have not currently been provided.

The updated costs also impact the budget impact calculation, however only administration costs are relevant here, since diagnostics and monitoring were excluded due to their identical values for each comparator. Table shows a small increase in overall savings based on the displacement of ranibizumab treatment to bevacizumab gamma treatment, delivering a more prominent saving when higher administration costs are considered.

Table 4 - Budget impact estimate update

	Year 1	Year 2	Year 3	Year 4	Year 5
Original budget impact estimate	*-£7,053,723*	*-£18,986,077*	*-£34,158,584*	*-£52,341,553*	*-£73,395,198*
Updated budget impact estimate	**-£7,049,208**	**-£19,006,281**	**-£34,203,916**	**-£52,412,325**	**-£73,491,718**
Difference	*-£4,515*	*£20,204*	*£45,332*	*£70,772*	*£96,520*

B3. CS section B.4.2.6 (p.95) states that "All costs are inflated to 2024 Great British Pounds (GBP) sterling". How was this inflation calculated, and how is it applied in the economic model? We note that it would not be usual to update the most recent available reference cost data (currently 2022/23) for inflation.

Thank you for your comment and note. This was an error in CS section B.4.2.6 (p.95). The company did not inflate the costs.

General population mortality

B4. The Mortality Table in the economic model (see note in Calculations!C7) states that ONS data from 1980-2020 are used. Please could you clarify which years the mortality data are taken from?

Thank you for your comment. Mortality is based on data for the year 2018-2020.

Section C: Textual clarification and additional points

No questions.

Supporting Documents

Question	Document Title	Document Format
A1.	Outlook Therapeutics_Clinical SLR in nAMD_Study update listing_07August2024_v4.0	Excel
A2.	NORSE ONE • ons-5010-001-protocol.pdf • ons-5010-001-report-body.pdf • ons-5010-001-sap.pdf NORSE TWO • ons-5010-002-protocol.pdf • ons-5010-002-report-body.pdf • ons-5010-002-sap.pdf	PDF's
A8.	Outlook wet AMD_Clinical SLR-NMA Final report Outlook MAIC Report August 2024	Word Word
B2.	Outlook BIM data 13AUG Outlook Cost Comparison Model 2August24	Excel Excel
References	NICE Clarification ID6320	Ris

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NICE National Institute for Health and Care Excellence

Cost Comparison Appraisal

Bevacizumab gamma for treating wet age-related macular degeneration [ID6320]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	MACULAR SOCIETY
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	The Macular Society is the leading national charity fighting to end sight loss caused by macular disease. Every day over 300 people in the UK face the shock of a diagnosis of macular disease. This sight loss can rob people of their independence, leaving them unable to drive, read or recognise their family. Our members tell us what a profoundly isolating condition it is. People with macular disease are seven times more likely to feel distressed or depressed. We help people adapt to life with sight loss, regain their confidence and independence and take back control of their lives. We are one of the few sight loss charities that actively fund and support medical research into macular disease. With the exception of the details in the answer to 4b, all our income is fundraised from legacies, grants, donations from individuals and fundraising activities such as our lottery, raffle, appeals and community and challenge events. We have 16,000 members who we communicate with on a regular basis, an e-newsletter that is sent monthly to 80,000 people, 370,000 website visitors a year and our Helpline responds to over 18,000 queries a year.

4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	Bayer (aflibercept) - £0 Biogen (ranibizumab) - £0 Genus Pharmaceuticals (ranibizumab) - £0 Novartis (ranibizumab, brolucizumab) - £745 (Jul 23 – Global Retina Council support) and £649 (Aug 23 – Volunteering Advisory Panel support) Roche (faricimab) - £20,000 (Jan 24 – grant towards Macular Society's patient information) Teva UK (ranibizumab) - £0
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	NO
5. How did you gather information about the experiences of patients and carers to include in your submission?	**Wet AMD survey** A survey was conducted by the Macular Society in 2020 to understand the burden that frequent anti-VEGF injections and ophthalmology appointments has on wet AMD patients and their carers or family. A total of 449 responses were received from across the UK. A full report was published August 2020. **Service users** Users of the charity's services, such as our Befriending service and Helpline are surveyed every other year. We also survey our volunteers every other year, most of our volunteers are also affected by macular disease.

	Local peer support groups Our Regional Managers who manage our network of around 350 local groups across the UK feedback regularly. They are our 'frontline', having face to face (or phone to phone) interaction every day with people affected by macular disease. We gather case studies which record the experiences of individuals living with macular disease and the impact on their families and carers. We use our social media channels to interact with people with macular disease and provide information and advice. It is also an important way for people to find others with the same condition where they have a rare form of macular disease and to share experiences.

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Macular disease is the biggest cause of sight loss in the UK with AMD affecting around 700,000 people, half of whom are registered as visually impaired. AMD is a progressive, chronic disease which affects people over 50. Prevalence increases with age and those most affected by loss of vision are those 70y and older. In the late stage of the condition wet AMD can develop, when abnormal blood vessels grow into the macula. These leak blood or fluid which leads to scarring of the macula and rapid loss of central vision over weeks or months. Wet AMD can develop suddenly and treatment needs to begin quickly. Fast referral to a hospital specialist is essential to confirm diagnosis and, where appropriate, to begin treatment to stabilise vision. The impact of losing sight cannot be underestimated. Many studies show that people fear sight loss more than serious illness or loss of a limb. It is associated with an increased risk of falls, social isolation, depression and suicidal feelings. Working age people face unemployment and poverty. There is also a significant burden on family and carers supporting a patient with AMD. A patient with AMD needs to adapt and change to the emotional and practical impacts of the condition and will often rely on family and carers to provide additional support. People affected by AMD told us: **“My poor vision means we are likely to need to sell our house in the country and move to one closer to public transport and other amenities. I also struggle to continue to play competitive golf which is my main pastime. My husband who works full time in his own business takes me to my clinic appointments which means he loses a morning or afternoon’s work regularly.”** **“As I am a carer for an adult son with Down’s syndrome, with no other family, I rely on friends to take me to appointments & take/collect him from day centres whilst I have treatment. Living in a**

	rural area without public transport means the worry of deterioration of my sight & being unable to drive is constant." **"I feel incredibly fortunate. I have had a total of 66 injections in my left eye (initially Lucentis and now Eylea) and am still having them. This has improved and maintained the level of sight. Because of having both eyes monitored on each visit wet AMD was spotted in my right eye and treatment began very early."** **"It has been difficult to come to terms with the need to rely on others to get routine things done. The injections are horrible but the alternative is worse!"** Vision loss can make daily tasks more difficult, including tasks needed to monitor and manage multi morbidities. Some people with AMD experience visual hallucinations called Charles Bonnet syndrome, which can be disturbing and add another level of impact on health and mental well being.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Responses from callers to the Helpline overwhelmingly report how wonderful the NHS is. Many agree their treatment maintains their sight and it can be anxious when treatment intervals are extended or stopped. However, personal experiences of cancelled appointments, frustration over communication with clinics, many hours spent waiting around in clinic, are all common themes. Injections are often not available in local health care settings, meaning many patients travel a good distance to attend injection clinics and need a driver to accompany them. Quotes from people who took part in our wet AMD survey: **“My daughters both live a distance from me so a whole day is needed plus an overnight stay for every appointment. So this impacts considerably on family life for them as well as me.”** **“Have had to travel by public transport over a fair distance to the hospital over the last 5 years. Especially after the injection, which can be over a two hour journey, when all you want to do is get home.”**
8. Is there an unmet need for patients with this condition?	There is no current cure for the condition and treatments can only manage and stabilise the sight loss. There is a need for longer acting treatments to reduce the time between injections and minimise the need to attend clinic appointments. Current drugs are also not able to stabilise the condition for everyone and, even where they are effective, there is often still a gradual decline in vision.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	There is now a range of drugs available to treat wet AMD. The most recent drugs coming to market are longer acting than bevacizumab gamma and extend intervals to as long as 5 months between injections for some patients. Longer acting drugs have therefore benefited patients and eye clinics as fewer appointments and injections are required. Bevacizumab gamma may not be viewed favourably by patients compared to longer acting drugs, such as faricimab.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	The main disadvantage is that it will be an intravitreal injection which will need to be given regularly, usually for several years. Appointments at an eye clinic, with all the attendant difficulties of travelling, needing someone to accompany them, costs of transport and hours at the hospital, will still be required.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Yes, age and disability are issues that need to be considered. As the drugs currently available are not a cure and do not work effectively in everyone, a proportion of patients will still experience significant sight loss such that they will be registered as sight impaired or severely sight impaired.

Other issues

13. Are there any other issues that you would like the committee to consider?	No

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• The number of people with AMD is increasing and over burdening hospital eye clinics • The impact of losing sight cannot be underestimated. Many studies show that people fear sight loss more than serious illness or loss of a limb • The treatment burden on patients and carers is significant and longer acting drugs can alleviate the problem. • Bevacizumab gamma may not be viewed favourably by patients compared to longer acting drugs, such as faricimab, as more eye injections will be required to treat the wet AMD.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

Please select YES if you would like to receive information about other NICE topics - YES or NO

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NICE National Institute for Health and Care Excellence

Cost Comparison Appraisal

Bevacizumab gamma for treating wet age-related macular degeneration [ID6320]

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you

1. Your name	[redacted]
2. Name of organisation	The College of Optometrists
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes ~~or No~~ A specialist in the treatment of people with this condition? Yes ~~or No~~ A specialist in the clinical evidence base for this condition or technology? ~~Yes or~~ No Other (please specify):
5a. Brief description of the organisation (including who funds it).	Shrewsbury and Telford Hospitals NHS Trust – Funded by local CCG/NHS England
5b. Has the organisation received any funding from the manufacturers of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal stakeholder list.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	No
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To treat and stop the progression of wet age-related macular degeneration in order to stabilise vision.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Improvement in visual acuity by more than 2 lines on EDTRS or Snellen Chart. Reduction in central retinal thickness of greater than 20%.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	No, as there are already several ways of treating and managing this condition.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	With the use of intravitreal injections such as Aflibercept, Ranibizumab and Brolucizumab. Bevacizumab can also be used but this would be outside its marketing authorisation in some NHS trusts. Photodynamic therapy can also be considered in appropriate patients but is rarely used in NHS Trusts.
9a. Are any clinical guidelines used in the	Yes, there are NICE clinical guidelines for the treatment of the condition with the following treatments: Ranibizumab NICE Technology Appraisal Guidance TA155

treatment of the condition, and if so, which?	Aflibercept NICE Technology Appraisal Guidance TA294 Brolucizumab NICE Technology Appraisal Guidance TA672 Faricimab NICE Technology Appraisal Guidance TA800
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Yes. Based on my experience within England, the guidance for usage of the above treatments is well adhered to, whilst taking into account patient circumstances.
9c. What impact would the technology have on the current pathway of care?	A new approved pathway of care would be required for this treatment. The introduction of this treatment would mean clinicians have access to another treatment option in addition to those currently in place.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes
10a. How does healthcare resource use differ between the technology and current care?	
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care within NHS Trusts as well as ISPs
10c. What investment is needed to introduce the technology? (For example,	Training of how this treatment is different to other options available. Other than this the existing infrastructure and models of care in place are more than sufficient and capable of using this treatment option immediately.

for facilities, equipment, or training.)	
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes
11a. Do you expect the technology to increase length of life more than current care?	Yes
11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Yes. There are patients where it may be more appropriate to use the other existing treatment options available for the management of wet age-related macular degeneration. This will be determined by the clinician who will decide the most effective treatment option for each patient based on their diagnosis and condition.

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant	Yes. Based on initial trials, the treatment should last longer than the current treatment options. This will help to reduce the overall number of treatments given and help to reduce the overall burden of treatment. This would be beneficial to both clinicians and patients. No new safety signals have been identified with this treatment compared to the existing treatment options already available based on current trials.

treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Yes. Further investigation will be needed to provide recommendations on the appropriate intervals between treatment. For example, Aflibercept and Ranibizumab are both recommended to be more effective on a Treat and Extend regime rather than PRN.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	There have not been any substantial related health benefits that have been highlighted for this treatment so far.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes
16a. Is the technology a 'step-change' in the	Yes

management of the condition?	
16b. Does the use of the technology address any particular unmet need of the patient population?	Yes
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Recent studies of this treatment have shown no new or unexpected side effects. However, one would expect any side effects to be similar or identical to those present for other treatment options that are delivered using the same method, intravitreal injection. These side effects include raised intraocular pressure, retinal detachment, vitreous haemorrhage, damage to intraocular lens, heart attack, stroke and artery occlusion. Although they are extremely rare they have the potential of affecting a patient's quality of life.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
18a. If not, how could the results be extrapolated to the UK setting?	
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	• Is the drug as effective/more effective than current treatment options in treating wet age-related macular degeneration? – This has been measured in trials. • Are there any new or unwanted side effects? - This has been measured in trials. • Is the drug more cost effective than current treatment options - This has been measured in trials.
18c. If surrogate outcome measures were used, do they adequately predict	

long-term clinical outcomes?	
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not that I am aware of.
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator treatments since the publication of NICE technology appraisal guidance TA155, TA294, TA672 and TA800?	No
21. How do data on real-world experience compare with the trial data?	There is yet to be more extensive real-world data in order to make a more accurate and reliable comparison with the trial data that is currently available.

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
22b. Consider whether these issues are different from issues with current care and why.	

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.	• Based on initial trials, the treatment should last longer than the current treatment options. This will help to reduce the overall number of treatments given and help to reduce the overall burden of treatment. This would be beneficial to both clinicians and patients. • No new safety signals have been identified with this treatment compared to the existing treatment options already available based on current trials • Training of how this treatment is different to other options available is required. Other than this the existing infrastructure and models of care in place are more than sufficient and capable of use this treatment option immediately. • The introduction of this treatment would mean clinicians have access to another treatment option in addition to those currently in place.

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NICE National Institute for Health and Care Excellence

Cost Comparison Appraisal
Bevacizumab gamma for treating wet age-related macular degeneration [ID6320]
Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you

1. Your name	[redacted]
2. Name of organisation	The Royal College of Ophthalmologists
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? Yes (A specialist in the clinical evidence base for this condition or technology? Yes Response compiled with input from two clinical representatives: Professor Andrew Lotery and Mr Martin McKibbin
5a. Brief description of the organisation (including who funds it).	The RCOphth is a membership organisation that promotes and supports the ophthalmic profession in the UK and overseas. As the voice of our members, we influence national eye health policy for the benefit of patients and the profession of ophthalmology.
5b. Has the organisation received any funding from the manufacturers of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal stakeholder list.] If so, please state the name of manufacturer, amount, and purpose of funding.	Outlook Therapeutics Limited (bevacizumab gamma) - No
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To stop progression of wet AMD & maintain and, in some cases, improve vision.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Visual acuity gains and anatomical outcomes similar to other approved anti-VEGF treatments for neovascular AMD e.g. aflibercept and faricimab
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, the main unmet need is durability of treatment as patients are currently required to attend hospital eye clinics for intra-vitreal injections over many years. For some patients, this may be as often as every 4 weeks. A further unmet need is that some patients do not respond to current anti-vegf therapies and lose significant vision eg 15 letters on an EDTRS chart. Data from national audit suggests that around 10% of eyes experience a deterioration of this magnitude despite treatment. Finally, while some improvement in vision is common, the majority of eyes do not currently achieve a significant increase in vision.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Approved NICE therapies eg ranibizumab, aflibercept, faricimab or their biosimilars. Off – label bevacizumab is sometimes used for patients outside the approved visual acuity range ie with vision better than 6/12 or worse than 6/96 for wet AMD. Off – label bevacizumab is also used for other non-NICE approved causes of choroidal neovascularization eg inflammatory or genetic eye diseases.
9a. Are any clinical guidelines used in the	NICE guidelines for treating AMD (NG82)

treatment of the condition, and if so, which?	
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The care pathway in the UK and elsewhere is well-defined. Treatment typically consists of a loading phase of initial monthly treatment, followed by maintenance phase of treatment at extended intervals, according to the response to treatment. There are differences of opinion on what the maximal interval between anti-vegf injections can be eg 12, 16 or even 24 weeks. Also there are different rules for when patient treatment intervals would be extended or reduced or when treatment should stop.
9c. What impact would the technology have on the current pathway of care?	It would allow us to use a bevacizumab product specifically designed and approved for intraocular use.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	I think it would be used in the same way as off – label bevacizumab is currently used in the NHS. I don't think it would be used in the same way as current care because the ability to extend the treatment interval beyond 4 weeks between doses has not been demonstrated in clinical trials and a treat and extend protocol is now the standard of care with alternative anti-vegf agents eg faricimab or aflibercept.
10a. How does healthcare resource use differ between the technology and current care?	A treat and extend protocol is now the standard of care with alternative anti-vegf agents eg faricimab or aflibercept. It may be possible to create a novel care pathway where bevacizumab is used for the initial monthly dosing (typically 3 injections at 4 weekly intervals) and then care is changed to a different anti-vegf agent for all patients eg Faricimab or aflibercept to allow patients to then extend their treatment interval potentially to 12 or 16 weeks or to use bevacizumab in a treat and extend protocol. Further clinical trials would be needed to provide the evidence that either of these approaches are sensible.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care, specialist clinics

10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	None as anti-vegf therapies are well established in the NHS.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	No
11a. Do you expect the technology to increase length of life more than current care?	No
11b. Do you expect the technology to increase health-related quality of life more than current care?	If used as the sole treatment for wet AMD it will likely reduce quality of life as it will require more hospital appointments as the treatment interval is likely to be more frequent cf. other anti-vegf agents.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant	More difficult as it will require more hospital appointments as the treatment interval is likely to be more frequent cf. other anti-vegf agents. Capacity to deliver these anti-vegf therapies is a major challenge for hospital eye departments so if used as the sole anti-vegf it is likely to make it more difficult for patients or healthcare professionals than current care.

treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	It is unclear if the product will be available in a pre-filled syringe or a galls vial. The latter requires an additional step before administration and this adds to the risk of serious infection, though the absolute risk is still small.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Same rules as current NICE AMD guidance.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	It will mean we have an option of a licensed version of bevacizumab. Some clinicians and hospitals have concerns regarding using off label bevacizumab but I do not think it will materially change the health-related benefits of current care and may decrease it due to increasing treatment due to a shorter interval between treatments. It may however make treatment cheaper for drug cost but this may be offset by more frequent injections and hospital visits. Furthermore the advent of biosimilar forms of both ranibizumab and aflibercept will mean that the potential cost savings from the use of bevacizumab will be reduced.
16a. Is the technology a 'step-change' in the management of the condition?	No

16b. Does the use of the technology address any particular unmet need of the patient population?	No
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Similar risks cf. other anti-vegf treatments eg small risk of endophthalmitis.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	No as the clinical trials with bevacizumab don't incorporate a treat and extend protocol.
18a. If not, how could the results be extrapolated to the UK setting?	As suggested above : It may be possible to create a novel care pathway where bevacizumab is used for the initial monthly dosing (typically 3 injections at 4 weekly intervals) and then care is changed to a different anti-vegf agent for all patients eg Faricimab or aflibercept to allow patients to then extend their treatment interval potentially to 12 or 16 weeks. This approach has been used particularly in the Netherlands but there is limited clinical trial data to support this approach. Or to use bevacizumab in a treat and extend protocol. Further clinical trials would be needed to provide the evidence that either of these approaches are sensible.
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Visual acuity outcomes have been measured but the ability to extend the treatment interval beyond 4 weeks has not been demonstrated and also there has been no direct comparison of efficacy and ability to maintain patients on a 12 or 16 week interval compared to current standard of care which is either aflibercept or faricimab.

18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	I think studies were not as long as previous anti-vegf studies ie 2 year follow up.
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	A combination approach of using bevacizumab and then switching to other anti-vegf agents after the fixed dosing initiation phase has been described in meetings.
20. Are you aware of any new evidence for the comparator treatments since the publication of NICE technology appraisal guidance TA155, TA294, TA672 and TA800?	No
21. How do data on real-world experience compare with the trial data?	In the US where off label bevacizumab is commonly used patients are often put on treat and extend protocols. Real-world data from the UK AMD Audit confirms that clinical trial outcomes are not achieved in real-world practice.

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
22b. Consider whether these issues are different from issues with current care and why.	NA

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.	• Useful to have a licenced ocular version of bevacizumab • This anti-vegf agent may be cheaper than alternatives. • Concerns that treatment interval may be shorter than alternative therapies that have been specifically developed to extend the treatment interval to 12, 16 or 20 weeks for treatment of wet AMD. • Visual acuity outcomes are likely to be equivalent to alternative anti-vegf agents. • Starting treatment with bevacizumab and then swapping to another agent may only be identified as necessary when visual acuity has already deteriorated.

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CONFIDENTIAL REPORT

External Assessment Group Report commissioned by the NIHR Evidence Synthesis Programme on behalf of NICE

Bevacizumab gamma for wet age-related macular degeneration

Produced by	Southampton Health Technology Assessments Centre (SHTAC)
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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.

Dr Chhabra declares fees from Bayer and Roche Products Limited for participation in advisory board meetings, plus speaker fees for educational meetings, travel and support for attending national and international conferences/meetings.

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.

Professor Lotery declares fee paid consulting with Outlook Therapeutics (bevacizumab gamma) in February 2024, and consulting for Roche (faricimab). He has received travel support to attend ophthalmology meetings from Bayer (aflibercept) and Roche (faricimab).

Professor Lotery is Chief Investigator of a research grant sponsored by Roche and the Macular Society. This does not involve the health technology or any of the comparators within the scope of this appraisal.

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.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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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.

Commercial in confidence (CON) information in blue

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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

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

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.

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]

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

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).

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

“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.

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.

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

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.

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.

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

	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).)

	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.

	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			

Source: Partly reproduced from CS Table 1-1

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.

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

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

- 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,

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)

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]

	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]

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)).

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

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.

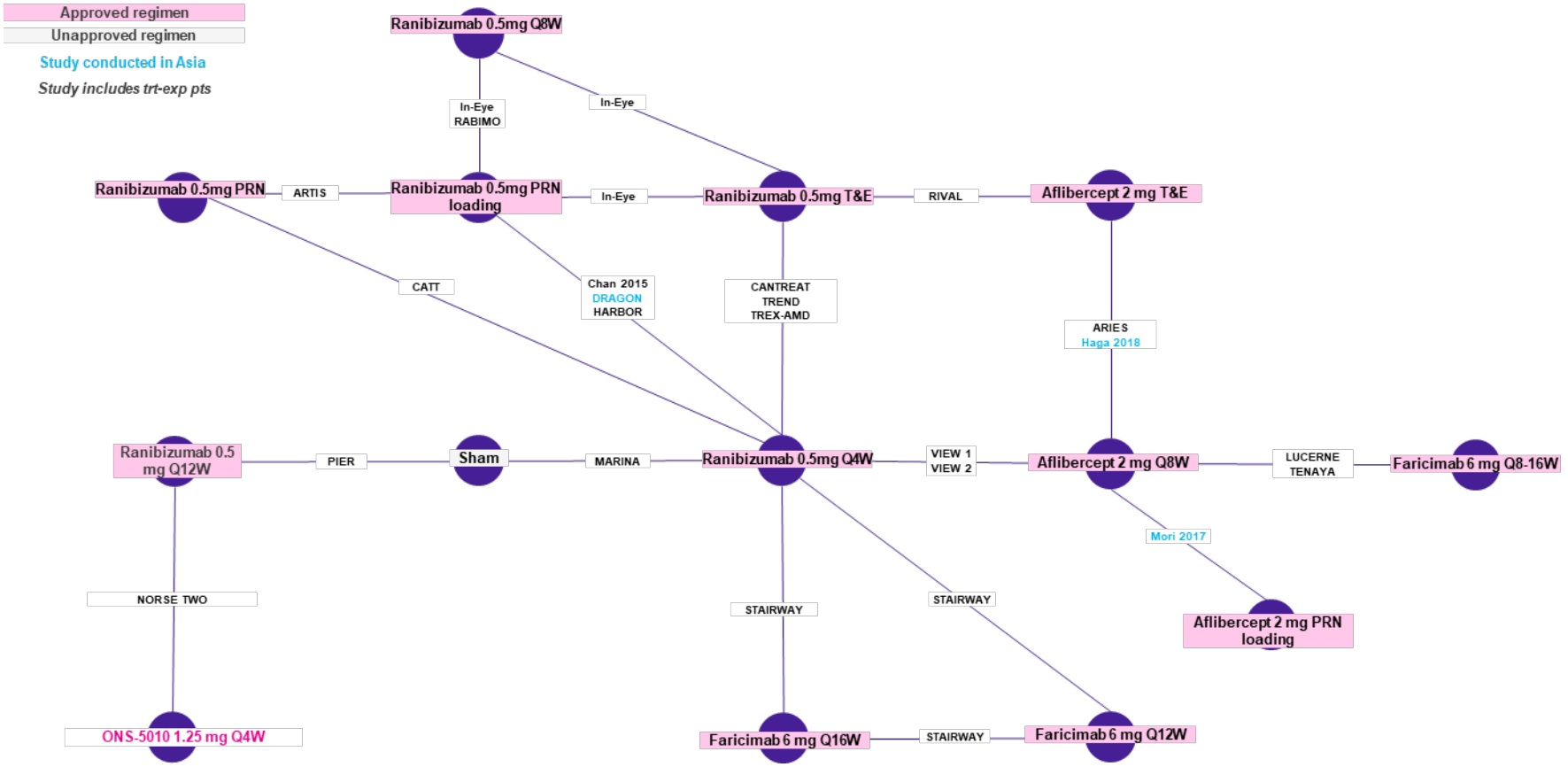

Figure 1 The overall evidence network

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.

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.

- **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.

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.

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

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

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.

- 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.

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

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.

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)

- 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]

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

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:

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

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.

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*

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*

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.

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).

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).

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

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

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

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.

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

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]

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]

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

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

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.

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.

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

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

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

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

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

Cost Comparison Appraisal

Bevacizumab gamma for treating wet age-related macular degeneration [ID6320]

EAG report – factual accuracy check and confidential information check

“Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release.” (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Monday 16 September 2024** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as ’confidential’ should be highlighted in turquoise and all information submitted as ‘depersonalised data’ in pink.

Issue 1 Editing

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Typo in 1.3 (line 1&2) ('However However') Typo in 1.4 (line 11) ('an' instead of 'and') Typo in 2.1 (line 2) ('Outlook Pharmaceuticals' instead of 'Outlook Therapeutics') Typo in 2.2.1 (para 5, line 4) ('least' instead of 'at least') Typo in 2.2.3 (para 5, line 3) ('5.1 5.1') Typo in 4.2 (para 3) ('The states' instead of 'The Company states') Typo in 5.1.5 ('ealthcare' instead of 'Healthcare' Link error in 5.3.5	Correction	N/A	The first typo (section 1.3 line 1 & 2) is correct in the updated version of the report uploaded to NICE on 09/09/24. All remaining typos have been corrected except for the suggested typo in section 2.2.3 (para 5, line 3) ('5.1 5.1'). The section number 5.1.5.1 is not incorrect. Section 5.1.5.1 discusses treatment dosing frequency, which section 2.2.3 paragraph 5 line 3 to 5 refers to. The EAG cannot detect a link error in section 5.3.5. However, we have corrected a link error in section 4.3.1.

Issue 2 Treatment intervals

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The assertion that bevacizumab gamma is expected have the same injection frequency as ranibizumab, is based on untested clinical opinion only, and does not accurately reflect the evidence presented in the CS (notably, evidence from the CATT, IVAN and LUCAS studies), and subsequent agreement of the MHRA and EMA to allow clinicians to extend treatment. This commentary is throughout the EAG report but prominent in sections 1.4, 2.2.1, 2.2.2 and 5.1.5.1 Notably in 2.2.1, the report states clinical opinion that *'ranibizumab dosing is monthly, aflibercept dosing*	A more accurate summary of the evidence would be to describe the real-world injection interval expected with bevacizumab gamma as 'unknown', and to also recognise the potential for some patients to extend their treatment interval up to 12 weeks. A more plausible conservative assumption would be to deliver three initial loading doses, and then to assume an average treatment interval of [redacted] When shorter treatment durations are predicted, the market share estimates in the budget impact calculation should be reduced accordingly.	A treatment frequency of 9.13 in year one equates to three monthly loading doses followed by six subsequent 6-weekly injections. This does not reflect the evidence presented in the CS ('*Supportive evidence (from prior bevacizumab (Avastin®) trials'*) pages 46-50) which describes multiple large studies confirming that bevacizumab (Avastin®) is an efficacious treatment when given in various regimens including with intervals of up to 12 weeks. Furthermore, these trials used repackaged, compounded bevacizumab, which has been shown to deliver reduced potency (CS page 50). It is therefore plausible that ophthalmic	Not a factual inaccuracy. For completeness we have updated the text in section 2.2.2 to acknowledge the company's assertion that the real-world injection interval expected with bevacizumab gamma is currently unknown. With regard to the EAG preferred assumptions on dosing frequency for the cost comparison model (EAR 5.1.5.1), we clearly state that these are based on clinical advice to the EAG, and we note the company's argument regarding 'bridging evidence' from Avastin® trials. We also report cost comparison

is every 2 months and faricimab dosing every 12-14 weeks.' We do not believe that this reflects the clinical opinion of other clinicians engaged by Outlook Therapeutics.		grade bevacizumab gamma is likely to be at least (or likely more) efficacious, allowing more patients the opportunity to extend to a 12-weekly regimen.	results for a scenario using the company's preferred dosing frequency assumptions (EAR Table 17).

Issue 3 Switching

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The behaviour of clinicians switching between anti-VEGF treatments is inconsistently reported. Section 2.2.1 states that clinicians would typically switch to a *'newer anti-VEGF*' [sic: in later line therapy]. Subsequently, section 2.2.3 states that bevacizumab gamma could be used '*as a second-line treatment if there is insufficient response to first line anti-VEGF treatment (e.g.*	Bevacizumab gamma should be considered as a potential option for patients in all lines of treatment, however the cost-benefit versus other branded options, make first-line use a logical and plausible assumption, simplifying the cost-comparison calculation, and aligning to cost-conscious UK clinical practice. Switching was not explored in the cost-comparison model since patients switching to, and from, bevacizumab gamma were thought likely to cancel out any cost impact over the longer term.	The predictions of potential positioning in the EAG report are driven by clinical factors only, while real-world switching decisions are often made to contain costs. Outlook Therapeutics have engaged with a number of UK clinicians and pharmacists who propose that switching may occur between 'newer' and first-generation anti-VEGF options, in any order, based on clinical factors (typically treatment duration under-performance), and that a	Not a factual inaccuracy. The EAG's clinical experts agreed that treatment switching occurs in practice. However, they were not necessarily agreed on the sequence of anti-VEGF treatments. It depends on which treatment was given at first line. One expert spoke in detail about switching, commenting that the newer 'better' treatments would be

following aflibercept or faricimab).' Lastly, section 2.2.3 (para 4) states 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…'*		further common motivator of switching is to control budgets, in particular in patients prescribed more expensive 'newer generation' options but in whom longer treatment intervals cannot be achieved. The sequence of anti-VEGF prescribing is known to be multi-factorial, circular, and highly variable across different ICS regions. The premise of our first line position described in the economic evaluation is to simplify the calculation, and makes the assumption that many clinicians will be motivated to try a less costly option (with the potential for 12 week dose extension) first, followed by subsequent switching to more costly options. Any switching of existing patients is likely to be driven by treatment extension underperformance seen with newer agents, and as such consideration of bevavcizumab	given first (e.g. faricimab/ aflibercept). In their experience most patients respond well to these. In the minority who have an insufficient response, a treatment switch can be justified. The expert explained there would be little point in switching to an older (less durable) treatment, such as ramiflixumab and bevacizumab gamma (NB. The expert regards bevacizumab gamma as an older, first generation, treatment). They do not regard bevacizumab gamma as an appropriate first or second line treatment. The other clinical expert spoke in less detail about switching. They were of the opinion that bevacizumab gamma could, potentially, be an

		gamma in this later line population, is likely to provide both a patient and economic upside.	appropriative second line treatment, but unlikely to be first choice.

Issue 4 Bevacizumab gamma positioning

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Both Table 3 and section 5.1.1 describe the population targeted for bevacizumab gamma as first line therapy. Outlook Therapeutics made the simplifying assumption that incident patients would be more likely to be prescribed bevacizumab gamma, based on clinical similarity to other anti-VEGF options and the likely cost-benefit of using a less costly option which has the potential to extend treatment intervals to up to 12 weeks.	Bevacizumab gamma should be considered for reimbursement in all stages of the wet-AMD treatment pathway, but first line use is expected to be a logical assumption for cost-analysis and decision making (Consistent with our response to Issue 3)	Based on the premise that outcomes are assumed largely similar for all anti-VEGF options, the positioning of bevacizumab gamma at any stage of treatment is likely to be cost-neutral/ saving, while maintaining clinician and patient flexibility. Given the variability in clinical practice across the UK, flexible positioning bevacizumab gamma in the treatment pathway would support broader decision making.	Not a factual inaccuracy. The CS gives little explanation of the company's intended position of bevacizumab in the pathway. It does not appear to state explicitly that bevacizumab could be used at all lines of therapy. There is no provision in the model for previously treated patients who have switched to bevacizumab (e.g. lower effect sizes). This limits the applicability of the cost effectiveness estimates

		(Justifications given in Issue 3 are also relevant here.)	to second / subsequent line patients. For completeness we have added a sentence to our report to state that the company is seeking reimbursement at all stages of the pathway. (section 3).

Issue 5 Dosing guidance

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 2.2.2 (para 1) misrepresents the full dosing guidance offered by the MHRA, by excluding the wording on treatment interval extension.	Please report the full dosing guidance from the SMPC or signpost to the later description of 'treat and extend' reported in section 2.2.3 (para 3).	Read in isolation, section 2.2.2 currently implies a monthly dosing regimen for bevacizumab gamma.	Not a factual inaccuracy. For completeness we have added a cross reference to section 2.2.3

Issue 6 Similarity to Avastin

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
2.2.2 (para 4) states that '*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*.'	The EAG and NICE Committee should recognise that while both Avastin® and bevacizumab gamma are formulations of bevacizumab, there are notable differences driven by the ophthalmic preparation. Furthermore, the similarities between these bevacizumab-based products does not by itself, allow the conclusion that bevacizumab and ranibizumab are similar.	As presented in the manufacturer's scoping response, there are several notable differences between Avastin® and bevacizumab gamma: Aside from the regulatory and commissioning restrictions associated with bevacizumab (Avastin®) use in wAMD, studies have shown repackaged, off-label bevacizumab requires aliquoting, which is associated with safety concerns. Efficacy limitations are also present, associated with inconsistent or degraded potency. Overall, repackaged, off-label bevacizumab does not meet the ophthalmic solution requirements set by regulators, in terms of sterility,	Not a factual inaccuracy. We are expressing our interpretation of information given in the CS and advice from our clinical experts. We recognise that there is a difference in preparation between the ophthalmic-grade formulation of bevacizumab licensed for use in patients with wet AMD and the non-ophthalmic preparation (Avastin), prescribed off-label for wet AMD. This is summarised in our report (section 2.2.2). Rather than repeat the technical detail of the manufacturing process and regulatory standards we refer the reader to the CS itself

		particulate levels, stability, shelf-life pH, or osmolarity, and should not be considered interchangeable with bevacizumab gamma. Lastly, the assertion that bevacizumab (all products) and ranibizumab are clinically similar, is an over-simplification, and the indirect evidence presented in the CS shows all anti-VEGF options (of all 'generations') to be broadly similar in terms of efficacy and safety.	for further information. We maintain our understanding that the active drug (bevacizumab) is the same or very similar between the two products. Furthermore, the CS mentions variations in efficacy and safety between the two preparations, citing evidence from laboratory studies. We don't necessarily disagree that there are variations in efficacy and safety. However, a critical appraisal of the strength of the evidence is needed before conclusions can be made. Finally we note the apparent contradiction between the company's position here and in the CS where it is stated

			that there is a “high similarity” between the two bevacizumab products. This similarity is used as a justification for the scientific bridge: “a scientific bridge was demonstrated, which included physicochemical and biological-functional parameters, showing a high similarity between Avastin® and bevacizumab gamma. Further confirmation comes from the human PK evaluations. This clinical PK comparison of the two products as well as modelling data demonstrated and confirmed the high level of similarity”. (CS page 27)”

Issue 7 Faricimab efficacy

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
2.2.2 describes that '*faricimab has a better anti-inflammatory and retinal drying action compared with aflibercept with the advantage of longer treatment effect durability and less frequent requirement for dosing*.'	Outlook Therapeutics believes that the real-world duration of faricimab is yet to be proven, and is still associated with uncertainty (as reported in TA800). It is also helpful to report that individual patients are likely to respond variably to each anti-VEGF treatment, with many faricimab patients requiring more frequent injections than those reported as possible via the SMPC.	Clinicians interviewed by Outlook Therapeutics, all reported variability in the duration of action of all anti-VEGF treatments, with the SMPC reported maximum possible durations only achievable by some, and not all, recipients. It is also relevant to reiterate that visual acuity is the key clinical measure in wAMD patients, rather than inflammatory response or retinal drying, and as such broad efficacy claims should not be based on these endpoints alone. Again, the indirect comparison presented in the CS demonstrates clinical similarity between all anti VEGF options across a breadth of clinical endpoints.	Not a factual inaccuracy. We have revised the quoted text with further information provided by one of our clinical experts. The sentence now reads: *"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" (EAG report, section 2.2.2).* The meaning of the sentence remains the same. We have made it clearer in the preceding sentence that this is based on expert clinical advice.

			Regarding the real-world effectiveness of faricimab - it is often the case that efficacy and safety in clinical trials is greater than that typically seen in routine practice. The company does not cite any evidence to substantiate their assertion about the durability of faricimab and we therefore refrain from commenting.

(please cut and paste further tables as necessary)