NICE National Institute for Health and Care Excellence

Cost Comparison Appraisal

Faricimab for treating visual impairment caused by macular oedema after retinal vein occlusion [ID6197]

Committee Papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

COST COMPARISON APPRAISAL

Faricimab for treating visual impairment caused by macular oedema after retinal vein occlusion [ID6197]

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 Roche:
   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

4. **External Assessment Report** prepared by Kleijnen Systematic Reviews

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

Cost-comparison appraisal

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

Document B

Company evidence submission

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Glossary

Acronym	Definition
ADA	anti-drug antibody
AESI	adverse events of special interest
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
APTC	Antiplatelet Trialists' Collaboration
AST	aspartate transferase
BCVA	best corrected visual acuity
BRVO	branch retinal vein occlusion
CFT	central foveal thickness
CMH	Cochran Mantel-Haenszel
COVID-19	coronavirus disease-19
CRC	central reading centre
CRT	central retinal thickness
CRVO	central retinal vein occlusion
CSFT	central subfield foveal thickness
CST	central subfield thickness
DMO	diabetic macular oedema
EMA	European Medicines Agency
ERG	Evidence Review Group
ETDRS	Early Treatment Diabetic Retinopathy Study
FA	fluorescein angiography
FFA	fundus fluorescein angiography
HRVO	hemiretinal vein occlusion
IAI	intravitreal aflibercept injection
ILM	internal limiting membrane
IOI	intraocular inflammation
IOP	intraocular pressure
IRF	intraretinal fluid
ITT	intention to treat
IVT	intravitreal injection
LOCF	last observation carried forward
LPLV	last patient last visit
MAA	marketing authorisation application
MAR	missing at random
MHRA	Medicines and Healthcare products Regulatory Agency
MMRM	mixed model for repeated measures
MNAR	missing not at random

MO	macular oedema
nAMD	neovascular age-related macular degeneration
NEI-VFQ-25	National Eye Institute Visual Function Questionnaire – 25
NHS	National Health Service
NICE	National Institute For Health And Care Excellence
NMA	network meta-analysis
PAS	patient access scheme
PRN	pro re nata (treatment as needed)
PTI	personalised treatment interval
QxW	one injection every x weeks
RAO	retinal artery occlusion
RCOphth	Royal College of Ophthalmologists
RCT	randomised clinical trial
RVO	retinal vein occlusion
SAE	serious adverse event
SAS	statistical analysis system
SD-OCT	spectral-domain optical coherence tomography
SOC	System Organ Class
SRF	subretinal fluid
T&E	treat and extend
VA	visual acuity
VEGF	vascular endothelial growth factor

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

B.1.1 Decision problem

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

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

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with macular oedema secondary to retinal vein occlusion	Adult patients with visual impairment due to macular oedema secondary to branched and central retinal vein occlusion	In line with the proposed SmPC, the decision problem addressed in the submission is for adults with macular oedema secondary to branched and central retinal vein occlusion.
Intervention	Faricimab (Vabysmo®)	Faricimab (Vabysmo®)	N/A
Comparator(s)	• Dexamethasone intravitreal implant (for BRVO only after laser photocoagulation has been tried, or is not suitable) • Ranibizumab (for BRVO only after laser photocoagulation has been tried, or is not suitable) • Aflibercept	• Ranibizumab (for BRVO only after laser photocoagulation has been used first line, or is not suitable) • Aflibercept (2mg)	The Company does not consider the following comparators as appropriate for this appraisal: • Dexamethasone intravitreal implant is used for BRVO only after laser photocoagulation has been tried, or is not suitable (1). Treatment with ranibizumab resulted in greater improvements in visual acuity and retinal anatomy caused by MO when compared to treatment with dexamethasone. Dexamethasone is associated with serious side effects

			including increased intraocular pressure and cataract formation (2). The ERG agreed with the manufacturer that ranibizumab is the main comparator and highlighted that dexamethasone may be used in patients who do not respond to anti-VEGF drugs (2). As such, the company believes the line of treatment is different. Clinical experts have confirmed dexamethasone is not routinely used in practice, only after anti-VEGF treatment has proven unsuccessful (3).
Outcomes	The outcome measures to be considered include: • Visual acuity (the affected eye) • Overall visual function • Central subfield foveal thickness (CSFT) • Adverse effects of treatment • Health-related quality of life (HRQoL)	The outcome measures to be considered include: • Visual acuity (the affected eye) • Overall visual function • Central subfield foveal thickness (CSFT) • Adverse effects of treatment • Health-related quality of life (HRQoL)	N/A
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in	A cost comparison case will be presented comparing the cost per patient per year of faricimab versus comparators. Costs will be considered from a National Health Service (NHS) and Personal Social Services perspective.	

	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 cost effectiveness analysis should include consideration of the benefit in the best and worst seeing eye.		
Subgroups to be considered	• People with macular oedema secondary to central retinal vein occlusion (CRVO) • People with macular oedema secondary to branch retinal vein occlusion (BRVO)	• People with macular oedema secondary to central retinal vein occlusion (CRVO) • People with macular oedema secondary to branch retinal vein occlusion (BRVO)	N/A
Special considerations, including equity or equality issues		If a person is registered as blind or partially sighted they are considered disabled, as stated in the Equality Act 2010 (4). Therefore, the patient population addressed in this submission is a protected group under this act.	

B.1.2 Description of the technology being evaluated

Table 2: Technology being evaluated

UK approved name and brand name	Faricimab (Vabysmo®)
Mechanism of action	Faricimab is a humanised bispecific immunoglobulin G1 (IgG1) antibody, that acts through inhibition of two distinct pathways by neutralisation of both angiopoietin-2 (Ang-2) and vascular endothelial growth factor A (VEGF-A). Ang-2 causes vascular instability by promoting endothelial destabilisation, pericyte loss, and pathological angiogenesis, thus potentiating vascular leakage and inflammation. It also sensitises blood vessels to the activity of VEGF-A resulting in further vascular destabilisation. Ang-2 and VEGF-A synergistically increase vascular permeability and stimulate neovascularisation. By dual inhibition of Ang-2 and VEGF-A, faricimab reduces vascular permeability and inflammation, inhibits pathological angiogenesis and restores vascular stability. See Section B.1.3.3 for further details.
Marketing authorisation/CE mark status	A marketing authorisation application (MAA) was submitted to the European Medicines Agency (EMA) in [redacted]; regulatory approval is anticipated in [redacted] in the EU. A submission for marketing authorisation of faricimab was made to the MHRA in [redacted], via the MHRA ACCESS route; approval is anticipated [redacted].
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	New proposed indication: [redacted]
Method of administration and dosage	[redacted]

	[redacted]
Additional tests or investigations	None required
List price and average cost of a course of treatment	£857
Patient access scheme/commercial arrangement (if applicable)	[redacted]

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

B.1.3.1 Disease overview

Incidence and prevalence

Macular oedema (MO) secondary to retinal vein occlusion (RVO) – henceforth referred to as MO-RVO – is a leading cause of visual impairment caused by an obstruction of the retinal venous system by thrombus formation and may involve the central, hemi-central or branch retinal vein (1). A global epidemiological review of RVO identified advanced age, hypertension, heart attack history, and stroke history were some of the strongest risk factors for any type of RVO (5).

Due to the growing prevalence of the aforementioned risk factors, visual impairment due to MO-RVO is a serious public health concern that is becoming increasingly relevant. In 2015, there were an estimated 28.06 million people with any RVO globally, of which 83.3% (23.38 million people) and 16.7% (4.67 million people) had branch retinal vein occlusion (BRVO) and central retinal vein occlusion (CRVO), respectively (5). This figure is expected to rise as the

proportion of people aged >60 increases (6). There is an annual incidence of BRVO of 0.12% and CRVO of 0.03% in people aged 45 years or older. Based on this, in England and Wales, it is estimated that approximately 11,600 people with MO-BRVO and 5,700 people with MO-CRVO suffer from visual impairment each year. A total of 85% of BRVO patients and 75% of CRVO patients developed MO within 2 months of diagnosis; while 50% of BRVO patients and 100% of CRVO patients experienced visual impairment due to MO (7).

Diagnosis

Optical coherence tomography (OCT) is a widely used imaging modality providing useful imaging of the macula. OCT is recommended in the diagnosis, monitoring and assessing treatment response of MO-RVO (1). Features commonly seen are intraretinal fluid and subretinal fluid with an average central subfield thickness (CST) of 665-694μm in CRVO and 555-559μm in BRVO (1). Fluorescein angiography (FA) is also useful in the diagnosis of a macular BRVO with identification of the affected vein with corresponding vascular changes – tortuous, narrowed, focally dilated vessels and capillary non-perfusion. It is particularly useful in determining the extent of macular oedema and ischaemia, as well as peripheral ischaemia. In suspected ischaemic CRVO cases, angiography is recommended to assess the extent of retinal nonperfusion (1).

Pathogenesis

MO-RVO occurs when there is an obstruction to the outflow of blood from the retina. This can occur in a branch resulting in BRVO or centrally, resulting in CRVO. MO or fluid leakage within the centre of the retina is a common complication of this condition and can result in poorer vision (1).

Three forms of RVO exist and are classified by the location of the occlusion and can be categorised as (8, 9):

- Central retinal vein occlusion (CRVO), which occurs due to obstruction of the retinal vein at or posterior to the optic nerve head.
- Branch retinal vein occlusion (BRVO), which occurs due to a complete or partial obstruction at a branch or tributary of the central retinal vein.
- Hemiretinal vein occlusion (HRVO), which occurs due to an occlusion occurring at the disc that commonly involves half of the neurosensory retinal venous drainage, either the superior or inferior hemifield.

This submission focuses on the two former subtypes, as per the scope of the Marketing Authorisation Application (MAA) license.

In general, RVOs involving the macula are acutely symptomatic with the sudden onset of decreasing central vision and/or a corresponding visual field defect (8). According to a meta-analysis of control arms of interventional studies, the vision of patients with untreated RVO is poor upon presentation and slowly starts to decline over 1 year (10).

Untreated CRVO is associated with poor visual acuity (VA) at presentation which usually worsens over time (8, 11). There are two types of CRVO: non-ischaemic and ischaemic. Untreated eyes with non-ischaemic CRVO may have symptoms that completely resolve without the presence of complications (1). However, 25–30% of eyes with non-ischaemic CRVO may convert to ischaemic CRVO over three years. In ischaemic CRVO, the vision loss may be sudden and severe (1, 11). Patients with CRVO generally develop MO (8). Secondary MO is the most common cause of vision loss in eyes with CRVO, with 75% of patients developing this condition within 2 months of diagnosis and all of these patients subsequently developing vision loss (7, 12).

Patients with BRVO generally present with acute visual symptoms in one eye due to MO (8). Approximately 85% of patients with BRVO develop MO (1). MO secondary to BRVO can dissipate over time, with secondary retinal pigment epithelial atrophy and suboptimal visual acuity remaining (8). However, in general, the MO and the visual defects remain unless treatment is initiated (8). The prognosis for vision loss is dependent on the degree of non-perfusion and the occlusion location which are both important prognostic factors for determining the final BRVO-related visual deficit (8).

Functional and structural alterations in the retina, including reduced retinal capillary blood flow, can result in hypoxia leading to the upregulation of pro-inflammatory cytokines such as vascular endothelial growth factor (VEGF) (13, 14). The expression of VEGF leads to disruption of the blood retinal barrier, stimulated vascular endothelial growth, and an increase in vascular permeability of those nascent immature blood vessels permeability (9, 14, 15).

Ang-2 is another cytokine that is elevated in the vitreous of patients with MO-RVO, suggesting that Ang-2 could be an additional driver for the progression of the disease (16, 17). Ang-2 causes vascular instability by promoting endothelial destabilisation, pericyte loss, and pathological angiogenesis, thus potentiating vascular leakage, inflammation and fibrosis. It

also sensitises blood vessels to the activity of VEGF-A resulting in further vascular destabilisation (16, 18-20). Ang-2 and VEGF-A synergistically increase vascular permeability and stimulate neovascularisation (19, 20).

Burden of disease on patients

There is a substantial symptom burden associated with RVO. Patients with MO-RVO experience acute visual symptoms, most commonly in a painless eye (8, 9, 21). Vision loss, and/or variable degrees of vision alteration, including a decrease in central vision and/or a corresponding visual field defect, are typically associated with the acute visual symptoms experienced by patients with RVO.

Vision loss can have a negative impact on the mental and physical functioning of patients, limiting their ability to perform everyday activities, which can challenge independent living (22, 23). Patients with vision loss often experience depression and social isolation because of continuous mental stress due to worries, anxiety, or fear (22). MO-RVO is a chronic disease and requires long-term treatment; cumulatively, patients may expect to receive a mean of 7–15 anti-VEGF injections across 3 years of treatment (12, 24). RVO is associated with higher healthcare costs than hypertension or glaucoma (25).

As aforementioned, MO is the primary complication associated with RVO and is characterised by acute visual symptoms including vision loss, or variable degrees of vision alteration caused by excessive retinal fluid leakage including retinal haemorrhage, and substantial retinal thickening (8, 9, 21). The decline in vision experienced by patients with MO secondary to RVO directly affects patient independence and self-care, negatively impacting patient physical functioning and ability to perform everyday activities (23). Approximately 75% and 85% of patients with CRVO and BRVO, respectively, develop MO (1).

A study conducted in-depth interviews with 17 Australian patients with RVO reported on a number of quality of life (QOL) themes about common concerns of living with the disease. Patient concerns reported under the theme of ‘activity limitation’ included having to give up their driver’s license; difficulty reading small print, identifying street signs and recognising people’s faces; and difficulty engaging in leisure activities (26). A study with a European sample of 131 retinal patients reported that each injection appointment took approximately 4.5 hours, comprising an average of 79 minutes of travel time and 188 minutes of appointment time. For the patients still in employment, ~50% needed to take 1 day off per appointment. More than 55% reported ‘moderate to large’ impact on their QoL. This is a greater impact

compared to other chronic conditions such as diabetes, asthma, glaucoma, hypertension, thyroid conditions (23).

Burden of disease on carers and the healthcare system

In addition to the impact of the disease on the patient, current intravitreal (IVT) anti-VEGF therapies used to treat patients with MO-RVO are associated with a substantial treatment burden on patients, caregivers, physicians, and the healthcare system due to the onerous schedule of frequent injections and patient monitoring visits (as often as once per month) required to achieve and maintain optimal long-term vision outcomes (23, 26). Patients who face multiple IVT injections also experience high levels of anxiety (23). The substantial burden associated with treatment creates a barrier to optimal anti-VEGF therapy, leading to unsustained vision outcomes that decline over time (27). As the demand for recommended follow-up appointments and the volume of treatment increase, many clinics in the UK are running at capacity and failing to meet the needs of their retinal disease patients (23, 28-30).

Out of the 131 retinal patients surveyed, 71% of patients required a carer's aid at the time of the injection appointment, totalling 6.3 hours of a carer's time per injection (23). Additionally, 50% of carers were employed, and of these, 59% required time away from their employment to support the patient highlighting the substantial burden associated with providing support for a patient undergoing treatment for RVO (23). An economic model to calculate societal costs of CRVO in the UK reported an annual cost of approximately £700 million, of which the average annual contribution per patient was £14,692 (31). The contributing factors were monitoring the disease (42%), cost of blindness (20%), drug treatment (16%), and adverse events (15%) (31). Additionally, a study of all-cause visual impairment and blindness in high-income countries found that long-term care, home-based nursing, assistive devices, and home modifications contribute to levels of non-medical services more than 10-fold higher than for those with normal vision (32).

B.1.3.2 Clinical management

Aflibercept and ranibizumab are considered the standard of care for treatment of RVO (1, 21). According to UK clinical experts, grid laser photocoagulation is no longer the standard of care for MO-RVO (3). Regarding dexamethasone implants, clinical experts confirmed anti-VEGFs have been shown to have greater efficacy with a better safety profile compared to the dexamethasone implant, which may cause side effects such as increased intraocular pressure and cataract. Based on this and clinical experience, dexamethasone may only be used in patients who do not respond to anti-VEGF drugs (33-37), and is used infrequently in clinical practice. As such, dexamethasone is considered by clinicians to be a second line treatment.

Based on these factors, the comparators to faricimab in this appraisal are the licensed anti-VEGF therapies aflibercept and ranibizumab. Both therapies have been evaluated by NICE and recommended for patients with RVO in NICE TA409 (aflibercept BRVO; published 2016) (38), TA305 (aflibercept CRVO; published 2014) (2), and TA283 (ranibizumab; published in 2013) (7), respectively.

[redacted]

[redacted] Reported safety data suggests that anti-VEGF therapy is generally well-tolerated, with aflibercept and ranibizumab having comparable safety profiles (40). Table 3 outlines the recommended dosing regimens for aflibercept and ranibizumab for the treatment and management of RVO patients.

Table 3: Aflibercept and ranibizumab dosing regimens and mechanism of action

Anti-VEGF agent	EMA label recommended dosing	Mechanism of action
Aflibercept (Eylea®)	The recommended dose for aflibercept is 2 mg aflibercept. This corresponds to an injection volume of 0.05 mL. After the initial injection, treatment is given monthly. The interval between two doses should not be shorter than one month. Treatment is initiated with one injection per month for three consecutive doses. The treatment interval is then extended to two months. If visual and anatomic outcomes indicate that the patient is not benefiting from continued treatment, aflibercept should be discontinued. Monthly treatment continues until maximum visual acuity is achieved and/or there are no signs of disease activity. Treatment may then be continued with a treat-and-extend regimen with gradually increased treatment intervals to maintain stable visual and/or anatomic outcomes, however there are insufficient data to conclude on the length of these intervals. If visual and/or anatomic outcomes deteriorate, the treatment interval should be shortened accordingly. The monitoring and treatment schedule should be determined by the treating physician based on the individual patient's response. Monitoring for disease activity may include clinical examination, functional testing, or imaging techniques (e.g. optical coherence tomography or fluorescein angiography).	Aflibercept is a soluble decoy receptor protein that binds to all VEGF-A isoforms, VEGF-B, and placental growth factor (PlGF).

Ranibizumab (Lucentis®)	The recommended dose for ranibizumab in adults is 0.5 mg given as a single IVT injection. This corresponds to an injection volume of 0.05 mL. The interval between two doses injected into the same eye should be at least four weeks. Treatment in adults 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 and in other signs and symptoms of the disease under continued treatment. Initially, three or more consecutive, monthly injections may be needed. Thereafter, monitoring and treatment intervals should be determined by the physician and should be based on disease activity, as assessed by visual acuity and/or anatomical parameters.	Ranibizumab is a recombinant, humanised antigen binding fragment of a monoclonal antibody, with a high affinity for VEGF-A.

The intensive IVT injection regimen for managing diseases such as RVO has a negative effect on a patient's QoL (23). Ocular injections are often a source of fear, stress, and anxiety for patients with retinal diseases (23, 41). A survey of patients with RVO (and diabetic macular oedema [DMO]) reported 50%, 18%, and 4% of patients felt uptight, had their sleep affected, and had reduced concentration, respectively, prior to their most recent injection (23). In addition, a study by Bhisitkul *et al.* concluded that the high treatment burden associated with injection and monitoring frequency which could not be replicated in the real-world setting, resulted in patients with lower vision outcomes that decline with time (27).

This highlights that for many patients, innovations that reduce the frequency of treatment while maintaining or improving vision may alleviate the anxiety, stress and fear burden experienced by patients with MO-RVO as well as maintaining vision outcomes. This represents a substantial unmet need for innovative therapeutic options capable of providing optimal disease control, leading to sustained efficacy with fewer injections and monitoring visits. It is for this reason, faricimab, with its dual action via Ang-2 and VEGF-A may facilitate a reduced treatment burden through extended treatment intervals and sustained clinical outcomes that are maintained for longer periods. Which in turn would alleviate the strain on ophthalmology clinics and the broader healthcare system within the NHS.

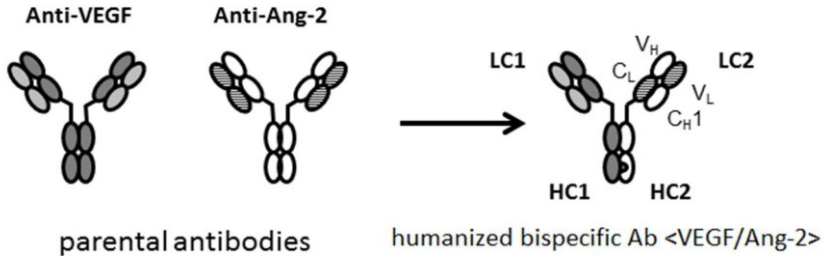
B.1.3.3 Faricimab for the treatment of visual impairment caused by RVO

In retinal diseases, Ang-2 and VEGF-A upregulation leads to vascular instability, by synergistically promoting angiogenesis and inflammation (16, 42). The Ang/Tie2 pathway plays an important role in the regulation of vascular stability, with Ang-1 (when bound to Tie2) stabilising the mature vasculature, promoting endothelial cell survival and barrier function

inflammation (18, 42, 43), and Ang-2 acting as a vascular destabilisation factor by blocking Ang-1-dependent Tie2 activation (43-45). Ang-2 levels can be upregulated by other pro-angiogenic factors, including VEGF-A promoting vascular leakage and neovascularisation, and have been shown to be increased during angiogenic stress triggered by hypoxia or hyperglycaemia.

Faricimab is a bispecific antibody that is composed of an anti-Ang-2 arm and an anti-VEGF-A arm, and therefore has a unique dual mechanism of action (Figure 1). Elevated vitreous levels of both Ang-2 and VEGF-A are also implicated in RVO pathology, suggesting that faricimab can be an effective treatment for RVO (16).

Figure 1: Design of the CrossMAb in faricimab



Ab, antibody; Ang-2, angiopoietin-2; HC, heavy chain; LC, light chain; VEGF, vascular endothelial growth factor. Source: Investigator's Brochure RO686746 (46).

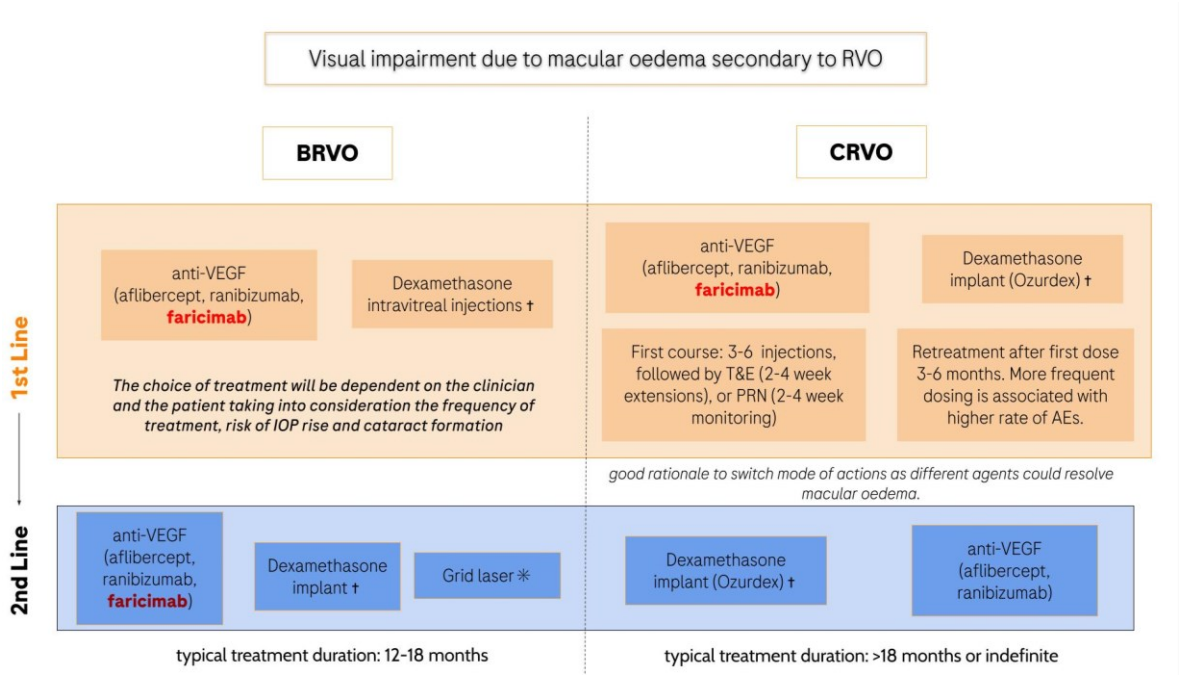
By dual inhibition of Ang-2 and VEGF-A, faricimab reduces vascular permeability and inflammation, inhibits pathological angiogenesis, and restores vascular stability. Results from the TENAYA and LUCERNE phase 3 trials evaluating dual Ang-2 and VEGF-A inhibition with faricimab for the treatment of nAMD, administered at up to Q16W, demonstrated vision benefits and anatomic outcomes comparable with VEGF pathway inhibition alone with Q8W aflibercept. The observed extended durability of effect with faricimab, was potentially driven by the vascular-stabilising effects of dual Ang-2 and VEGF pathway inhibition. The anticipation is the vascular stability afforded by the unique dual mechanism of action of faricimab would provide comprehensive disease control, allowing physicians to extend treatment intervals up to Q16W, while maintaining vision gains and safety comparable to shorter interval dosing seen in anti-VEGF treatments. This inference was validated by clinical experts based on their experience of faricimab in nAMD and DMO (3). See Section B.3.6.3 for proportions of patients on Q16W treatment intervals.

Roche conducted a study to assess real-world treatment patterns, VA outcomes, and the incidence of pre-defined ocular safety outcomes in patients with macular oedema secondary to BRVO, CRVO, or HRVO (47). The results showed that the percentage of BRVO patients achieving an average treatment interval of ≥Q12W and Q16W, 18 months after treatment

initiation with aflibercept were 6.47% and 1.89%, respectively. With ranibizumab at 18 months, ≥Q12W and Q16W, were 9.48% and 3.05%, respectively (47). In CRVO patients, those achieving ≥Q12W and Q16W with aflibercept were 7.24% and 1.36%, respectively; whilst for ranibizumab, 6.83% and 1.40% were seen to have achieved ≥Q12W and Q16W, respectively (47). Compared to approximately 52% (BRVO) and 37% (CRVO) of patients achieving Q16W with faricimab at 68 weeks in BALATON and COMINO, respectively.

Based on the anticipated marketing authorisation indication, which covers the equivalent populations as the comparators aflibercept and ranibizumab, faricimab is positioned as an alternative option to these medicines for the treatment of adults with visual impairment due to MO-RVO, as presented in Figure 2 below.

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



† *Dexamethasone intravitreal implant is a NICE approved treatment but not considered a relevant comparator, as it is used for BRVO only after grid laser photocoagulation has been tried, or is deemed not suitable (1).*
✳ *Grid laser photocoagulation is not considered a relevant comparator as it is no longer the standard of care for RVO (1).*

The treatment durability provided by faricimab suggests its introduction as a treatment option will reduce the number of injections and monitoring visits required to treat RVO. This would result in more efficient use of healthcare resources and long-term cost savings, through the alleviation of capacity constraints within ophthalmology clinics. This is of long-term importance given the increasing prevalence of RVO risk factors, there is likely to be an increase in demand for eye care management relative to MO-RVO.

B.1.4 Equality considerations

If a person is registered as blind or partially sighted they are considered disabled, as stated in the Equality Act 2010 (4). Therefore, the patient population addressed in this submission is a protected group under this act**.**

B.2 Key drivers of the cost effectiveness of the comparators

B.2.1 Clinical outcomes and measures

The comparators for faricimab in this appraisal are the licensed anti-VEGF therapies aflibercept and ranibizumab. Both therapies have been evaluated by NICE and recommended for patients with RVO in NICE TA305 (aflibercept for treating visual impairment caused by MO secondary to central vein occlusion) (2) and TA409 (aflibercept for treating visual impairment caused by MO after branch retinal vein occlusion) (38) and NICE TA283 (ranibizumab for treating visual impairment caused by MO secondary to retinal vein occlusion) (7). See Table 4 for outcome measures detailed in the published NICE guidance for aflibercept and ranibizumab.

Aflibercept (TA305)

The pivotal studies for aflibercept considered in TA305 (2) were COPERNICUS and GALILEO.

- COPERNICUS (n=187) was a randomised, double blind, multicentre trial conducted in 6 non-European countries. Patients received aflibercept 2 mg every 4 weeks (n=114) or sham injections (n=73) every 4 weeks up to Week 24. During Weeks 24 to 52, patients in both arms were evaluated monthly and received aflibercept if they met protocol-specified retreatment criteria; if retreatment was not indicated they received sham injection. After the first year, patients continued in a 1-year extension phase (up to 100 weeks) with aflibercept as needed (no sham injection).

- GALILEO (n=171) was a randomised, double-blind, multicentre trial conducted in 10 European and Asian-Pacific countries. None of the study centres was located in the UK. From Week 0 to Week 24, patients in the intervention group (n=103) received aflibercept every 4 weeks and patients in the comparator group (n=68) received a sham injection every 4 weeks. From Week 24 to Week 52, patients in the intervention group received aflibercept if they met protocol-specified retreatment criteria, or sham

injection. Patients in the comparator group continued to receive sham injection from Week 24 to Week 52. From Week 52 to Week 76, both groups received aflibercept every 8 weeks. All patients were eligible to receive pan retinal photocoagulation at any time if they developed neovascularisation.

The primary endpoint for both studies was the proportion of patients who gained at least 15 letters in BCVA at Week 24; as measured by ETDRS letter score.

Ranibizumab (TA283)

Ranibizumab technology appraisal (TA283) (7), presented data from the BRAVO and CRUISE pivotal trials. Both studies were 3-armed randomised controlled trials conducted at multiple centres in the USA. Patients were randomised equally to sham injection, monthly intraocular ranibizumab 0.3 mg or monthly intraocular ranibizumab 0.5 mg, investigating the efficacy and safety of ranibizumab 0.3mg and 0.5mg. BRAVO (n=397) and CRUISE (n=392) were both 3-armed randomised controlled trials conducted at multiple centres in the USA. Patients were randomised 1:1:1 to receive monthly intraocular injections of 0.3 mg or 0.5 mg of ranibizumab or sham injections. Both trial populations were patients with visual impairment caused by macular oedema who had been diagnosed in the 12 months prior to study initiation. There was a 6-month treatment phase, during which monthly injections were given. In the treatment phase of BRAVO, patients in both the sham injection and ranibizumab groups could receive grid laser photocoagulation for rescue treatment from 3 months. In both BRAVO and CRUISE, the treatment phase was followed by a 6-month observation phase during which all groups (that is, the sham group and the 2 ranibizumab groups) could receive ranibizumab as needed. Patients in the observation phase of BRAVO (but not CRUISE) could receive grid laser photocoagulation for rescue treatment from 3 months (that is, at Month 9 of the study). The final treatment in both BRAVO and CRUISE was given at Month 11, with a final study visit at Month 12.

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

TA	Outcome	Source
Aflibercept for RVO [TA305] (2)	BCVA: Proportion of patients with ≥ 15 ETDRS letter gain from baseline to Week 24	GALILEO (48), CORPENICUS (49)
	Mean change in BCVA from baseline at Week 24	GALILEO (48), CORPENICUS (49)
	Change in CRT from baseline to Week 24	GALILEO (48), CORPENICUS (49)
	Proportion of patients progressing to neovascularisation of the anterior segment, optic disc, or elsewhere in the retina from baseline to Week 24	CORPENICUS (49)
	Ocular AEs; non-ocular AEs	GALILEO (48), CORPENICUS (49)
	Change in total NEI VFQ-25 from baseline to Week 24	GALILEO (48), CORPENICUS (49)
	Change in EQ-5D from screening	GALILEO (48)
Aflibercept for RVO [TA409] (38)	BCVA: Proportion of patients with ≥ 15 ETDRS letter gain from baseline to Week 24	VIBRANT (50)
	Mean change in BCVA from baseline at Week 24	
	Change in CRT from baseline to Week 24	
	Change in total NEI VFQ-25 from baseline to Week 24	
	Change in EQ-5D from screening	
Ranibizumab for RVO [TA283] (7)	Mean change from baseline in BCVA score at 6 months	BRAVO (51), CRUISE (52)
	Percentage of participants who gained ≥ 15 letters in BCVA score at Month 6 compared with baseline	
	Percentage of participants who lost < 15 letters in BCVA score at Month 6 compared with baseline	
	Percentage of participants with a CFT of ≤ 250 µm at Month 6	
	Mean absolute change from baseline in CFT at Month 6	
	Change in total NEI VFQ-25 from baseline over time	
	Change from baseline in the National Eye Institute Visual Functioning	

AE, adverse event; BCVA, best corrected visual acuity, CFT, central foveal thickness; CRT, central retinal thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; EQ-5D, 5-dimension European Quality of Life questionnaire; NEI, National Eye Institute; VFQ25, Visual Functioning Questionnaire.

Summary of the key drivers of the cost-effectiveness of the comparators

The key drivers of the aflibercept cost-effectiveness analysis, as described in TA305, included:

- Number of aflibercept and ranibizumab injections, as this has a direct impact of drug cost component;
- Risk ratio of gaining vision as the main determinant of treatment effect;
- Frequency of monitoring;
- Utility values.

Within the ranibizumab cost-effectiveness analysis, as described in TA283, the key drivers included: treatment of the best seeing eye (the proportion of patients treated in their 'better-seeing eye'), time horizon and the utility values.

The key drivers of the cost-effectiveness from TA305 and TA283, relevant to the cost comparison analysis, have been explored in scenario analyses and are presented in Section B.4.4.

B.2.2 Resource use assumptions

The resource assumptions, which were relevant to previous appraisals, were:

- Intervention and comparator costs;
- Health state costs;
- AE costs;
- Administration and OCT costs.

Given the analyses used is a cost comparison, the only relevant assumption to this submission is the intervention and comparator costs.

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

A summary of the clinical effectiveness evidence pertinent to the current appraisal is provided below.

Table 5: Clinical effectiveness evidence

Study	BALATON/GR41984, NCT04740905 (53)			COMINO/GR41986, NCT04740931(54)						
Study publications	Clinical study report (55, 56)			Clinical study report (57, 58)						
Study design	Phase III, multicentre, randomised, double-masked, active comparator-controlled, parallel-group, 2-part studies evaluating the efficacy, safety and pharmacokinetics of faricimab administered by intravitreal injection at 4-week intervals (i.e., fixed monthly dosing) until Week 24 (Part 1), followed by a period of study without active control (Part 2) to evaluate faricimab administered according to a personalised treatment interval (PTI) dosing regimen in patients with macular oedema secondary to BRVO (BALATON), and CRVO or HRVO (COMINO). BALATON and COMINO have identical study designs.									
Population	Adult patients who were naive to anti-VEGF treatment, with visual impairment due to MO secondary to BRVO (BALATON), and CRVO or HRVO (COMINO).									
Intervention(s)	Faricimab solution for intravitreal injection at a dose of 6 mg									
Comparator(s)	Aflibercept solution for intravitreal injection at a dose of 2 mg									
Indicate if trial supports application for marketing authorisation	**Yes**	✓	Indicate if trial used in the economic model	**Yes**	✓	**Yes**	✓	Indicate if trial used in the economic model	**Yes**	✓
	No			**No**		**No**			**No**	
Rationale for use/non-use in the model	BALATON and COMINO are Phase III trials providing efficacy, safety and durability evidence for faricimab in patients with RVO. Data from BALATON and COMINO were used to inform the efficacy and safety of faricimab in the economic model.									
Reported outcomes specified in the decision problem	• Visual acuity (the affected eye) • Overall visual function • Central subfield foveal thickness (CSFT) • Adverse effects of treatment • Health-related quality of life (HRQoL)									

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

Unless otherwise stated, information on the BALATON and COMINO studies were sourced from the clinical study reports (47-50).

B.3.3.1 Study design

BALATON (Study GR41984) and COMINO (Study GR41986) were identically designed Phase III, multicentre, randomised, double-masked, active comparator controlled, parallel-group, 2-part studies evaluating the efficacy, safety and pharmacokinetics of faricimab administered by

IVT injection at 4-week intervals (i.e., fixed monthly dosing). Both trials consisted of two parts: Week 0 to Week 24 (Part 1), followed by a period of study without active control (Part 2) to evaluate faricimab administered according to a personalised treatment interval (PTI) dosing regimen in patients with MO due to BRVO (BALATON), and CRVO or HRVO (COMINO). Investigators and patients are masked to treatment assignment in Part 1 and to both original treatment assignment and faricimab treatment interval in Part 2.

In Part 1 (Q4W dosing), a total of 570 and 750 patients were planned to be enrolled and randomised during the global enrolment phase of BALATON and COMINO respectively. These numbers will allow >90% power in each treatment arm to demonstrate non-inferiority of faricimab compared to aflibercept with regards change in BCVA from baseline to week 24 in the ITT population. The patients were randomised in a 1:1 ratio to one of two treatment arms, with treatment arms defined as follows:

- Arm A (n=285 [BALATON] and n=375 [COMINO]): Patients randomly assigned to Arm A received 6 mg faricimab IVT injections Q4W from Week 0 through Week 20 (6 injections).
- Arm B (comparator arm, n=285 [BALATON and n= 375 [COMINO]): Patients randomly assigned to Arm B received 2 mg aflibercept IVT injections Q4W from Week 0 through Week 20 (6 injections).

Only one eye was assigned as the study eye. If both eyes were considered eligible, the eye with the worse BCVA, as assessed at screening, was selected as the study eye, unless the investigator deemed the other eye to be more appropriate for treatment in the study.

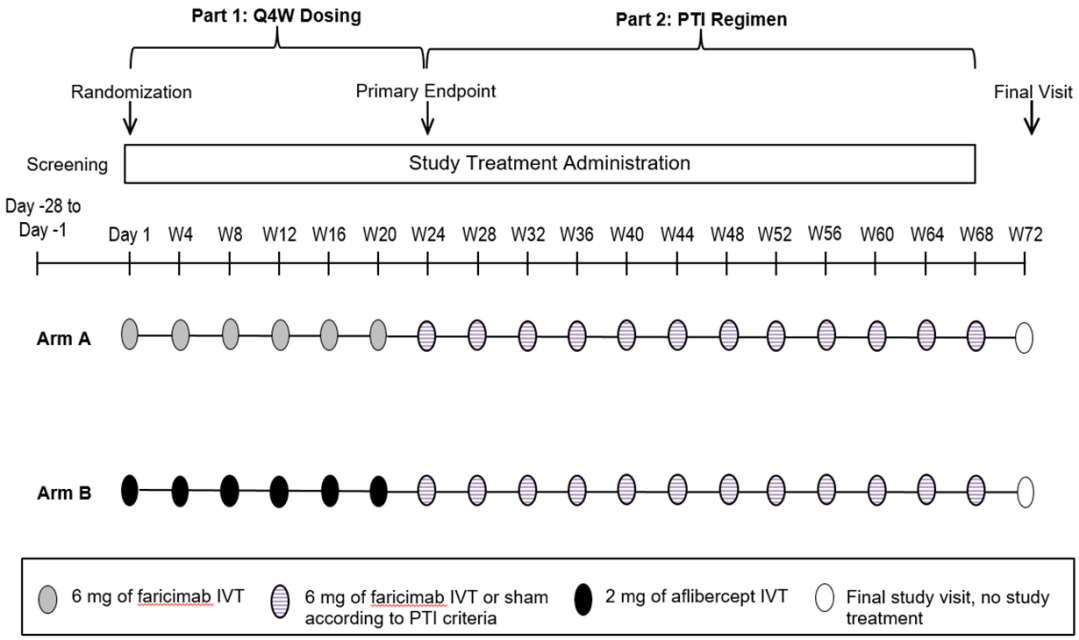
Randomisation was stratified by the following baseline factors as assessed on Day 1:

- Baseline BCVA Early Treatment Diabetic Retinopathy Study (ETDRS) letter score
  - For COMINO: ≤ 34 letters, 35–54 letters, and ≥55 letters
  - For BALATON: ≥ 55 letters vs. ≤ 54 letters
- Region (United States, Asia, and the rest of the world)

In Part 2 (PTI regimen), patients in Arm A (6 mg faricimab), continued to receive faricimab and patients in Arm B (2 mg aflibercept), stopped aflibercept treatment and switched to 6 mg faricimab according to a PTI dosing regimen from Week 24 through Week 68. All patients completed the scheduled study visits every Q4W for the entire study duration (72 weeks) (Figure 3).

The primary analysis was performed when all patients from the global enrolment phase had either completed the study through Week 24 or had discontinued from the study prior to Week 24. To preserve the masking of faricimab treatment intervals from Week 24 through Week 68, a sham procedure was administered during study visits at which (according to the PTI dosing regimen) no faricimab treatment was administered maintaining the Q4W dosing interval.

Figure 3: Study schema for BALATON and COMINO



IVT=intravitreal; PTI= personalised treatment; Q4W= every 4 weeks; W= week.

PTI treatment schedule for patients in Arms A and B

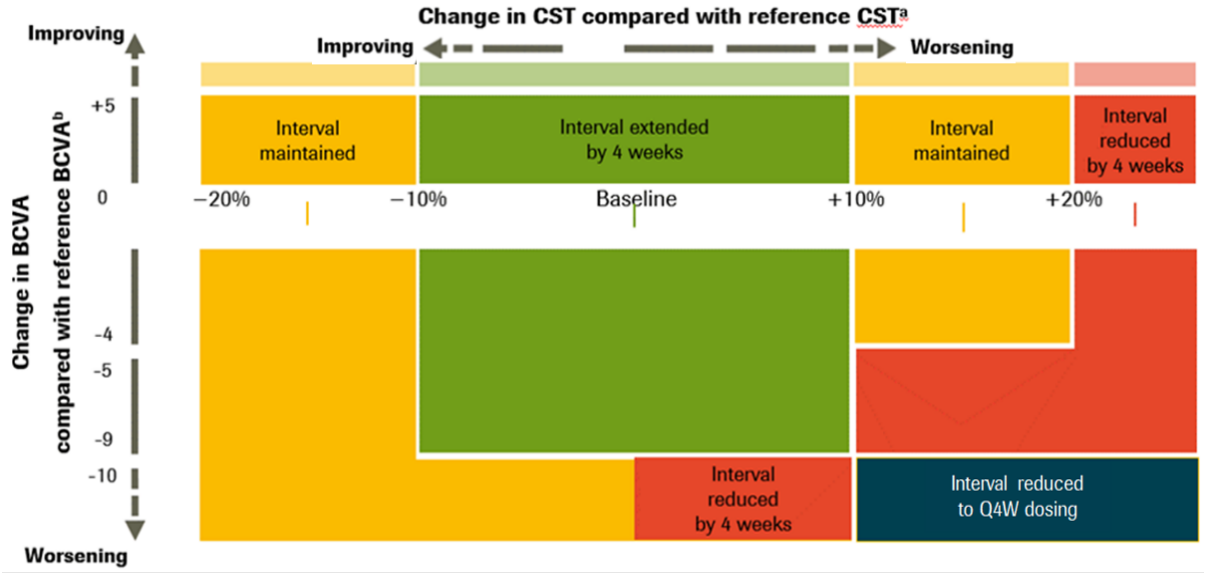
In Part 2 of the study, patients in both the faricimab Q4W and aflibercept Q4W arms in Part 1 received 6 mg faricimab IVT injections administered according to a PTI dosing regimen in intervals between Q4W and Q16W. At faricimab dosing visits, treatment intervals were maintained or decreased or extended, calculated automatically using an interactive web-based response system (IxRS) based on CST and BCVA values (see Figure 4 for details on the PTI dosing algorithm). Patients therefore received between 3 and 12 injections during the period from Week 24 through Week 68.

Of note, patients whose dosing interval had been previously extended and who experience disease worsening that triggered an interval reduction were not allowed to extend the interval again, with the exception of patients whose dosing intervals were reduced to Q4W; their interval could be extended again but only to an interval that was 4 weeks less than their original maximum extension. For example, a patient on a Q12W interval who required a reduction in

treatment interval to Q4W in 4 week increments could not be extended beyond a Q8W interval for the remainder of the study.

Both the faricimab Q4W and aflibercept Q4W arms maintained Q4W study visits for the 72-week study duration. To preserve the masking of faricimab treatment intervals for Week 24 through Week 68, a sham procedure was administered during study visits at which (according to the PTI dosing regimen) no faricimab treatment was administered (hereafter referred to as the faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arms).

Figure 4: Algorithm for IxRS-determined faricimab PTI dosing intervals in Part 2



BCVA=best-corrected visual acuity; CST=central subfield thickness; IxRS=interactive web-based response system; Q4W=every 4 weeks.

[a] *Initial reference CST=CST value when the initial CST threshold criteria are met, but no earlier than Week 20. Reference CST is adjusted if CST decreases by >10% from the previous reference CST for two consecutive faricimab dosing visits and the values obtained are within 30 μm. The CST value obtained at the latter visit will serve as the new reference CST, starting immediately at that visit.*

[b] *Reference BCVA=mean of the three best BCVA scores obtained at any prior dosing visit.*

Table 6: Summary of study methodology

	BALATON, NCT04740905 (53)	COMINO, NCT04740931 (54)
Settings and locations of data collection	BALATON was conducted in 22 countries: Argentina, Australia, Austria, Brazil, China, Czech Republic, France, Germany, Hong Kong, Hungary, Israel, Italy, Japan, Korea, Poland, Portugal, Russian Federation, Singapore, Spain, Taiwan, United Kingdom, and United States.	COMINO was conducted in 22 countries: Argentina, Australia, Austria, Brazil, China, Czech Republic, France, Germany, Hong Kong, Hungary, Israel, Italy, Japan, Korea, Poland, Portugal, Russian Federation, Singapore, Spain, Taiwan, United Kingdom, and United States.

	There were six sites in the UK.	There were ten sites in the UK.
Trial design	Phase III, double masked, multicentre, randomised, parallel-group study in patients with RVO	
Eligibility criteria	**Key inclusion criteria** • Age ≥18 years at time of signing Informed Consent Form • Foveal centre involved MO secondary to BRVO (BALATON, GR41984) or CRVO/HRVO (COMINO, GR41986) • BCVA of 73 to 19 letters, inclusive (20/40 to 20/400 approximate Snellen equivalent), as assessed on the ETDRS VA chart at a starting test distance of 4 meters on Day 1 • CST ≥ 325 µm, as measured on Spectralis spectral-domain optical coherence tomography (SD-OCT), or ≥ 315 µm, as measured on Cirrus SD-OCT or Topcon SD-OCT at screening (swept-source optical coherence tomography [SS-OCT] acceptable after confirmation with Central Reading Centre [CRC]) **Key exclusion criteria** • Uncontrolled blood pressure, defined as systolic blood pressure >180 mmHg and/or diastolic blood pressure >110 mmHg while a patient is at rest on Day 1 • Stroke (cerebral vascular accident) or myocardial infarction within 6 months prior to Day 1 • Pregnant or breastfeeding, or intention to become pregnant during the study • History of previous episodes of MO-RVO or persistent MO-RVO diagnosed more than 4 months before screening • History of retinal detachment or macular hole (Stage 3 or 4) • Any prior or current treatment for MO-RVO, including anti−VEGF IVT injections for MO-RVO • Macular laser (focal/grid) in the study eye at any time prior to Day 1 • Any IVT treatment for any other retinal diseases that can lead to MO complication • Any prior or current treatment for MO, macular neovascularisation, and vitreomacular interface abnormalities • Any major illness or major surgical procedure within 1 month before screening • Any current ocular condition which, in the opinion of the investigator, is currently causing or could be expected to contribute to irreversible vision loss due to a cause other than MO-RVO in the study eye	

Trial drugs and concomitant medications	**Trial drugs** • **Arm A:** In Part 1 of the study, patients received 6 mg faricimab IVT injections Q4W from Day 1 through Week 20. In Part 2, patients in both arms received 6 mg faricimab IVT injections administered according to a PTI dosing regimen in intervals between Q4W and Q16W. • **Arm B:** In Part 1, patients received 2 mg aflibercept IVT injections Q4W from Day 1 through Week 20, for a total of 6 injections. In Part 2, patients in both arms received 6 mg faricimab IVT injections administered according to a PTI dosing regimen in intervals between Q4W and Q16W. **Sham procedure** • The sham is a procedure that mimics an IVT injection to preserve the study masking and involves the blunt end of an empty syringe, without a needle, being pressed against an anaesthetised eye. **Concomitant medications** **Prohibited concomitant medications:** The following medications and treatments are prohibited from use during a patient's study treatment participation. Patients may be discontinued from study treatment and/or the study to receive these therapies: • Systemic anti-VEGF therapy • Systemic drugs known to cause macular oedema (fingolimod, tamoxifen) • IVT anti-VEGF agents (other than study-assigned aflibercept or faricimab) in study eye • IVT, periocular (subtenon), steroid implants (i.e., Ozurdex®, Iluvien®), or chronic topical ocular corticosteroids in study eye • Treatment with verteporfin (Visudyne®) in study eye • Administration of micropulse and focal or grid laser in study eye • Other experimental therapies (except those comprising vitamins and minerals **Permitted concomitant medications:** Patients who use maintenance therapies should continue their use. Of note, the following are common therapies that are permitted: • Treatment for onset of ocular hypertension or glaucoma in the study eye during a patient's study participation, as clinically indicated • Treatment of onset of cataract or posterior capsular opacification in either eye during a patient's study participation, as clinically indicated. Dose interruption criteria may apply with cataract surgery • Short-term use of topical ocular corticosteroids after cataract surgery, yttrium-aluminium garnet (YAG) capsulotomy, peripheral iridotomy, argon/selective laser trabeculoplasty, or ocular allergic conditions in study eye or fellow eye

	• Complete, sector, or local panretinal photocoagulation in the study eye or fellow eye may be allowed if needed for the treatment of ischemic RVO or new peripheral neovascularisation after discussion with the Medical Monitor. These conditions will be recorded as serious adverse events. The patient should remain on study treatment and continue unchanged on the IxRS-assigned interval. • Vitrectomy may be performed at the discretion of the masked investigator in the event that study eye develops sight-threatening vitreous haemorrhage or retinal detachment. These conditions will be recorded as serious adverse events and will be recorded as a concomitant procedure. Study treatment should be interrupted and may restart based on the patient's status after consultation with the Medical Monitor. The patient should remain in the study and complete all study visits as planned. • Fellow (non-study) eye may be treated with anti-VEGF therapy licensed for ocular use, if diagnosed with an ocular condition for which the selected anti-VEGF therapy is approved by the country regulatory agency and at the discretion of the masked investigator Consult with the region-specific anti-VEGF prescribing information for the recommended dose and frequency of treatment. The Sponsor will cover the cost of approved licensed ocular anti-VEGF therapy in accordance with local regulations. Note: bevacizumab (Avastin®) is not licensed for ophthalmic use in any country; therefore, it is prohibited from use. If (per the masked investigator's judgment) treatment with anti-VEGF is to be given to the fellow (non-study) eye at the same visit as the study eye treatment, all study eye assessments (including study eye study treatment administration) must be completed first. If there are no safety concerns, the site may proceed with the fellow eye treatment administered by the unmasked physician to preserve masking. Individual trays and sterile preparation must be separately prepared for each eye treatment. If the fellow eye anti-VEGF treatment is performed outside of the study visit, a qualified investigator, in either masked or unmasked role, can administer the treatment. At the discretion of the investigator, patients may continue to receive medications and standard treatments administered for other conditions.
Primary outcome	**Primary endpoint:** • Change in best-corrected visual acuity (BCVA) from baseline to Week 24
Other outcomes used in the economic model/specified in the scope	**Secondary endpoints:** • Visual acuity (the affected eye) • Overall visual function • Central subfield foveal thickness (CSFT) • Adverse effects of treatment • Health-related quality of life (HRQoL)

Pre-planned subgroups	In the intent to treat (ITT) population, the primary endpoint of change in BCVA from baseline to Week 24 was analysed across subgroups including:
	• Baseline BCVA:
	  • BALATON (BRVO) ≤ 54 letters and ≥ 55 letters);
	  • COMINO (C/HRVO): ≤ 34 letters, 35-54 letters, and ≥ 55 letters
	• Baseline BCVA (low vision of ≤ 23 letters and ≥ 24 letters)
	• Region (United States, Asia, and the rest of the world)
	• Age (< 65 years and ≥ 65 years)
	• Gender (female and male)
	• Race (White, Asian, and other)
	• COMINO: RVO subtype (CRVO and HRVO)

BCVA, best corrected visual acuity; CST, central subfield thickness; NEI VFQ-25, National Eye Institute 25-Item Visual Function Questionnaire; OCT, optical coherence tomography; PTI, personalised treatment interval; SD-OCT, spectral-domain optical coherence tomography; VEGF, vascular endothelial growth factor.

B.3.3.2 Patient demographics and baseline characteristics

Patient demographics were generally comparable between treatment arms and across both RVO studies (BALATON and COMINO) in the intent-to-treat (ITT) population (Table 7).

Table 7: Baseline demographics and patient characteristics: BALATON and COMINO (ITT population)

	BALATON			COMINO		
	Faricimab 6mg Q4W (N=276)	**Aflibercept 2mg Q4W (N=277)**	**All patients (N=553)**	**Faricimab 6mg Q4W (N=366)**	**Aflibercept 2mg Q4W (N=363)**	**All patients (N=729)**
Region						
n	276	277	553	366	363	729
Rest of the World	129 (46.7%)	128 (46.2%)	257 (46.5%)	187 (51.1%)	187 (51.5%)	374 (51.3%)
US	62 (22.5%)	64 (23.1%)	126 (22.8%)	95 (26.0%)	93 (25.6%)	188 (25.8%)
Asia	85 (30.8%)	85 (30.7%)	170 (30.7%)	84 (23.0%)	83 (22.9%)	167 (22.9%)
Age (years)						
n	276	277	553	366	363	729
Mean (SD)	64.3 (10.7)	63.8 (10.6)	64.1 (10.7)	65.6 (13.1)	64.7 (13.3)	65.1 (13.2)
Median	65.0	64.0	64.0	67.0	66.0	66.0
Min - Max	35-93	28-88	28-93	22-100	27 - 95	22-100
Age group (years)						
n	276	277	553	366	363	729
<65	133 (48.2%)	144 (52.0%)	277 (50.1%)	162 (44.3%)	158 (43.5%)	320 (43.9%)
>=65	143 (51.8%)	133 (48.0%)	276 (49.9%)	204 (55.7%)	205 (56.5%)	409 (56.1%)
<65	133 (48.2%)	144 (52.0%)	277 (50.1%)	162 (44.3%)	158 (43.5%)	320 (43.9%)
>=65 – <75	100 (36.2%)	93 (33.6%)	193 (34.9%)	113 (30.9%)	119 (32.8%)	232 (31.8%)
>=75 – <85	33 (12.0%)	36 (13.0%)	69 (12.5%)	71 (19.4%)	74 (20.4%)	145 (19.9%)
>=85	10 (3.6%)	4 (1.4%)	14 (2.5%)	20 (5.5%)	12 (3.3%)	32 (4.4%)
Sex						
n	276	277	553	366	363	729
Male	143 (51.8%)	130 (46.9%)	273 (49.4%)	193 (52.7%)	200 (55.1%)	393 (53.9%)
Female	133 (48.2%)	147 (53.1%)	280 (50.6%)	173 (47.3%)	163 (44.9%)	336 (46.1%)
Ethnicity						
n	276	277	553	366	363	729

Not Hispanic or Latino	224 (81.2%)	224 (80.9%)	448 (81.0%)	286 (78.1%)	283 (78.0%)	569 (78.1%)
Hispanic or Latino	47 (17.0%)	51 (18.4%)	98 (17.7%)	66 (18.0%)	73 (20.1%)	139 (19.1%)
Unknown	4 (1.4%)	1 (0.4%)	5 (0.9%)	10 (2.7%)	3 (0.8%)	13 (1.8%)
Not reported	1 (0.4%)	1 (0.4%)	2 (0.4%)	4 (1.1%)	4 (1.1%)	8 (1.1%)
Race						
n	276	277	553	366	363	729
American Indian or Alaska Native	3 (1.1%)	0	3 (0.5%)	2 (0.5%)	3 (0.8%)	5 (0.7%)
Black or African American	6 (2.2%)	7 (2.5%)	13 (2.4%)	10 (2.7%)	13 (3.6%)	23 (3.2%)
Native Hawaiian or other Pacific Islander	1 (0.4%)	0	1 (0.2%)	0	1 (0.3%)	1 (0.1%)
White	172 (62.3%)	172 (62.1%)	344 (62.2%)	243 (66.4%)	253 (69.7%)	496 (68.0%)
Multiple	-	-	-	1 (0.3%)	0	1 (0.1%)
Unknown	4 (1.4%)	4 (1.4%)	8 (1.4%)	21 (5.7%)	5 (1.4%)	26 (3.6%)
Asian	90 (32.6%)	94 (33.9%)	184 (33.3%)	89 (24.3%)	88 (24.2%)	177 (24.3%)
Chinese	41 (45.6%)	44 (46.8%)	85 (46.2%)	36 (40.4%)	33 (37.5%)	69 (39.0%)
Taiwanese	0	0	0	0	0	0
Asian Indian	1 (1.1%)	2 (2.1%)	3 (1.6%)	1 (1.1%)	0	1 (0.6%)
Korean	29 (32.2%)	21 (22.3%)	50 (27.2%)	21 (23.6%)	22 (25.0%)	43 (24.3%)
Malaysian	0	0	0	0	0	0
Vietnamese	0	0	0	1 (1.1%)	0	1 (0.6%)
Japanese	14 (15.6%)	22 (23.4%)	36 (19.6%)	24 (27.0%)	27 (30.7%)	51 (28.8%)
Filipino	0	1 (1.1%)	1 (0.5%)	0	3 (3.4%)	3 (1.7%)
Other Asian	5 (5.6%)	4 (4.3%)	9 (4.9%)	6 (6.7%)	3 (3.4%)	9 (5.1%)

Age is at randomisation. Asian origin percentages are based on the overall Asian denominator. Ethnicity= not reported if it cannot collected due to local regulations.

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

B.3.4.1 Analysis timing

The primary endpoint for the global population was performed when all patients had either completed the study through Week 24 or had discontinued from the study prior to Week 24, whichever came later (i.e., timing is defined as the primary endpoint last patient last visit [LPLV]). At the time of the primary analysis, the study was ongoing.

The final analyses for the global population were performed when all patients had either completed the study through Week 72 or have discontinued early from the study, dependent of which event comes first, and all data was entered into the database, cleaned and verification of critical variables had been completed.

B.3.4.2 Statistical hypothesis

The primary endpoint was the change in BCVA from baseline to Week 24. The following hypotheses were tested:

- Non-inferiority (NI) of faricimab Q4W compared with aflibercept Q4W at Week 24 in the ITT population (at a one-sided 0.02485 significance level)
- Superiority of faricimab Q4W compared with aflibercept Q4W at Week 24 in the ITT population (at a two-sided 0.0497 significance level)

The hypotheses on the primary endpoint were tested in the order shown above, proceeding sequentially starting from the non-inferiority test and only testing the superiority after achieving statistical significance on the non-inferiority test. There was no impact on the type I error rate for the superiority test following the NI test, therefore a claim of superiority after NI can be made without multiplicity adjustment (59).

The null and alternative hypotheses for NI test are as follows:

- The null hypothesis (H_0) is: $\mu^{faricimab} - \mu^{aflibercept} \leq -4$ letters
- The alternative hypothesis (H_a) is: $\mu^{faricimab} - \mu^{aflibercept} > -4$ letters

where $\mu^{faricimab}$ and $\mu^{aflibercept}$ are the expected change in BCVA from baseline to Week 24 for the faricimab Q4W arm and the active comparator (aflibercept Q4W) arm, respectively.

B.3.4.3 Planned sample size

Determination of sample size was based on patients enrolled in the global enrolment phase. Approximately 570 patients for BALATON and 750 patients for COMINO were randomised in a 1:1 ratio to receive treatment with faricimab (Arm A) or aflibercept (Arm B).

A sample size of approximately 285 patients in each treatment arm for BALATON and 375 patients for each treatment arm in COMINO will provide $>$90% power to calculate NI (using an NI margin of 4 letters) of faricimab compared to aflibercept for the change in BCVA from baseline to Week 24 in the ITT population and under the following assumptions:

- No difference in the mean change in BCVA from baseline to week 24 between the two treatment arms
- Standard deviation (SD) of 13 letters for BALATON and 15 letters for COMINO for the change from baseline in BCVA at Week 24
- Two-sample t-tests
- 2.5% one-sided type I error rate
- 10% dropout rate

The sample size will also provide greater than 80% power to calculate a 3.5-letter superiority of faricimab over aflibercept, under the same SD, test, and dropout assumptions above, and a two-sided type I error rate of 5%.

B.3.4.4 Analysis populations

Table 8: BALATON and COMINO analysis populations

Population	Definition
ITT	All patients who were randomised in the study. For analyses based on this patient population, patients were grouped according to the treatment assigned at randomisation. Note: Subjects who were wrongly randomised to one study (BALATON or COMINO), discontinued without treatment, and then randomised to the other study (COMINO or BALATON respectively) are included in the latter study only.
Per-protocol	All patients randomised in the study who receive at least one dose of study treatment and who do not have a major protocol violation that impacts the efficacy evaluation. Patients were grouped according to actual treatment received through Week 20. If by error, a patient received a combination of different active study drugs (faricimab and aflibercept) in the study eye, the patient's treatment group will be as randomised.

Safety-evaluable	All patients who received at least one injection of active study drug (faricimab or aflibercept) in the study eye. Patients were grouped according to actual treatment received through Week 20. If by error a patient received a combination of different active study drugs (faricimab and aflibercept) in the study eye, the patient's treatment group will be as randomised.

B.3.4.5 Efficacy analysis and statistical methods

General considerations for the analysis, as well as statistical methods for the primary, secondary and exploratory endpoints, and safety analyses are provided in Appendix E.

B.3.5 Critical appraisal of the relevant clinical effectiveness evidence

An overview of the quality assessment for BALATON and COMINO is presented in Table 9. Please refer to Appendix D.3 for the full quality assessment.

Table 9: Clinical effectiveness evidence quality assessment

Study question	BALATON (NCT04740905)	COMINO (NCT04740931)
Was randomisation carried out appropriately?	Yes	Yes
Was the concealment of treatment allocation adequate?	Yes	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Yes
Were there any unexpected imbalances in drop-outs between groups?	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes

B.3.6 Clinical effectiveness results of the relevant studies

Data pooling was not conducted across the Phase III studies (BALATON and COMINO). The pre-specified rationale for not pooling efficacy data across both studies was because each RVO subtype may impact the retina differently (BRVO and C/HRVO. The primary and secondary efficacy analyses were based on the ITT population, unless otherwise specified, with patients grouped according to the treatment arm assigned at randomisation.

B.3.6.1 Primary endpoint: Change in BCVA from baseline to Week 24 in the study eye

In both BALATON and COMINO, faricimab demonstrated non-inferiority to aflibercept with the change from in BCVA between baseline and Week 24. The primary endpoint analyses was consistent between the ITT and per protocol (PP) populations, and generally comparable between the two studies (Table 10).

At Week 24 in BALATON, the adjusted mean BCVA change from baseline was 16.9 and 17.5 letters in the faricimab Q4W and aflibercept Q4W arms, respectively; the difference was -0.6 letters (95% CI: -2.2, 1.1). In COMINO, the adjusted mean change in BCVA from baseline was 16.9 and 17.3 letters in the faricimab Q4W and aflibercept Q4W arms, respectively; the difference was -0.4 letters (95% CI: -2.5, 1.6). The difference in BCVA letter between faricimab and aflibercept in both BALATON and COMINO was within the +/- 4 letter non inferiority margin.

Table 10: BALATON (GR41984) and COMINO (GR41986): Change from baseline in BCVA in the study eye at Week 24

	BALATON			COMINO		
	Faricimab 6 mg Q4W [N=276] Adjusted mean (95% CI)	Aflibercept 2 mg Q4W [N=277] Adjusted mean (95% CI)	Difference in adjusted means (95% CI)	Faricimab 6 mg Q4W [N=366] Adjusted mean (95% CI)	Aflibercept 2 mg Q4W [N=363] Adjusted mean (95% CI)	Difference in adjusted means (95% CI)
Mean (SE) baseline BCVA [a]	57.5 (0.78)	57.6 (0.73)	—	50.2 (0.85)	50.7 (0.86)	—
Main analysis – MMRM method						
ITT population	16.9 (15.7, 18.1)	17.5 (16.3, 18.6)	–0.6 (–2.2, 1.1) [b]	16.9 (15.4, 18.3)	17.3 (15.9, 18.8)	–0.4 (–2.5, 1.6) [b]
Sensitivity analysis – Multiple imputation: ANCOVA method						
ITT population	15.7 (14.3, 17.1)	15.7 (14.3, 17.2)	–0.1 (–1.9, 1.7)	16.5 (14.6, 18.3)	16.6 (14.7, 18.4)	–0.1 (–2.2, 2.0)
Supplementary analyses						
PP analysis – MMRM method; PP population	17.1 (15.8, 18.3)	17.4 (16.2, 18.6)	–0.3 (–2.1, 1.4)	17.3 (15.8, 18.8)	18.4 (16.9, 19.9)	–1.1 (–3.2, 0.9)
Analysis of distinguishing COVID and non-COVID intercurrent events – MMRM method; ITT population	17.0 (15.8, 18.2)	17.5 (16.3, 18.7)	–0.5 (–2.1, 1.2)	16.9 (15.5, 18.4)	17.4 (15.9, 18.8)	–0.4 (–2.5, 1.6)
Analysis of hypothetical strategy for all intercurrent events – MMRM method; ITT population	16.9 (15.7, 18.1)	17.5 (16.3, 18.7)	–0.6 (–2.3, 1.0)	16.8 (15.4, 18.3)	17.3 (15.9, 18.8)	-0.5 (-2.5, 1.6)

ANCOVA=analysis of covariance; BCVA=best corrected visual acuity; COVID=coronavirus disease; ITT=intent-to-treat; MI=multiple imputation; MMRM=mixed model for repeated measures; MNAR=missing not at random; PP=per protocol; Q4W=every four weeks.

Notes: ITT population: faricimab Q4W=276; aflibercept Q4W=277. PP population: faricimab Q4W=241; aflibercept Q4W=243 (BALATON) ITT population: faricimab Q4W=366; aflibercept Q4W=363. PP population: faricimab Q4W=328; aflibercept Q4W=311 (COMINO).

For the primary analysis, an MMRM analysis was performed; the model was adjusted for treatment group, visit, visit-by-treatment group interaction, Baseline BCVA (BALATON: <=54 letters vs. >=55 letters; COMINO: ≤ 34 letters, 35-54 letters, and ≥ 55 letters), and region (United States, Asia, and the rest of the world). An unstructured covariance structure was used. Observed BCVA assessments were used regardless of the occurrence of intercurrent events. Missing data were implicitly imputed by MMRM. Invalid BCVA values were excluded from analysis. 95% CI was a rounding of 95.03% CI.

For the sensitivity analysis using MI, an ANCOVA analysis was performed; the model used the non-missing change from baseline in BCVA at Week 24 as the response variable adjusted for the treatment group, baseline BCVA (continuous), baseline BCVA score (BALATON: <=54 letters vs. >=55 letters; COMINO: ≤ 34 letters, 35-54 letters, and ≥ 55 letters), and region (United States, Asia, and the rest of the world). Observed BCVA assessments were used regardless of the occurrence of intercurrent events. Missing primary endpoint BCVA assessments were imputed using MI assuming MNAR and imputed using the worse outcomes. Invalid BCVA values are excluded from analysis. 95% CI is a rounding of 95.03% CI.

For the analysis distinguishing COVID and non-COVID intercurrent events, the analysis was conducted following the same analysis method as the primary analysis except a treatment policy strategy and hypothetical strategy were applied to non-COVID-19 related and COVID-19 related intercurrent events, respectively.

For the analysis using a hypothetical strategy for all intercurrent events, the analysis was conducted following the same analysis method as the primary analysis except a hypothetical strategy was applied to the intercurrent events.

a The mean baseline BCVA values presented in this row are non-adjusted.

b For the primary analysis, if the lower bound of the two-sided 95% CI for the difference in adjusted means of the two treatments is greater than − 4 letters (the non-inferiority margin), then faricimab is considered non-inferior to aflibercept.

B.3.6.2 Secondary endpoin ts

Change in BCVA from baseline at Week 64/68/72

In both BALATON and COMINO, [redacted]. In BALATON, in the ITT population, the adjusted mean change in BCVA from baseline was [redacted] and [redacted] letters in the faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arms, respectively at Week 64/68/72. In COMINO, in the ITT population, the adjusted mean change in BCVA from baseline was [redacted] and [redacted] letters in the faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arms, respectively (Table 11).

Table 11: Change in BCVA from baseline in the study eye at Week 64/68/72

	BALATON		COMINO	
	Faricimab 6 mg Q4W to Faricimab 6 mg PTI [N=276] **Adjusted mean (95% CI)**	**Aflibercept 2 mg Q4W to Faricimab 6 mg PTI [N=277]** **Adjusted mean (95% CI)**	**Faricimab 6 mg Q4W to Faricimab 6 mg PTI [N=366]** **Adjusted mean (95% CI)**	**Aflibercept 2 mg Q4W to Faricimab 6 mg PTI [N=363]** **Adjusted mean (95% CI)**
Mean (SE) baseline BCVA [a]	57.5 (0.78)	57.7 (0.73)	50.2 (0.85)	50.7 (0.86)
Main analysis – MMRM method				
ITT population	18.1 (16.9, 19.4)	18.8 (17.5, 20.0)	16.9 (15.2, 18.6)	17.1 (15.4, 18.8)
Sensitivity analysis – Multiple imputation: ANCOVA method				
ITT population	16.5 (15.0, 18.0)	17.1 (15.5, 18.6)	16.3 (14.1, 18.6)	16.3 (14.2, 18.5)
Supplementary analyses				
PP analysis – MMRM method; PP population	18.3 (17.0, 19.7)	19.4 (18.0, 20.7)	18.5 (16.8, 20.3)	18.6 (16.8, 20.4)
Analysis of distinguishing COVID and non-COVID intercurrent events – MMRM method; ITT population	18.2 (16.9, 19.5)	18.9 (17.6, 20.2)	16.9 (15.2, 18.6)	17.0 (15.3, 18.8)
Analysis of hypothetical strategy for all intercurrent events – MMRM method; ITT population	18.2 (16.9, 19.5)	18.8 (17.5, 20.1)	16.9 (15.2, 18.6)	17.0 (15.2, 18.7)

ANCOVA=analysis of covariance; BCVA=best corrected visual acuity; COVID=coronavirus disease; ITT=intent-to-treat; MMRM=mixed model for repeated measures; PP=per protocol; PTI = personalized treatment interval; Q4W=every 4 weeks; SE = standard error.

Notes:

ITT population (BALATON): faricimab Q4W to faricimab PTI=276; aflibercept Q4W to faricimab PTI=277. PP population: faricimab Q4W to faricimab PTI=225; aflibercept Q4W to faricimab PTI=221.

ITT population (COMINO): faricimab Q4W to faricimab PTI=366; aflibercept Q4W to faricimab PTI=363. PP population: faricimab Q4W to faricimab PTI=296; aflibercept Q4W to faricimab PTI=277

For the main analysis, an MMRM analysis was performed; the model was adjusted for treatment group, visit, visit-by-treatment group interaction, baseline BCVA (continuous), Baseline BCVA (BALATON: <=54 letters vs. >=55 letters; COMINO: ≤ 34 letters, 35–54 letters, and ≥ 55 letters) and region (United States, Asia, and the rest of the world). An unstructured covariance structure was used. Observed BCVA assessments were used regardless of the occurrence of intercurrent events. Missing data were implicitly imputed by MMRM. Invalid BCVA values were excluded from analysis. 95% CI is a rounding of 95.03% CI.

For the sensitivity analysis using MI, an ANCOVA analysis was performed; the model used the non-missing change from baseline in BCVA averaged over Weeks 64, 68 and 72 as the response variable adjusted for the treatment group, baseline BCVA (continuous), baseline BCVA score (<= 54 letters and >= 55 letters), and region (United States, Asia, and the rest of the world). Observed BCVA assessments were used regardless of the occurrence of intercurrent events. Missing post-baseline BCVA assessments were imputed using multiple imputation (MI) assuming missing not at random (MNAR) and imputed using the worse outcomes. Invalid BCVA values were excluded from analysis. 95% CI is a rounding of 95.03% CI.

For the analysis distinguishing COVID and non-COVID intercurrent events, the analysis was conducted following the same analysis method as the main analysis except a treatment policy strategy and hypothetical strategy were applied to non-COVID-19 related and COVID-19 related intercurrent events, respectively.

For the analysis using a hypothetical strategy for all intercurrent events, the analysis was conducted following the same analysis method as the main analysis except a hypothetical strategy was applied to the intercurrent events.

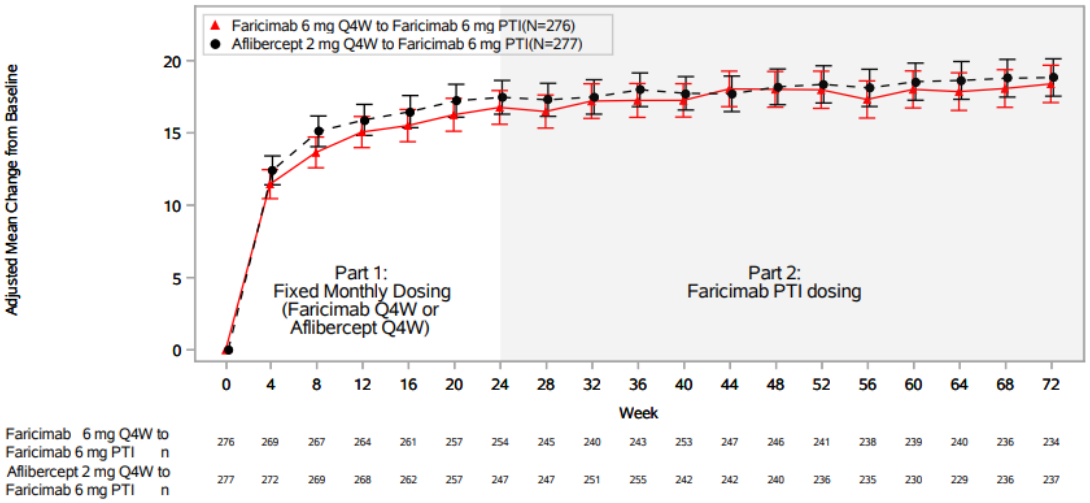
[a] *The mean baseline BCVA values presented in this row are non-adjusted.*

Change in BCVA from baseline over time at Week 72

The change from baseline in BCVA through Week 24 was [redacted]. The BCVA gains achieved at Week 24 [redacted] (Figure 5, Figure 6).

Figure 5: Change in BCVA from baseline in the study eye through Week 72: MMRM method, ITT population [BALATON]

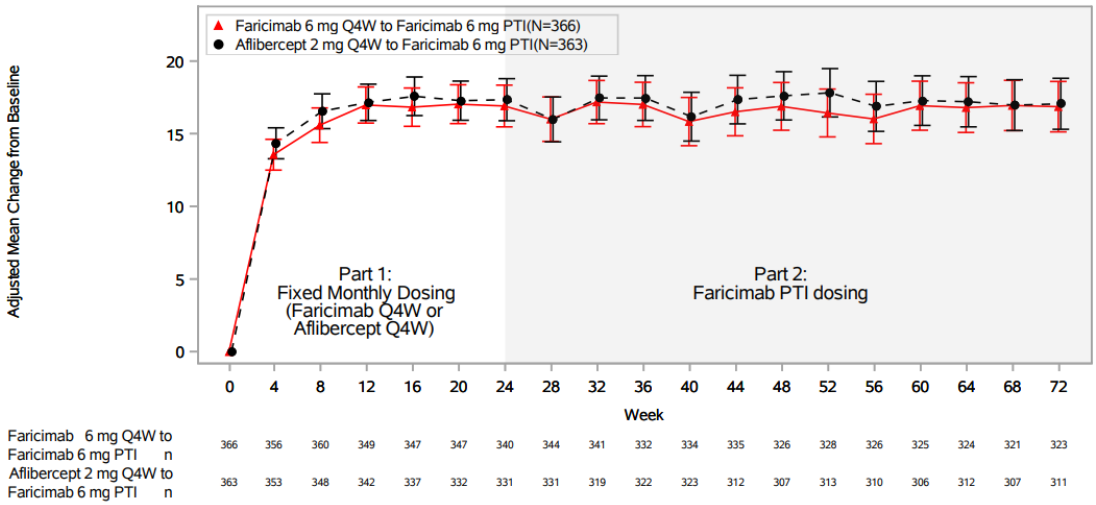
Protocol: GR41984



Units: letters. BCVA = Best Corrected Visual Acuity; MMRM = Mixed-Model Repeated-Measures; n = Number of patients at the visit. For the MMRM analysis, the model adjusted for treatment group, visit, visit-by-treatment group interaction, baseline BCVA (continuous), baseline BCVA (<=54 letters vs. >=55 letters) and region (U.S. and Canada, Asia, and the rest of the world). An unstructured covariance structure is used. Observed BCVA assessments were used regardless of the occurrence of intercurrent events. Missing data were implicitly imputed by MMRM. Invalid BCVA values are excluded from analysis. The bars represent 95.03% confidence interval.

Figure 6: Change in BCVA from baseline in the study eye through Week 72: MMRM method, ITT population [COMINO]

Protocol: GR41986

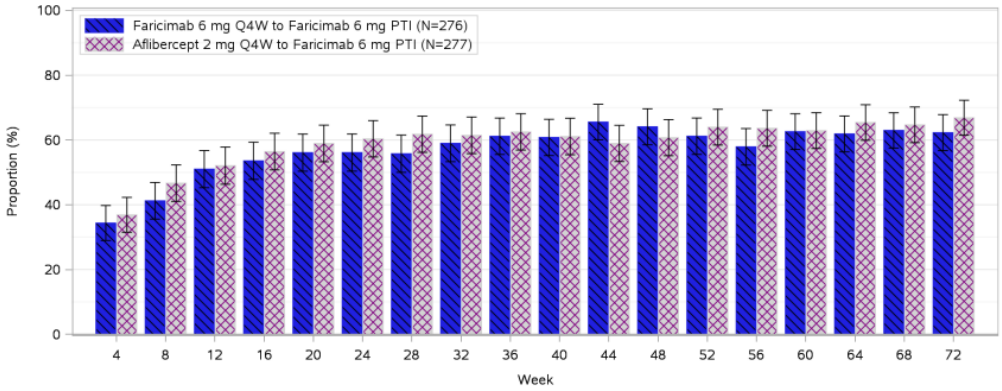


Units: letters. BCVA = Best Corrected Visual Acuity; MMRM = Mixed-Model Repeated-Measures; n = Number of patients at the visit. For the MMRM analysis, the model adjusted for treatment group, visit, visit-by-treatment group interaction, baseline BCVA (continuous), baseline BCVA (<=34 letters, 35-54 letters, and >=55 letters) and region (U.S. and Canada, Asia, and the rest of the world). An unstructured covariance structure is used. Observed BCVA assessments were used regardless of the occurrence of intercurrent events. Missing data were implicitly imputed by MMRM. Invalid BCVA values are excluded from analysis. The bars represent 95.03% confidence interval.

Proportion of patients gaining ≥ 15, ≥ 10, ≥ 5, or > 0 letters in BCVA at Week 72

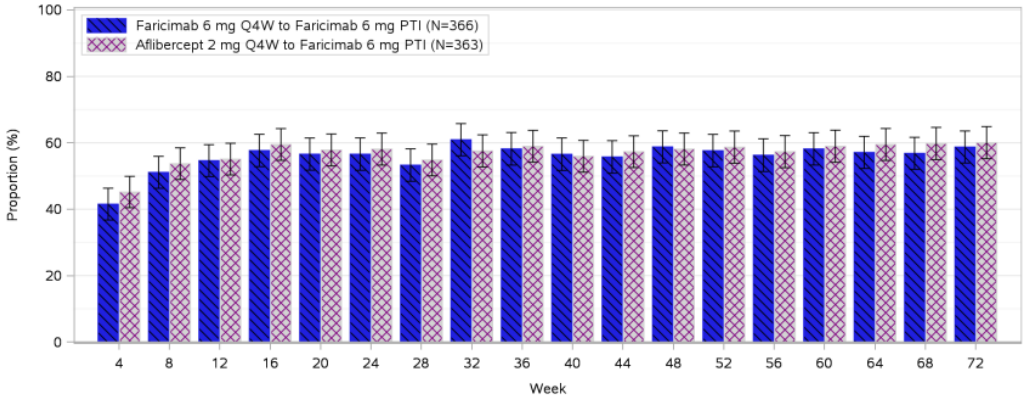
In BALATON, at Week 64/68/72, [redacted] and [redacted] of patients gained at least 15 letters in BCVA score from baseline in the faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arms, respectively (Figure 7**Error! Reference source not found.**). In COMINO, [redacted] and [redacted] of patients gained at least 15 letters in BCVA score from baseline in the faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arms, respectively (Figure 8). The proportion of patients gaining ≥ 10, ≥ 5, or > 0 letters in BCVA from baseline at Week 64/68/72 are shown in Table 12.

Figure 7: Proportion of patients gaining ≥ 15 letters in BCVA from baseline in the study eye over time through Week 72: CMH method, ITT population [BALATON]



BCVA = Best Corrected Visual Acuity; CMH = Cochran-Mantel-Haenszel; LOCF= Last Observation Carried Forward.
The proportion is the weighted estimate based on CMH weights stratified by baseline BCVA score (<=54 letters vs. >=55 letters) and region (U.S. and Canada vs. Asia vs. the rest of the world). All observed values are used regardless of the occurrence of intercurrent events. Missing assessments were imputed by LOCF. Invalid BCVA values are excluded from analysis. Baseline is defined as the last available measurement obtained on or prior to randomization. Error bars represent the 95.03% confidence interval for the CMH weighted estimates.

Figure 8: Proportion of patients gaining ≥ 15 letters from in BCVA from baseline in the study eye over time through Week 72: CMH method, ITT population [COMINO]



BCVA = Best Corrected Visual Acuity; CMH = Cochran-Mantel-Haenszel; LOCF= Last Observation Carried Forward.
The proportion is the weighted estimate based on CMH weights stratified by baseline BCVA score (<=34 letters, 35-54 letters, and >=55 letters) and region (U.S. and Canada vs. Asia vs. the rest of the world). All observed values are used regardless of the occurrence of intercurrent events. Missing assessments were imputed by LOCF. Invalid BCVA values are excluded from analysis. Baseline is defined as the last available measurement obtained on or prior to randomization. Error bars represent the 95.03% confidence interval for the CMH weighted estimates.

Table 12: Proportion of patients gaining letters by category in BCVA from baseline in the study eye at Week 64/68/72: CMH method, ITT population

		BALATON		COMINO	
		Faricimab 6 mg Q4W to Faricimab 6 mg PTI (N = 276)	Aflibercept 2 mg Q4W to Faricimab 6 mg PTI (N = 277)	Faricimab 6 mg Q4W to Faricimab 6 mg PTI (N = 366)	Aflibercept 2 mg Q4W to Faricimab 6 mg PTI (N = 363)
Gaining letters by category					
Gaining ≥ 15 letters in BCVA from BL	CMH weighted estimate	61.5%	65.8%	57.6%	59.5%
	(95% CI)	(56.0%, 67.0%)	(60.3%, 71.2%)	(52.8%, 62.5%)	(54.7%, 64.3%)
Gaining ≥ 10 letters in BCVA from BL	CMH weighted estimate	78.9%	79.1%	71.3%	70.5%
	(95% CI)	(74.2%, 83.7%)	(74.3%, 83.9%)	(66.8%, 75.8%)	(65.9%, 75.1%)
Gaining ≥ 5 letters in BCVA from BL	CMH weighted estimate	89.1%	87.0%	82.5%	80.4%
	(95% CI)	(85.5%, 92.8%)	(83.1%, 91.0%)	(78.7%, 86.3%)	(76.4%, 84.5%)
Gaining 0 letters in BCVA from BL	CMH weighted estimate	96.4%	95.0%	86.6%	86.5%
	(95% CI)	(94.2%, 98.6%)	(92.4%, 97.5%)	(83.2%, 90.1%)	(83.0%, 89.9%)

BCVA = best-corrected visual acuity; BL = baseline; CMH = Cochran-Mantel-Haenszel; ITT = Intent-to-Treat; PTI = personalized treatment interval; Q4W = every four weeks.

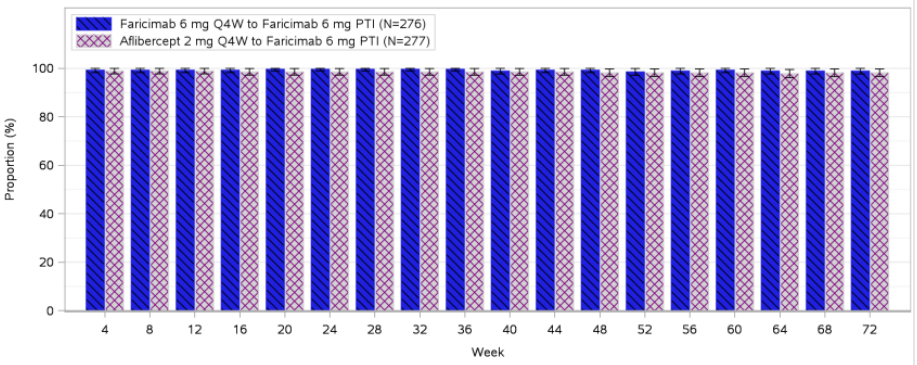
The weighted estimate was based on CMH weights stratified by baseline BCVA score (≤ 54 letters and ≥ 55 letters) and region (United States, Asia, and the rest of the world). 95% CI is a rounding of 95.03% CI and estimates below 0% or above 100% were imputed as 0% or 100% respectively. Baseline is defined as the last available measurement obtained on or prior to randomisation. Invalid BCVA were excluded.

All observed values were used regardless of the occurrence of the intercurrent events. Missing assessments were imputed by last observation carried forward (LOCF). Proportion was calculated after LOCF imputation. N in the header is the number of patients randomised (used as the denominator when calculating proportion).

Proportion of patients avoiding a loss of ≥ 15, ≥ 10, or ≥ 5 letters in BCVA from baseline at Week 64/68/72

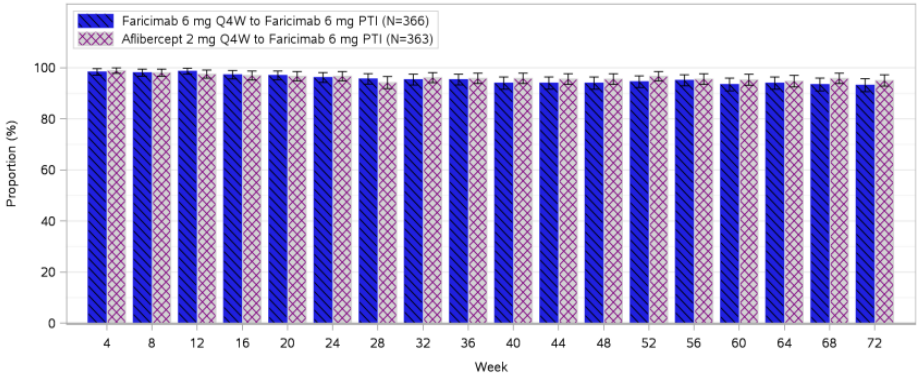
In BALATON, at Week 64/68/72, [redacted] and [redacted] of patients avoided a loss of ≥15 letters in BCVA score from baseline in the faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arms, respectively (Figure 9). In COMINO, [redacted] and [redacted] of patients avoided a loss of ≥ 15 letters in BCVA score from baseline in the faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arms, respectively (Figure 10). The proportion of patients avoiding a loss of ≥ 10 or ≥ 5 letters in BCVA from baseline at Week 64/68/72 are shown in Table 13.

Figure 9: Proportion of patients avoiding a loss of ≥ 15 letters in BCVA from baseline in the study eye over time through Week 72: CMH method, ITT population [BALATON]



BCVA = Best Corrected Visual Acuity; CMH = Cochran-Mantel-Haenszel; LOCF= Last Observation Carried Forward.
The proportion is the weighted estimate based on CMH weights stratified by baseline BCVA score (<=54 letters vs. >=55 letters) and region (U.S. and Canada vs. Asia vs. the rest of the world). All observed values are used regardless of the occurrence of intercurrent events. Missing assessments were imputed by LOCF. Invalid BCVA values are excluded from analysis. Baseline is defined as the last available measurement obtained on or prior to randomization. Error bars represent the 95.03% confidence interval for the CMH weighted estimates.

Figure 10: Proportion of patients avoiding a loss of ≥ 15 letters in BCVA from baseline in the study eye over time through Week 72: CMH method, ITT population [COMINO]



BCVA = Best Corrected Visual Acuity; CMH = Cochran-Mantel-Haenszel; LOCF= Last Observation Carried Forward.
The proportion is the weighted estimate based on CMH weights stratified by baseline BCVA score (<=34 letters, 35-54 letters, and >=55 letters) and region (U.S. and Canada vs. Asia vs. the rest of the world). All observed values are used regardless of the occurrence of intercurrent events. Missing assessments were imputed by LOCF. Invalid BCVA values are excluded from analysis. Baseline is defined as the last available measurement obtained on or prior to randomization. Error bars represent the 95.03% confidence interval for the CMH weighted estimates.

Table 13: Proportion of patients avoiding loss of letters by category in BCVA from baseline in the study eye at Week 64/68/72: CMH method, ITT population

		BALATON		COMINO	
		Faricimab 6 mg Q4W to Faricimab 6 mg PTI (N = 276)	Aflibercept 2 mg Q4W to Faricimab 6 mg PTI (N = 277)	Faricimab 6 mg Q4W to Faricimab 6 mg PTI (N = 366)	Aflibercept 2 mg Q4W to Faricimab 6 mg PTI (N = 363)
Avoiding loss of letters by category					
Avoiding a loss of ≥ 15 letters in BCVA from BL	CMH weighted estimate	98.9%	98.2%	93.7%	95.6%
	(95% CI)	(97.7%, 100.0%)	(96.7%, 99.8%)	(91.3%, 96.2%)	(93.5%, 97.7%)
Avoiding a loss of ≥ 10 letters in BCVA from BL	CMH weighted estimate	98.6%	97.9%	93.5%	93.9%
	(95% CI)	(97.2%, 100.0%)	(96.2%, 99.5%)	(91.0%, 96.0%)	(91.5%, 96.4%)
Avoiding a loss of ≥ 5 letters in BCVA from BL	CMH weighted estimate	97.5%	97.1%	91.3%	92.6%
	(95% CI)	(95.6%, 99.3%)	(95.2%, 99.1%)	(88.4%, 94.1%)	(89.9%, 95.2%)

BCVA = best-corrected visual acuity; BL = baseline; CMH = Cochran-Mantel-Haenszel; ITT = Intent-to-Treat; PTI = Personalized Treatment Interval; Q4W = every four weeks.

The weighted estimate was based on CMH weights stratified by baseline BCVA score (≤54 letters and ≥55 letters) and region (United States, Asia, and the rest of the world). 95% CI is a rounding of 95.03% CI and estimates below 0% or above 100% are imputed as 0% or 100% respectively. Baseline is defined as the last available measurement obtained on or prior to randomization. Invalid BCVA were excluded.

All observed values were used regardless of the occurrence of the intercurrent events. Missing assessments were imputed by last observation carried forward (LOCF). Proportion was calculated after LOCF imputation. N in the header is the number of patients randomised (used as the denominator when calculating proportion).

Anatomic outcomes

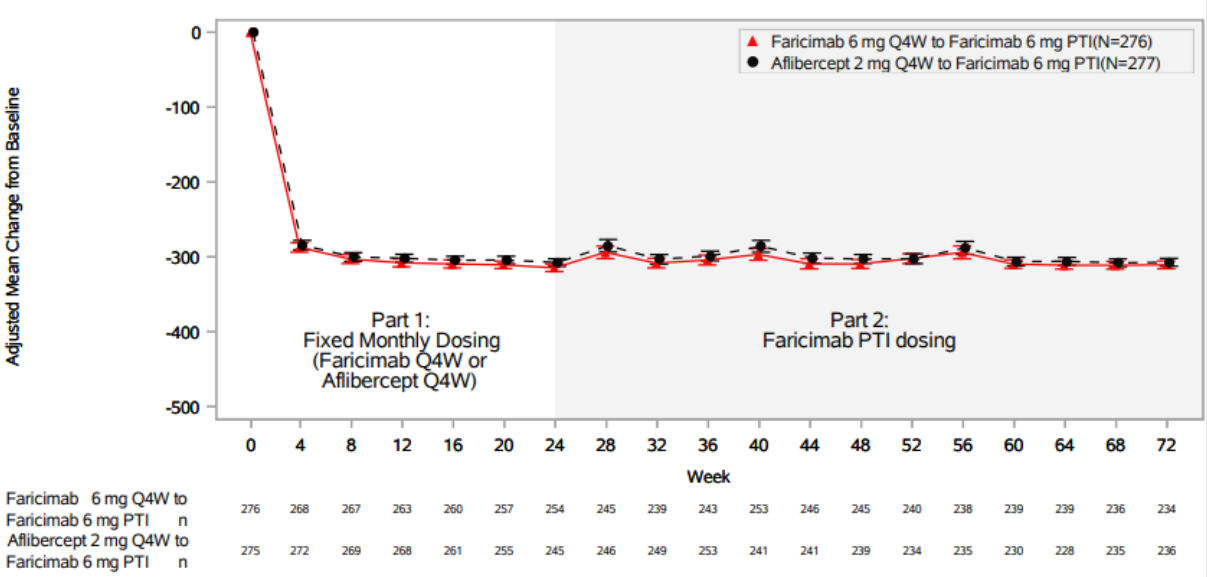
Change in CST (ILM-BM) from baseline over time at Week 72

Patients treated with faricimab Q4W consistently had comparable reductions in mean change from baseline in CST through Week 24 compared with the aflibercept Q4W arm. In BALATON, at Week 24, the adjusted mean change in CST from baseline was [redacted] in the faricimab and aflibercept arms, respectively. The difference in adjusted mean change from in CST baseline between the faricimab when compared with the aflibercept arm at Week 24 was [redacted].

In COMINO, at Week 24, the adjusted mean change in CST from baseline was [redacted] in the faricimab and aflibercept arms, respectively. The difference in adjusted mean change in CST from baseline between the faricimab arm when compared with the aflibercept arm at Week 24 was [redacted].

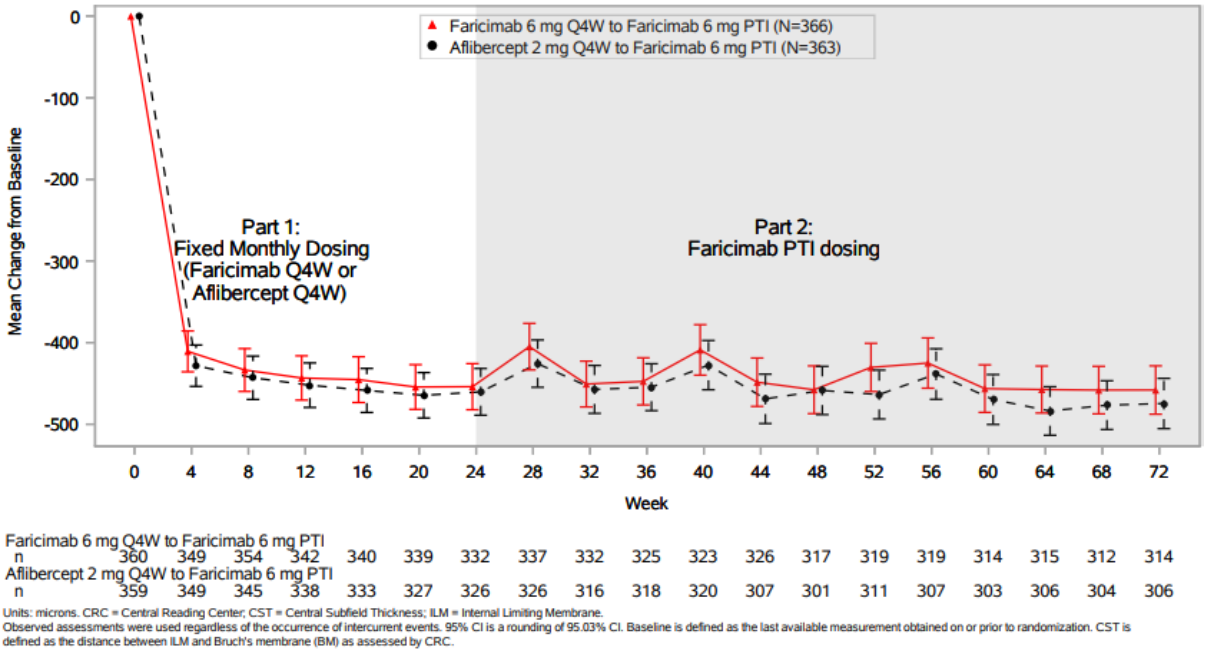
The CST reductions achieved at Week 24 [redacted] (Figure 11 and Figure 12). [redacted]

Figure 11: Change in CST (ILM-BM) from baseline in the study eye over time through Week 72: MMRM method, ITT population [BALATON]



Units: microns. CRC = Central Reading Center; CST = Central Subfield Thickness; ILM = Internal Limiting Membrane; MMRM = Mixed-Model Repeated-Measures; n = Number of patients at the visit. For the MMRM analysis, the model adjusted for treatment group, visit, visit-by-treatment group interaction, baseline CST (continuous), baseline BCVA score (<=54 letters vs. >=55 letters) and region (U. S. and Canada, Asia, and the rest of the world). An unstructured covariance structure is used. Observed assessments were used regardless of the occurrence of intercurrent events. Missing data were implicitly imputed by MMRM. The bars represent 95.03% confidence interval. CST is defined as the distance between ILM and Bruch's membrane (BM) as assessed by CRC. The bars represent 95.03% confidence interval.

Figure 12: Change in CST (ILM-BM) from baseline in the study eye over time through Week 72: MMRM method, ITT population [COMINO]



Units: microns. CRC = Central Reading Center; CST = Central Subfield Thickness; ILM = Internal Limiting Membrane.
Observed assessments were used regardless of the occurrence of intercurrent events. 95% CI is a rounding of 95.03% CI. Baseline is defined as the last available measurement obtained on or prior to randomization. CST is defined as the distance between ILM and Bruch's membrane (BM) as assessed by CRC.

B.3.6.3 Faricimab PTI treatment intervals in study Part 2

Proportion of patients on a Q4W, Q8W, Q12W, or Q16W faricimab treatment interval at Week 68

The criteria for extending or decreasing a dosing interval in Part 2 are described in Section B.3.3.1 Study design.

In BALATON, at Week 68, [redacted] of patients in the faricimab Q4W to faricimab PTI arm and [redacted] of patients in the aflibercept Q4W to faricimab PTI arm were on a Q4W, Q8W, Q12W or Q16W treatment interval, respectively.

In COMINO, At Week 68, [redacted] of patients in the faricimab Q4W to faricimab PTI arm and 32.4%, [redacted] of patients in the aflibercept Q4W to faricimab PTI arm were on a Q4W, Q8W, Q12W or Q16W treatment interval, respectively (Table 14).

Table 14: Proportion of patients on a Q4W, Q8W, Q12W, or Q16W faricimab treatment interval at Week 68, ITT population

	BALATON				COMINO			
	Faricimab 6 mg Q4W to Faricimab 6 mg PTI (N=276)		Aflibercept 2 mg Q4W to Faricimab 6 mg PTI (N=277)		Faricimab 6 mg Q4W to Faricimab 6 mg PTI (N=366)		Aflibercept 2 mg Q4W to Faricimab 6 mg PTI (N=363)	
Visit	Proportion n (%)	%95 CI of Proportion	Proportion n (%)	%95 CI of Proportion	Proportion n (%)	%95 CI of Proportion	Proportion n (%)	%95 CI of Proportion
Week 68								
N	248	N/A	244	N/A	330	N/A	315	N/A
Q4W	56 (22.6%)	17.4%, 27.8%	61 (25.0%)	19.6%, 30.4%	114 (34.5%)	29.4%, 39.7%	102 (32.4%)	27.2%, 37.6%
Q8W	33 (13.3%)	9.1%, 17.5%	44 (18.0%)	13.2%, 22.9%	66 (20.0%)	15.7%, 24.3%	55 (17.5%)	13.3%, 21.7%
Q12W	29 (11.7%)	7.7%, 15.7%	23 (9.4%)	5.8%, 13.1%	28 (8.5%)	5.5%, 11.5%	35 (11.1%)	7.6%, 14.6%
Q16W	130 (52.4%)	46.2%, 58.6%	116 (47.5%)	41.3%, 53.8%	122 (37.0%)	31.8%, 42.2%	123 (39.0%)	33.7%, 44.4%

Percentages are based on randomised patients who have not discontinued the study at Week 68. Treatment interval at Week 68 is defined as the treatment interval decision followed at that visit.

Patients randomised to faricimab arm receive 6 mg of intravitreal (IVT) faricimab Q4W up to Week 20. Patients randomised to aflibercept arm receive 2mg of intravitreal (IVT) aflibercept Q4W up to Week 20. From Week 24 (when all patients are scheduled to receive faricimab) onward, patients were treated according to the personalized treatment interval (PTI) dosing regimen up to Week 68. 95% CI is a rounding of 95.03% CI.

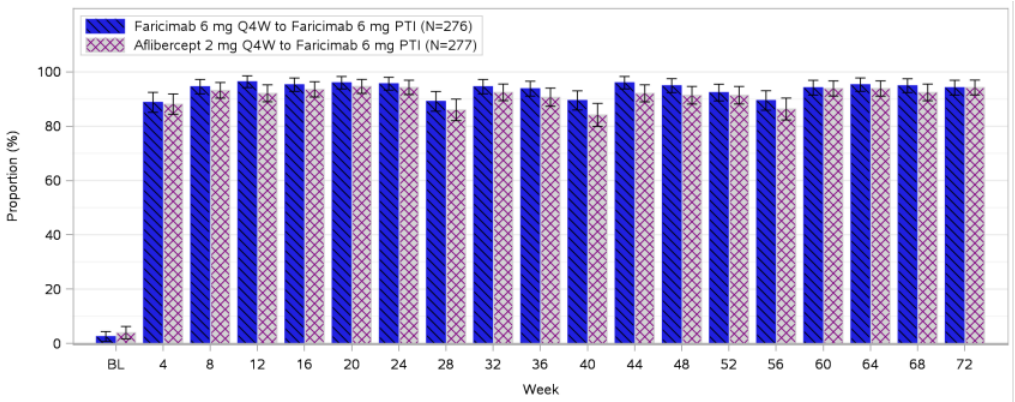
B.3.6.4 Exploratory endpoints

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

[redacted]

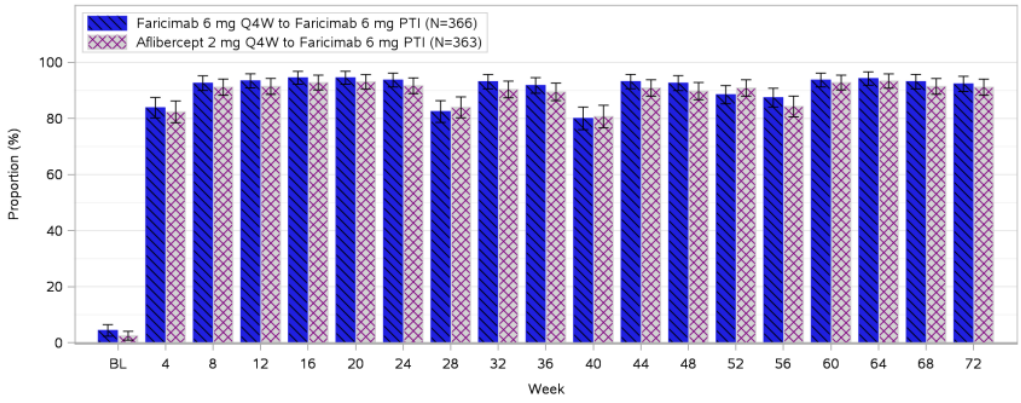
[redacted] *13* [redacted] *14*[redacted]

Figure 13: Proportion of patients with absence of macular oedema in the study eye over time through Week 72: CMH method, ITT population [BALATON]



CMH = Cochran-Mantel-Haenszel; LOCF = Last Observation Carried Forward.
The proportion is the weighted estimate based on CMH weights stratified by baseline BCVA score (<=54 letters vs. >=55 letters) and region (U.S. and Canada vs. Asia vs. the rest of the world). All observed values are used regardless of the occurrence of the intercurrent event. Missing assessments were imputed by LOCF. Baseline is defined as the last available measurement obtained on or prior to randomization. Absence of macular edema is defined as CST of < 325 um. Error bars represent the 95.03% confidence interval for the CMH weighted estimates.

Figure 14: Proportion of patients with absence of macular oedema in the study eye over time through Week 72: CMH method, ITT population [COMINO]



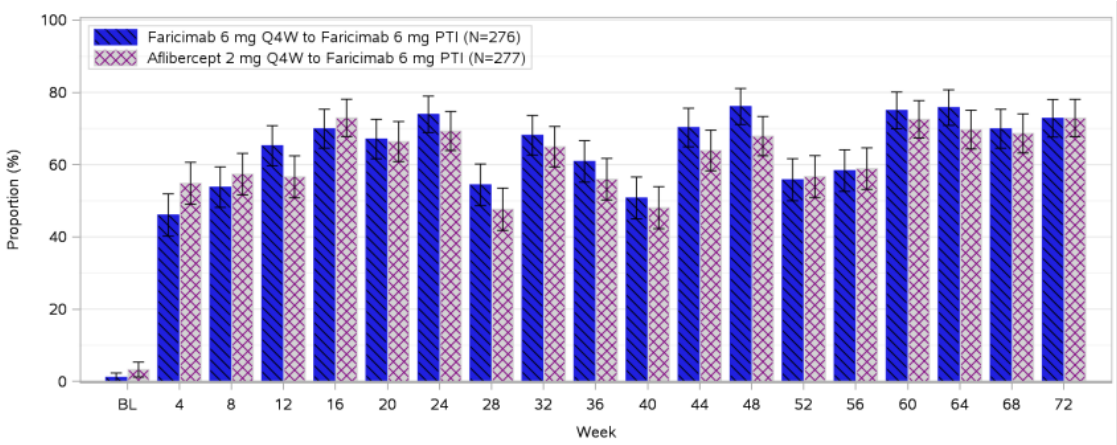
CMH = Cochran-Mantel-Haenszel; LOCF = Last Observation Carried Forward.
The proportion is the weighted estimate based on CMH weights stratified by baseline BCVA score (<=34 letters, 35-54 letters, and >=55 letters) and region (U.S. and Canada vs. Asia vs. the rest of the world). All observed values are used regardless of the occurrence of the intercurrent event. Missing assessments were imputed by LOCF. Baseline is defined as the last available measurement obtained on or prior to randomization. Absence of macular edema is defined as CST of < 325 um. Error bars represent the 95.03% confidence interval for the CMH weighted estimates.

Proportion of patients with absence of intra-retinal fluid (IRF) over time

[redacted]

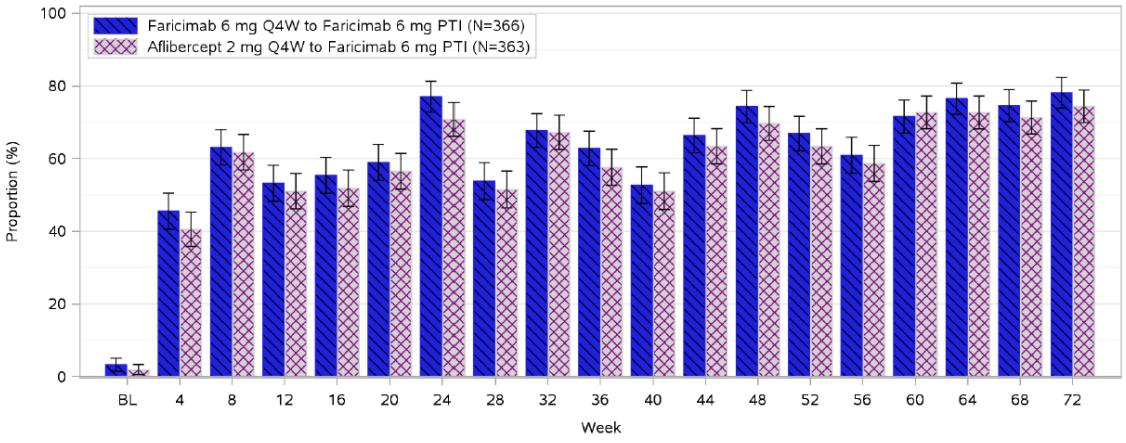
15 [redacted] *16*.

Figure 15: Proportion of patients with absence of IRF in the study eye over time through Week 72: CMH method, ITT population [BALATON]



CMH = Cochran-Mantel-Haenszel; BCVA = Best Corrected Visual Acuity; LOCF= Last Observation Carried Forward; The proportion is the weighted estimate based on CMH weights stratified by baseline BCVA score (<=54 letters vs. >=55 letters) and region (U.S. and Canada vs. Asia vs. the rest of the world). All observed values are used regardless of the occurrence of intercurrent events. Missing assessments were imputed by LOCF. Invalid BCVA values are excluded from analysis. Baseline is defined as the last available measurement obtained on or prior to randomization. Intraretinal fluid is as measured in the central subfield (center 1 mm). Error bars represent the 95.03% confidence interval for the CMH weighted estimates.

Figure 16: Proportion of patients with absence of IRF in the study eye over time through Week 72: CMH method, ITT population [COMINO]



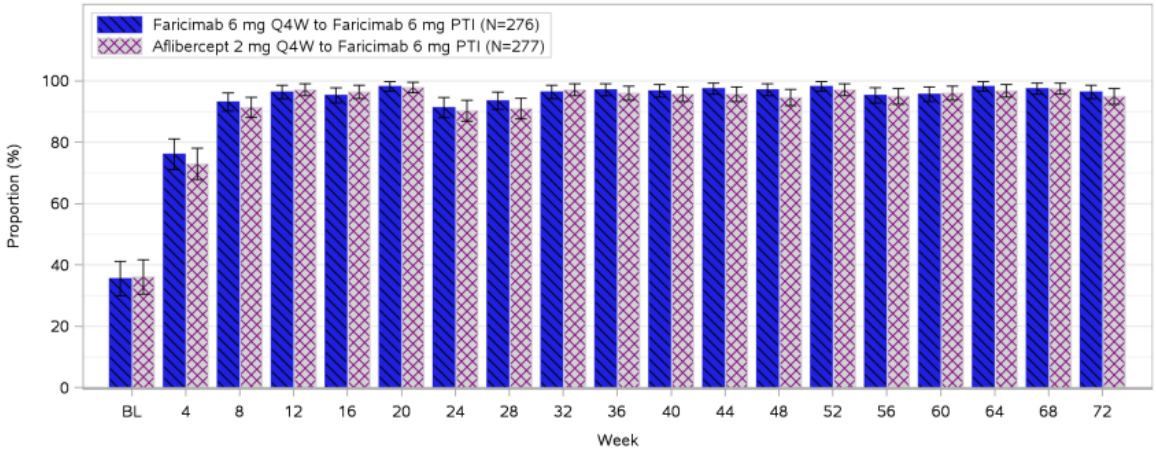
CMH = Cochran-Mantel-Haenszel; BCVA = Best Corrected Visual Acuity; LOCF= Last Observation Carried Forward; The proportion is the weighted estimate based on CMH weights stratified by baseline BCVA score (<=34 letters, 35-54 letters, and >=55 letters) and region (U.S. and Canada vs. Asia vs. the rest of the world). All observed values are used regardless of the occurrence of intercurrent events. Missing assessments were imputed by LOCF. Invalid BCVA values are excluded from analysis. Baseline is defined as the last available measurement obtained on or prior to randomization. Intraretinal fluid is as measured in the central subfield (center 1 mm). Error bars represent the 95.03% confidence interval for the CMH weighted estimates.

Proportion of patients with absence of sub-retinal fluid (SRF) over time

[redacted]

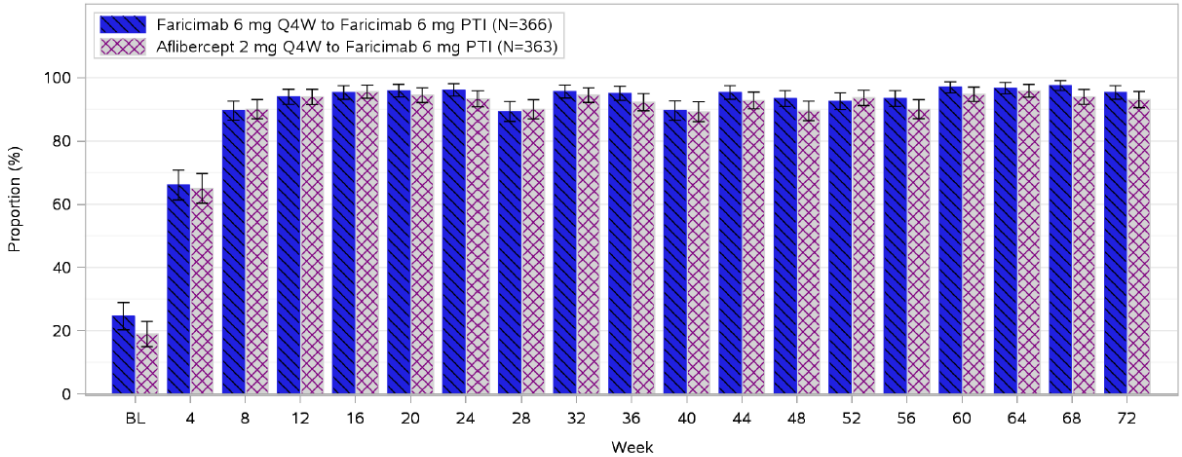
17

Figure 17: Proportion of patients with absence of SRF in the study eye over time through Week 72: CMH method, ITT population [BALATON]



CMH = Cochran-Mantel-Haenszel; BCVA = Best Corrected Visual Acuity; LOCF= Last Observation Carried Forward.
The proportion is the weighted estimate based on CMH weights stratified by baseline BCVA score (<=54 letters vs. >=55 letters) and region (U.S. and Canada vs. Asia vs. the rest of the world). All observed values are used regardless of the occurrence of intercurrent events. Missing assessments were imputed by LOCF. Invalid BCVA values are excluded from analysis. Baseline is defined as the last available measurement obtained on or prior to randomization. Subretinal fluid is as measured in the central subfield (center 1 mm). Error bars represent the 95.03% confidence interval for the CMH weighted estimates.

Figure 18: Proportion of patients with absence of SRF in the study eye over time through Week 72: CMH method, ITT population [COMINO]



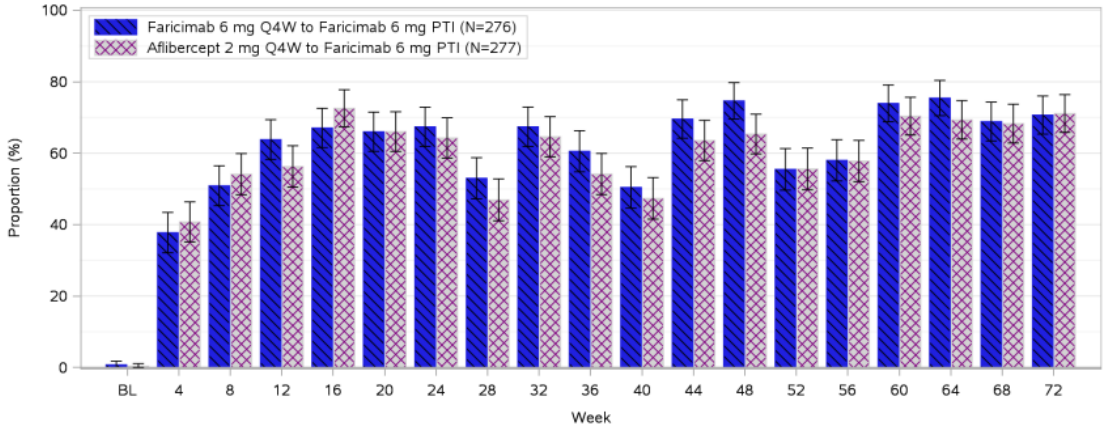
CMH = Cochran-Mantel-Haenszel; BCVA = Best Corrected Visual Acuity; LOCF= Last Observation Carried Forward.
The proportion is the weighted estimate based on CMH weights stratified by baseline BCVA score (<=34 letters, 35-54 letters, and >=55 letters) and region (U.S. and Canada vs. Asia vs. the rest of the world). All observed values are used regardless of the occurrence of intercurrent events. Missing assessments were imputed by LOCF. Invalid BCVA values are excluded from analysis. Baseline is defined as the last available measurement obtained on or prior to randomization. Subretinal fluid is as measured in the central subfield (center 1 mm). Error bars represent the 95.03% confidence interval for the CMH weighted estimates.

Proportion of patients with absence of both IRF and SRF over time

[redacted]

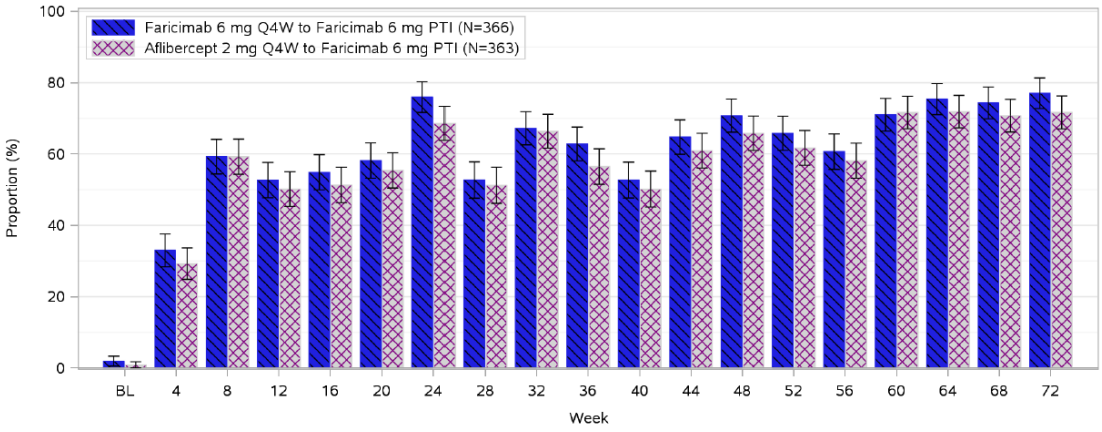
19[redacted] 20[redacted]

Figure 19: Proportion of patients with absence of IRF and SRF in the study eye over time through Week 72: CMH method, ITT population [BALATON]



CMH = Cochran-Mantel-Haenszel; BCVA = Best Corrected Visual Acuity; LOCF= Last Observation Carried Forward.
The proportion is the weighted estimate based on CMH weights stratified by baseline BCVA score (<=54 letters vs. >=55 letters) and region (U.S. and Canada vs. Asia vs. the rest of the world). All observed values are used regardless of the occurrence of intercurrent events. Missing assessments were imputed by LOCF. Baseline is defined as the last available measurement obtained on or prior to randomization. Intraretinal fluid and subretinal fluid is as measured in the central subfield (center 1 mm). Error bars represent the 95.03% confidence interval for the CMH weighted estimates.

Figure 20: Proportion of patients with absence of IRF and SRF in the study eye over time through Week 72: CMH method, ITT population [COMINO]



CMH = Cochran-Mantel-Haenszel; BCVA = Best Corrected Visual Acuity; LOCF= Last Observation Carried Forward.
The proportion is the weighted estimate based on CMH weights stratified by baseline BCVA score (<=34 letters, 35-54 letters, and >=55 letters) and region (U.S. and Canada vs. Asia vs. the rest of the world). All observed values are used regardless of the occurrence of intercurrent events. Missing assessments were imputed by LOCF. Baseline is defined as the last available measurement obtained on or prior to randomization. Intraretinal fluid and subretinal fluid is as measured in the central subfield (center 1 mm). Error bars represent the 95.03% confidence interval for the CMH weighted estimates.

Proportion of patients with absence of macular leakage on FFA over time

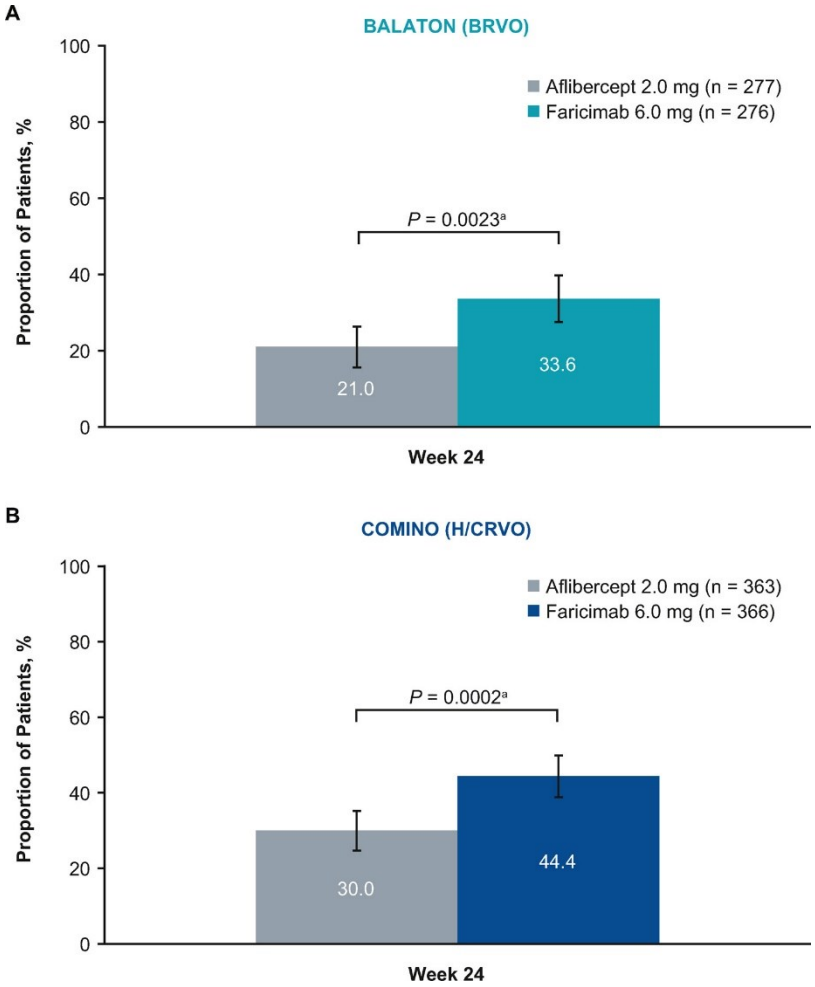
Week 24

At baseline in BALATON, 264/276 and 258/277 patients in the faricimab Q4W and aflibercept Q4W arms, respectively, had fundus fluorescein angiography (FFA) images of sufficient quality for macular leakage grading. Of these patients, there were no patients in the faricimab Q4W arm and two patients (0.8%) in the aflibercept Q4W arm with absence of macular leakage on FFA. At Week 24, 229/276 and 224/277 patients in the faricimab Q4W and aflibercept Q4W arms, respectively, had FFA images of sufficient quality for macular leakage grading. Of these patients, the proportion of patients with an absence of macular leakage increased in a greater percentage of patients treated with faricimab Q4W as compared with patients treated with aflibercept Q4W. At Week 24, 33.6% (77/229) and 21.0% (47/224) of patients had an absence of macular leakage in the faricimab Q4W and aflibercept Q4W arms, respectively.

At baseline in COMINO, 343/366 and 344/363 patients in the faricimab Q4W and aflibercept Q4W arms, respectively, had FFA images of sufficient quality for macular leakage grading. Of these patients, there were no patients in the faricimab Q4W arm and one patient (0.3%) in the aflibercept Q4W arm with absence of macular leakage on FFA. At Week 24, 311/366 and 297/363 patients in the faricimab Q4W and aflibercept Q4W arms, respectively, had FFA images of sufficient quality for macular leakage grading. Of these patients, the proportion of patients with an absence of macular leakage increased in a greater percentage of patients treated with faricimab Q4W as compared with patients treated with aflibercept Q4W. At Week 24, 44.4% (138/311) and 30.0% (89/297) of patients had an absence of macular leakage in the faricimab Q4W and aflibercept Q4W arms, respectively.

The proportion of patients achieving absence of macular leakage with faricimab vs. aflibercept at Week 24 for BALATON and COMINO is shown in Figure 21.

Figure 21: Proportion of patients achieving absence of macular leakage with faricimab vs. aflibercept at week 24 in BALATON (A) and COMINO (B)



Macular leakage area within ETDRS grid was assessed by the reading centres based on FA images obtained at baseline and predefined follow-up intervals. Absence was defined as area of leakage within the macula of 0 mm^2 per FA. The pre-specified exploratory analysis only included patients with evaluable FA data (BALATON: aflibercept, n = 224; faricimab, n = 229; COMINO: aflibercept, n = 297; faricimab, n = 311). All observed values were used regardless of the occurrence of the intercurrent events. Error bars represent 95.03% CIs. [a] Nominal P *values are based on the risk difference test (Wald method) and are not adjusted for multiplicity. No formal statistical conclusions should be made based on the* P *values. BRVO = branch retinal vein occlusion; CI = confidence interval; CRVO = central retinal vein occlusion; ETDRS = Early Treatment Diabetic Retinopathy Study; FA = fluorescein angiography; HRVO = hemiretinal vein occlusion. Source: 'Efficacy and Safety of Faricimab for Macular Oedema due to Retinal Vein Occlusion: 24-Week Results from the BALATON and COMINO Trials' (60).*

Week 72

At baseline in BALATON, [redacted] and [redacted] patients in the faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arms, respectively, had FFA images of sufficient quality for macular leakage grading. Of these patients, there were [redacted] in the faricimab Q4W to faricimab PTI arm and [redacted] in the aflibercept Q4W to faricimab PTI arm with absence of macular leakage on FFA. At Week 72, [redacted] and [redacted] patients in the faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arms, respectively, had

FFA images of sufficient quality for macular leakage grading. Of these, the proportion of patients with an absence of macular leakage was [redacted] in the faricimab Q4W to faricimab PTI arm and [redacted] in the aflibercept Q4W to faricimab PTI arm.

At baseline in COMINO, [redacted] and [redacted] patients in the faricimab Q4W and aflibercept Q4W arms, respectively, had FFA images of sufficient quality for macular leakage grading. Of these patients, there were [redacted] in the faricimab Q4W arm and [redacted] in the aflibercept Q4W arm with absence of macular leakage on FFA. At Week 72, [redacted] and [redacted] patients in the faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arms, respectively, had FFA images of sufficient quality for macular leakage grading. Of these, the proportion of patients with an absence of macular leakage was [redacted] in the faricimab Q4W to faricimab PTI arm and [redacted] in the aflibercept Q4W to faricimab PTI arm.

B.3.6.5 Patient-reported outcomes

Change from baseline in NEI VFQ-25 composite score over time through Week 72

In BALATON, at baseline, the mean NEI VFQ-25 composite scores were [redacted] and [redacted] points out of a maximum score of 100 for the faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arms, respectively. Patients treated with faricimab Q4W had comparable adjusted mean changes from baseline in the NEI VFQ-25 composite score at Week 24 compared with patients treated with aflibercept Q4W, [redacted]. At Week 72, adjusted mean changes from baseline in the NEI VFQ-25 composite score were [redacted] and [redacted] in the faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arms, respectively.

In COMINO, at baseline, the mean NEI VFQ-25 composite scores were [redacted] and [redacted] points out of a maximum score of 100 for the faricimab Q4W and aflibercept Q4W arms, respectively. Patients treated with faricimab Q4W had comparable adjusted mean changes from baseline in the NEI VFQ-25 composite score at Week 24 compared with patients treated with aflibercept Q4W, [redacted]. At Week 72, adjusted mean changes from baseline in the NEI VFQ-25 composite score were [redacted] and [redacted] in the faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arms, respectively.

B.3.7 Subgroup analysis

A summary of the results for the subgroups is provided in Appendix F.

B.3.8 Meta-analysis

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

B.3.9 Indirect and mixed treatment comparisons

See Appendix D for full details of the methodology for the indirect comparison or mixed treatment comparison, feasibility assessment and network meta-analysis.

B.3.10 Adverse reactions

Safety finding from Part 2 of the BALATON and COMINO studies (Week 24 through Week 72) are provided below. Please refer to Appendix H for safety findings from Part 1 of the studies (baseline through Week 24).

B.3.10.1 Treatment duration and exposure

Study Part 2 (Week 24 through Week 72)

In the BALATON and COMINO trials, patients treated with faricimab Q4W to faricimab PTI had median exposure durations of [redacted], whereas those in the aflibercept Q4W to faricimab PTI arms had exposure durations ranging from [redacted] (BALATON) to [redacted] weeks (COMINO) (Table 15). [redacted] (BALATON: [redacted] and [redacted]; COMINO: [redacted] and [redacted] in the faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arms, respectively), [redacted] (Table 15). Treatment interruptions were reported in approximately [redacted] (BALATON) and from [redacted] (COMINO, aflibercept Q4W to faricimab PTI) to [redacted] (COMINO, faricimab Q4W to faricimab PTI) of patients across both trials. In BALATON, a total of [redacted] and [redacted] of patients received at least one anti-VEGF administration in the fellow eye in the faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arms, respectively, [redacted] (Table 15). In COMINO, a total of [redacted] and [redacted] received at least one anti-VEGF administration in the fellow eye in the faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arms, respectively, [redacted] (Table 15).

Table 15: Summary of study treatment exposure in the study eye in study Part 2 (Week 24 through Week 72), safety-evaluable population

	BALATON		COMINO	
	Faricimab (6 mg) Q4W Part 1 to Faricimab (6 mg) PTI Part 2 (N=270)	Aflibercept (2 mg Q4W) to Faricimab 6 mg PTI Part 2 (N=267)	Faricimab (6 mg Q4W) Part 1 to Faricimab (6 mg PTI) Part 2 (N=359)	Aflibercept (2 mg Q4W) Part 1 to Faricimab (6 mg PTI) Part 2 (N=342)
Treatment duration (weeks)				
n	265	267	354	342
Mean (SD)	42.3 (7.04)	37.8 (8.28)	42.3 (6.86)	38.6 (6.98)
Median	44.1	40.1	44.1	40.1
Min-max	0 - 46	0 - 46	3 - 46	0 - 46
Number of study drug administrations				
n	263	267	353	342
Mean (SD)	4.8 (2.64)	4.9 (2.79)	5.6 (3.02)	5.5 (2.93)
Median	4.0	4.0	5.0	4.0
Min-max	1 - 12	1 - 12	1 - 12	1 - 12
Study treatment interruption				
Number of study treatment interrupted	29	22	68	40
At least one interrupted treatment	16 (5.9%)	16 (6.0%)	44 (12.3%)	28 (8.2%)
BCVA decrease	2 (0.7%)	0	2 (0.6%)	0
Elevated intraocular pressure	0	1 (0.4%)	1 (0.3%)	3 (0.9%)
Rhegmatogenous retinal break	1 (0.4%)	0	0	0
Active or suspected infection	2 (0.7%)	0	3 (0.8%)	3 (0.9%)
Cataract surgery in the study eye	1 (0.4%)	2 (0.7%)	3 (0.8%)	3 (0.9%)
Vitrectomy	1 (0.4%)	0	1 (0.3%)	0
Intraocular surgery in study eye	1 (0.4%)	0	1 (0.3%)	1 (0.3%)

Intraocular inflammation	NR	NR	8 (2.2%)	3 (0.9%)
On-study prohibited medications	NR	NR	0	1 (0.3%)
Other	11 (4.1%)	15 (5.6%)	31 (8.6%)	20 (5.8%)
Interruptions per patient				
n	16	16	44	28
1	12 (4.4%)	13 (4.9%)	33 (9.2%)	21 (6.1%)
2	1 (0.4%)	2 (0.7%)	5 (1.4%)	5 (1.5%)
3	1 (0.4%)	0	3 (0.8%)	0
4	1 (0.4%)	0	1 (0.3%)	1 (0.3%)
5	0	1 (0.4%)	0	1 (0.3%)
8	1 (0.4%)	0	2 (0.6%)	0

NR = not reported. Study drug corresponds to faricimab or aflibercept. Study treatment corresponds to faricimab, aflibercept or sham.

Part 2 treatment duration is the date of the last dose of study treatment or the date of the last treatment dose hold (whichever is later) minus, for the faricimab Q4W to faricimab PTI arm, Week 24 treatment or dose hold or if none Day 168 or, for the aflibercept Q4W to faricimab PTI arm, the date of the first faricimab dose, plus one day. Percentages are based on N in the column headings. The number of study drug administered may include any active drug administered including medication errors. The number of injections does not take into account the use of prohibited therapies. Active or suspected ocular infection are ocular.

B.3.10.2 Overview of safety profile

The safety data from study Part 1 (baseline through Week 24) indicated that faricimab Q4W had a comparable safety profile to aflibercept Q4W. Faricimab was generally well-tolerated as evidenced by the low incidence of AEs leading to study treatment withdrawal (Appendix H).

[redacted]

Key safety results from study Part 2 (Week 24 through Week 72) are presented in Table 16.

Table 16: Safety summary in study Part 2 (Week 24 through Week 72), safety-evaluable population

	BALATON		COMINO	
	Faricimab (6 mg Q4W) Part 1 to Faricimab (6 mg PTI) Part 2 (N=270)	Aflibercept (2 mg Q4W) Part 1 to Faricimab (6 mg PTI) Part 2 (N=267)	Faricimab (6 mg Q4W) Part 1 to Faricimab (6 mg PTI) Part 2 (N=359)	Aflibercept (2 mg Q4W) Part 1 to Faricimab (6 mg PTI) Part 2 (N=342)
Total number of patients with at least one AE	172 (63.7%)	167 (62.5%)	247 (68.8%)	227 (66.4%)
Total number of AEs	557	475	782	723
Total number of patients with at least one SAE	29 (10.7%)	26 (9.7%)	55 (15.3%)	51 (14.9%)
Total number of SAEs	42	32	79	84
Total number of deaths	1 (0.4%)	2 (0.7%)	4 (1.1%)	1 (0.3%)
Total number of patients withdrawn from study due to an AE	0	5 (1.9%)	9 (2.5%)	4 (1.2%)
Total number of patients withdrawn from study treatment due to an AE	0	4 (1.5%)	8 (2.2%)	6 (1.8%)
Total number of patients with at least one AESI	1 (0.4%)	1 (0.4%)	22 (6.1%)	9 (2.6%)
Ocular events: study eye total number of patients with at least one ocular event				
AE	76 (28.1%)	81 (30.3%)	130 (36.2%)	118 (34.5%)
SAE	4 (1.5%)	3 (1.1%)	26 (7.2%)	12 (3.5%)
AE leading to withdrawal from study treatment	0	1 (0.4%)	5 (1.4%)	3 (0.9%)
Treatment related AEs	7 (2.6%)	8 (3.0%)	14 (3.9%)	11 (3.2%)
Treatment related SAEs	0	0	4 (1.1%)	0
AE of Special Interest	1 (0.4%)	1 (0.4%)	21 (5.8%)	9 (2.6%)
Drop in VA score >=30	1 (0.4%)	1 (0.4%)	15 (4.2%)	7 (2.0%)
Associated with severe IOI	0	0	0	1 (0.3%)
Intervention req. to prevent permanent vision loss	0	0	6 (1.7%)	1 (0.3%)
Suspected transmission of infectious agent by study drug	0	0	0	0

Ocular events: fellow eye total number of patients with at least one ocular event				
AE	37 (13.7%)	30 (11.2%)	70 (19.5%)	51 (14.9%)
SAE	0	0	1 (0.3%)	0
AE of Special Interest	0	0	1 (0.3%)	0
Drop in VA score >=30	0	0	1 (0.3%)	0
Associated with severe IOI	0	0	0	0
Intervention req. to prevent permanent vision loss	0	0	0	0
Suspected transmission of infectious agent by study drug	0	0	0	0
Non-ocular events: total number of patients with at least one event				
AE	136 (50.4%)	126 (47.2%)	191 (53.2%)	174 (50.9%)
SAE	25 (9.3%)	23 (8.6%)	30 (8.4%)	41 (12.0%)
AE leading to withdrawal from study treatment	0	3 (1.1%)	3 (0.8%)	3 (0.9%)
AE of Special Interest	0	0	0	0
Elevated ALT or AST with either elevated bilirubin or clinical jaundice	0	0	0	0
Adjudicated APTC events	2 (0.7%)	8 (3.0%)	8 (2.2%)	6 (1.8%)
Non-fatal MI	1 (0.4%)	2 (0.7%)	3 (0.8%)	2 (0.6%)
Non-fatal Stroke	0	5 (1.9%)	3 (0.8%)	3 (0.9%)
Death	1 (0.4%)	2 (0.7%)	2 (0.6%)	1 (0.3%)

AESI = Adverse Event of Special Interest; APTC = Antiplatelet Trialists' Collaboration; IOI = Intraocular Inflammation; MedDRA = Medical Dictionary for Regulatory Activities; SAE = Serious Adverse Event; VA = Visual Acuity; AE = Adverse Event; MI = Myocardial Infarction.
Part 2, for faricimab Q4W to faricimab PTI arm, includes AEs with onset on or after the Week 24 treatment or dose hold or if none onset on or after Day 168 through Week 72, or for the aflibercept Q4W to faricimab PTI arm, includes AEs with an onset on or after the date of the first faricimab dose through Week 72.
APTC events are defined as non-fatal strokes or non-fatal myocardial infarctions or vascular deaths (including deaths of unknown cause). Investigator text for AEs encoded using MedDRA version 26.0.
Drop in VA score >=30 is defined as causing a decrease of >=30 VA score lasting more than 1 hour.
Intervention req. to prevent permanent vision loss is defined as required surgical or medical intervention to prevent permanent loss of sight.
Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once except for the "Total number of AEs" row in which multiple occurrences of the same AE are counted separately.

B.3.10.2.1 Intercurrent events through Week 72

In BALATON through Week 72, [redacted] in the faricimab Q4W to faricimab PTI arm and [redacted] in the aflibercept Q4W to faricimab PTI arm experienced at least one intercurrent event (Table 17). Of these, [redacted] in faricimab Q4W to faricimab PTI arm and [redacted] in the aflibercept Q4W to faricimab PTI arm experienced [redacted] in the faricimab Q4W to faricimab PTI arm and [redacted] in the aflibercept Q4W to faricimab PTI arm received prohibited systemic treatment or prohibited therapy in the study eye.

In COMINO through Week 72, [redacted] in the faricimab Q4W to faricimab PTI arm and [redacted] in the aflibercept Q4W to faricimab PTI arm experienced at least one intercurrent event (Table 17). Of these, [redacted] in faricimab Q4W to faricimab PTI arm and [redacted] in the aflibercept Q4W to faricimab PTI arm experienced [redacted]. Of note, none of these patients discontinued study treatment due to lack of efficacy. [redacted] in the faricimab Q4W to faricimab PTI and [redacted] in the aflibercept Q4W to faricimab PTI arm received prohibited systemic treatment or prohibited therapy in the study eye.

Table 17: Summary of Intercurrent events in study Part 2 (Week 24 through Week 72), ITT population

	BALATON		COMINO	
	Faricimab 6 mg Q4W to Faricimab 6 mg PTI (N=276)	**Aflibercept 2mg Q4W to Faricimab 6 mg PTI (N=277)**	**Faricimab 6 mg Q4W to Faricimab 6 mg PTI (N=366)**	**Aflibercept 2mg Q4W to Faricimab 6 mg PTI (N=363)**
Patients with at least one type of intercurrent event*	5 (1.8%)	10 (3.6%)	19 (5.2%)	16 (4.4%)
Patients who discontinued study treatment due to AEs or lack of efficacy**	3 (1.1%)	4 (1.4%)	11 (3.0%)	10 (2.8%)
Patients who received any prohibited systemic treatment or prohibited therapy in the study eye***	2 (0.7%)	8 (2.9%)	9 (2.5%)	6 (1.7%)

VEGF = Vascular Endothelial Growth Factor.
Percentages are based on N, % in the column headings.
**Includes events occurring on or prior to Day 524 (last day of Week 72 analysis visit window).*
***Discontinuation due to AE includes any adverse event that leads to discontinuation of study treatment or any AE with an action taken of 'drug withdrawn'. Lack of efficacy was determined by investigator judgment, with the terms lack of efficacy, progressive disease, disease relapse, or symptomatic deterioration qualifying as lack of efficacy.*

****Prohibited therapy is concurrent use of any systemic anti-VEGF agents or any protocol defined prohibited study eye therapy.*

B.3.10.3 Ocular AEs in the study eye

B.3.10.3.1 Common ocular adverse events in the study eye

Study Part 2 (Week 24 through Week 72)

In BALATON, a total of [redacted] and [redacted] experienced at least one ocular AE in the study eye in the faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arms, respectively. [redacted] (Table 18). [redacted].

In COMINO, a total of [redacted] and [redacted] experienced at least one ocular AE in the study eye in the faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arms, respectively. [redacted]

Table 18: Common ocular adverse events (≥ 1% in any treatment arm) in the study eye in study Part 2 (Week 24 through Week 72), safety-evaluable population

	BALATON		COMINO	
	Faricimab (6 mg Q4W) to Faricimab (6 mg PTI) Part 2 (N=270)	Aflibercept (2 mg Q4W) to Faricimab (6 mg PTI) Part 2 (N=267)	Faricimab (6 mg Q4W) to Faricimab (6 mg PTI) Part 2 (N=359)	Aflibercept (2 mg Q4W) to Faricimab (6 mg PTI) Part 2 (N=342)
Total number of patients with at least one adverse event	76 (28.1%)	81 (30.3%)	130 (36.2%)	118 (34.5%)
Total number of events	151	126	219	236
Conjunctival haemorrhage	11 (4.1%)	10 (3.7%)	10 (2.8%)	7 (2.0%)
Intraocular pressure increased	13 (4.8%)	8 (3.0%)	17 (4.7%)	15 (4.4%)
Cataract	9 (3.3%)	10 (3.7%)	14 (3.9%)	15 (4.4%)
Vitreous detachment	7 (2.6%)	9 (3.4%)	6 (1.7%)	14 (4.1%)
Vitreous floaters	0	9 (3.4%)	1 (0.3%)	7 (2.0%)
Dry eye	4 (1.5%)	4 (1.5%)	8 (2.2%)	3 (0.9%)
Retinal vein occlusion	9 (3.3%)	8 (3.0%)	11 (3.1%)	8 (2.3%)
Macular oedema	10 (3.7%)	5 (1.9%)	10 (2.8%)	14 (4.1%)
Epiretinal membrane	2 (0.7%)	7 (2.6%)	4 (1.1%)	11 (3.2%)
Eye pain	3 (1.1%)	0	7 (1.9%)	2 (0.6%)
Retinal haemorrhage	2 (0.7%)	5 (1.9%)	NR	NR
Cystoid macular oedema	4 (1.5%)	2 (0.7%)	17 (4.7%)	10 (2.9%)
Retinal ischaemia	2 (0.7%)	3 (1.1%)	NR	NR
Visual acuity reduced	4 (1.5%)	1 (0.4%)	4 (1.1%)	1 (0.3%)
Conjunctivitis allergic	3 (1.1%)	0	5 (1.4%)	3 (0.9%)
Retinal cyst	4 (1.5%)	0	NR	NR
Glaucoma	3 (1.1%)	0	5 (1.4%)	10 (2.9%)
Ocular hypertension	NR	NR	3 (0.8%)	6 (1.8%)
Iridocyclitis	NR	NR	3 (0.8%)	4 (1.2%)
Vitritis	NR	NR	4 (1.1%)	0
Medication error	NR	NR	0	4 (1.2%)

NR = not reported. Investigator text for AEs encoded using MedDRA version 26.0. Percentages are based on N in the column headings.

For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

B.3.10.3.2 Serious ocular AEs in the study eye

Study Part 2 (Week 24 through Week 72)

In BALATON, [redacted] (Table 19). In COMINO, serious ocular AEs occurred in [redacted] and [redacted] in the faricimab Q4W to faricimab PTI arm and the aflibercept Q4W to faricimab PTI arm, respectively. [redacted] (Table 19).

Table 19: Serious ocular adverse events by preferred terms in the study eye in study Part 2 (Week 24 through Week 72), safety-evaluable population

	BALATON		COMINO	
	Faricimab (6 mg Q4W) to Faricimab (6 mg PTI) Part 2 (N=270)	Aflibercept(2 mg Q4W) to Faricimab (6 mg PTI) Part 2 (N=267)	Faricimab (6 mg Q4W) to Faricimab (6 mg PTI) Part 2 (N=359)	Aflibercept (2 mg Q4W) to Faricimab (6 mg PTI) Part 2 (N=342)
Total number of patients with at least one AE	4 (1.5%)	3 (1.1%)	26 (7.2%)	12 (3.5%)
Total number of events	5	3	28	12
Retinal ischaemia	0	2 (0.7%)	1 (0.3%)	0
Retinal vein occlusion	0	0	5 (1.4%)	3 (0.9%)
Cataract	0	1 (0.4%)	0	1 (0.3%)
Macular ischaemia	1 (0.4%)	0	1 (0.3%)	0
Macular oedema	1 (0.4%)	0	3 (0.8%)	0
Retinal neovascularisation	1 (0.4%)	0	1 (0.3%)	1 (0.3%)
Rhegmatogenous retinal detachment	1 (0.4%)	0	0	0
Tractional retinal detachment	1 (0.4%)	0	NR	NR
Vitreous haemorrhage	0	0	1 (0.3%)	0
Cystoid macular oedema	NR	NR	5 (1.4%)	1 (0.3%)
Retinal artery occlusion	NR	NR	0	2 (0.6%)
Retinal tear	NR	NR	1 (0.3%)	0
Uveitis	NR	NR	1 (0.3%)	0
Macular hole	NR	NR	1 (0.3%)	1 (0.3%)
Endophthalmitis	NR	NR	0	1 (0.3%)
Retinal artery embolism	NR	NR	1 (0.3%)	0
Glaucoma	NR	NR	0	1 (0.3%)
Iris neovascularisation	NR	NR	0	1 (0.3%)
Epiretinal membrane	NR	NR	1 (0.3%)	0
Iridocyclitis	NR	NR	1 (0.3%)	0
Posterior capsule opacification	NR	NR	1 (0.3%)	0
Retinal detachment	NR	NR	1 (0.3%)	0
Visual acuity reduced	NR	NR	1 (0.3%)	0
Vitritis	NR	NR	1 (0.3%)	0
Intraocular pressure increased	NR	NR	0	0
Non-infectious endophthalmitis	NR	NR	0	0
Eye injury	NR	NR	0	0

NR = not reported. Investigator text for AEs encoded using MedDRA version 26.0. Percentages are based on N in the column headings. For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

B.3.10.4 Adverse events of special interest (AESIs) and selected AEs

A summary of AESIs and selected AEs from study Part 2 are presented in Table 20.

Table 20: Adverse events of special interest in the study eye in study Part 2 (Week 24 through Week 72), safety-evaluable population

	BALATON		COMINO	
	Faricimab (6 mg Q4W) to Faricimab (6 mg PTI) Part 2 (N=270)	Aflibercept (2 mg Q4W) to Faricimab (6 mg PTI) Part 2 (N=267)	Faricimab (6 mg Q4W) to Faricimab (6 mg PTI) Part 2 (N=351)	Aflibercept (2 mg Q4W) to Faricimab (6 mg PTI) Part 2 (N=342)
Total number of patients with at least one AE	1 (0.4%)	1 (0.4%)	21 (5.8%)	9 (2.6%)
Overall total number of events	1	1	22	9
Causes a decrease of >=30 letters in VA score lasting more than 1 hour				
Total number of patients with at least one AE	1 (0.4%)	1 (0.4%)	15 (4.2%)	7 (2.0%)
Total number of events	1	1	16	7
Retinal vein occlusion	0	0	4 (1.1%)	3 (0.9%)
Cataract	0	1 (0.4%)	0	1 (0.3%)
Macular oedema	1 (0.4%)	0	3 (0.8%)	0
Vitreous haemorrhage	0	0	NR	NR
Cystoid macular oedema	NR	NR	5 (1.4%)	1 (0.3%)
Retinal artery occlusion	NR	NR	0	2 (0.6%)
Macular ischaemia	NR	NR	1 (0.3%)	0
Cataract	NR	NR	0	1 (0.3%)
Endophthalmitis	NR	NR	0	0
Posterior capsule opacification	NR	NR	1 (0.3%)	0
Visual acuity reduced	NR	NR	1 (0.3%)	0
Requires surgical or medical intervention to prevent permanent loss of sight				

Total number of patients with at least one AE	NR	NR	6 (1.7%)	1 (0.3%)
Total number of events	NR	NR	6	1
Retinal tear	NR	NR	1 (0.3%)	0
Macular hole	NR	NR	1 (0.3%)	1 (0.3%)
Epiretinal membrane	NR	NR	1 (0.3%)	0
Eye injury	NR	NR	0	0
Intraocular pressure increased	NR	NR	0	0
Non-infectious endophthalmitis	NR	NR	0	0
Retinal artery embolism	NR	NR	0	0
Retinal detachment	NR	NR	1 (0.3%)	0
Retinal ischaemia	NR	NR	0	0
Retinal neovascularisation	NR	NR	1 (0.3%)	0
Rhegmatogenous retinal detachment	NR	NR	0	0
Vitritis	NR	NR	1 (0.3%)	0
Associated with severe intraocular inflammation				
Total number of patients with at least one AE	NR	NR	0	1 (0.3%)
Total number of events	NR	NR	0	1
Endophthalmitis	NR	NR	0	1 (0.3%)

AE = Adverse Event; MedDRA = Medical Dictionary for Regulatory Activities; NR = Not Reported; VA = Visual Acuity.
Investigator text for AEs encoded using MedDRA version 26.0. AESI's that qualify under multiple categories are counted in each category. Percentages are based on N in the column headings.
Part 2, for faricimab Q4W to faricimab PTI arm, includes AEs with onset on or after the Week 24 treatment or dose hold or if none onset on or after Day 168 through Week 72, or for the aflibercept Q4W to faricimab PTI arm, includes AEs with an onset on or after the date of the first faricimab dose through Week 72.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

B.3.10.4.1 Intraocular inflammation

Study Part 2 (Week 24 through Week 72)

In BALATON, the incidence of IOI events occurring in the study eye [redacted] (Table 21). All IOI events were [redacted]

In COMINO, the majority of IOI events were mild and moderate in severity (Table 21). There were no severe IOI reported. IOI events in the study eye occurred in [redacted] in the faricimab Q4W to faricimab PTI arm and [redacted] in the aflibercept Q4W to faricimab PTI arms. [redacted]

Table 21: Adverse events of intraocular inflammation (IOI) in the study eye in study Part 2 (Week 24 through Week 72), safety-evaluable population

	BALATON		COMINO	
	Faricimab 6 mg Q4W to Faricimab 6 mg PTI Part 2 (N=270)	**Aflibercept 2 mg Q4W to Faricimab 6 mg PTI Part 2 (N=267)**	**Faricimab 6 mg Q4W to Faricimab 6 mg PTI Part 2 (N=359)**	**Aflibercept 2 mg Q4W to Faricimab 6 mg PTI Part 2 (N=342)**
Total number of patients with at least one AE	2 (0.7%)	3 (1.1%)	10 (2.8%)	5 (1.5%)
Total number of events	2	3	13	5
Iritis	0	2 (0.7%)	3 (0.8%)	1 (0.3%)
Iridocyclitis	1 (0.4%)	1 (0.4%)	3 (0.8%)	4 (1.2%)
Vitritis	1 (0.4%)	0	4 (1.1%)	0
Uveitis	NR	NR	1 (0.3%)	0
Non-infectious endophthalmitis	NR	NR	1 (0.3%)	0
Keratic precipitates	NR	NR	1 (0.3%)	0

AE = Adverse Event; MedDRA = Medical Dictionary for Regulatory Activities; NR= Not Reported.
Intraocular Inflammation events include anterior chamber cell, anterior chamber flare, anterior chamber inflammation, chorioretinitis, choroiditis, cyclitis, eye inflammation, iridocyclitis, iritis, keratic precipitates, keratouveitis, non-infective chorioretinitis, non-infectious endophthalmitis, ocular vasculitis, post procedural inflammation, retinal occlusive vasculitis, retinal vasculitis, haemorrhagic occlusive retinal vasculitis, uveitis, vitritis, and vitreal cells.
Investigator text for AEs encoded using MedDRA version 26.0. Percentages are based on N in the column headings. Part 2, for faricimab Q4W to faricimab PTI arm, includes AEs with onset on or after the Week 24 treatment or dose hold or if none onset on or after Day 168 through Week 72, or for the aflibercept Q4W to faricimab PTI arm, includes AEs with an onset on or after the date of the first faricimab dose through Week 72.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

B.3.10.4.2 Retinal vascular occlusive disease

Study Part 2 (Week 24 through Week 72)

In BALATON, [redacted] and [redacted] experienced an event of retinal vascular occlusive disease in the study eye in the faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arms, respectively (Table 22). [redacted] and [redacted] experienced an RVO event in the faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arms, respectively; [redacted]

In COMINO, [redacted] and [redacted] experienced an event of retinal vascular occlusive disease (defined as either RVO, RAO, or retinal artery embolism) in the study eye in the faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arms, respectively (Table 22). [redacted] and [redacted] experienced an RVO event in the faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arms, respectively; [redacted]

Table 22: Adverse events of retinal vascular occlusive disease in the study eye in study Part 2 (Week 24 through Week 72), safety-evaluable population

	BALATON		COMINO	
	Faricimab 6 mg Q4W to Faricimab 6 mg PTI Part 2 (N=270)	Aflibercept 2 mg Q4W to Faricimab 6 mg PTI Part 2 (N=267)	Faricimab 6 mg Q4W to Faricimab 6 mg PTI Part 2 (N=359)	Aflibercept 2 mg Q4W to Faricimab 6 mg PTI Part 2 (N=342)
Total number of patients with at least one AE (RVO and/or RAO)	10 (3.7%)	9 (3.4%)	13 (3.6%)	10 (2.9%)
Overall total number of events	13	11	14	10
RVO events				
Total number of patients with at least one AE	9 (3.3%)	9 (3.4%)	11 (3.1%)	8 (2.3%)
Total number of events	12	11	11	8
Retinal vein occlusion	9 (3.3%)	8 (3.0%)	11 (3.1%)	8 (2.3%)
Venous occlusion	0	1 (0.4%)	NR	NR
RAO events				
Total number of patients with at least one AE	1 (0.4%)	0	2 (0.6%)	2 (0.6%)
Total number of events	1	0	3	2
Retinal artery embolism	1 (0.4%)	0	1 (0.3%)	0
Retinal artery occlusion	NR	NR	2 (0.6%)	2 (0.6%)
Number of patients with at least one adverse event (RVO and/or RAO) and available BCVA				
n	10	9	13	10
Associated with vision loss >=15 letters*	0	0	5 (38.5%)	2 (20.0%)
Associated with vision loss >=30 letters*	0	0	3 (23.1%)	1 (10.0%)
Number of patients with RAO events and available BCVA				
n	1	0	2	2
Associated with vision loss >=15 letters*	0	0	1 (50.0%)	1 (50.0%)
Associated with vision loss >=30 letters*	0	0	1 (50.0%)	1 (50.0%)
n	9	9	11	8
Associated with vision loss >=15 letters*	0	0	4 (36.4%)	1 (12.5%)
Associated with vision loss >=30 letters*	0	0	2 (18.2%)	0

AE = Adverse Event; MedDRA = Medical Dictionary for Regulatory Activities; NR= Not reported.
**For Part 2 percentages are calculated using the number of patients with the event and BCVA after event onset as the denominator.*
Vision loss is calculated: For Part 2 as the difference in BCVA between the closest BCVA recorded before the event onset date and last available BCVA after event onset. If a patient had several events, vision loss is calculated based on BCVA before first IOI onset and last available BCVA after event onset.
Part 2, for faricimab Q4W to faricimab PTI arm, includes AEs with onset on or after the Week 24 treatment or dose hold or if none onset on or after Day 168 through Week 72, or for the aflibercept Q4W to faricimab PTI arm, includes AEs with an onset on or after the date of the first faricimab dose through Week 72.
RVO events include retinal vein occlusion, venous occlusion, retinal vein thrombosis, and retinal vascular thrombosis. RAO events include arterial occlusive disease, retinal artery embolism, and retinal artery occlusion. Retinal vascular occlusive events include RVO and RAO events.

B.3.10.4.3 Adjudicated Antiplatelet Trialists' Collaboration (APTC) events

Study Part 2 (Week 24 through Week 72)

In BALATON, [redacted]

23 [redacted]

In COMINO, the incidence of externally adjudicated APTC-defined [redacted]) in the faricimab Q4W to faricimab PTI and the aflibercept Q4W to faricimab PTI arm, respectively (Table 23). [redacted]

Table 23: Adjudicated APTC-defined adverse events in the study eye in study Part 2 (Week 24 through Week 72), safety-evaluable population

	BALATON		COMINO	
	Faricimab 6 mg Q4W to Faricimab 6 mg PTI Part 2 (N=270)	**Aflibercept 2 mg Q4W to Faricimab 6 mg PTI Part 2 (N=267)**	**Faricimab 6 mg Q4W to Faricimab 6 mg PTI Part 2 (N=359)**	**Aflibercept 2 mg Q4W to Faricimab 6 mg PTI Part 2 (N=342)**
Total number of patients with at least one AE	2 (0.7%)	8 (3.0%)	8 (2.2%)	6 (1.8%)
Overall total number of events	2	9	8	6
Non-fatal stroke				
Total number of patients with at least one AE	0	5 (1.9%)	3 (0.8%)	3 (0.9%)
Total number of events	0	5	3	3
Cerebral infarction	0	1 (0.4%)	NR	NR
Cerebrovascular accident	0	2 (0.7%)	0	0
Ischaemic stroke	NR	NR	1 (0.3%)	1 (0.3%)
Cerebral haematoma	0	1 (0.4%)	NR	NR
Cerebral thrombosis	0	1 (0.4%)	NR	NR
Retinal artery occlusion	NR	NR	2 (0.6%)	2 (0.6%)
Non-fatal MI				

Total number of patients with at least one AE	1 (0.4%)	2 (0.7%)	3 (0.8%)	2 (0.6%)
Total number of events	1	2	3	2
Acute myocardial infarction	0	1 (0.4%)	0	2 (0.6%)
Myocardial infarction	1 (0.4%)	1 (0.4%)	2 (0.6%)	0
Stress cardiomyopathy	NR	NR	1 (0.3%)	0
Death				
Total number of patients with at least one AE	1 (0.4%)	2 (0.7%)	2 (0.6%)	1 (0.3%)
Total number of events	1	2	2	1
Cerebrovascular accident	0	0	NR	NR
Coronary artery disease	0	1 (0.4%)	NR	NR
Aortic dissection	NR	NR	1 (0.3%)	0
Cardiac failure	NR	NR	0	1(0.3%)
Death	0	1 (0.4%)	1 (0.3%)	0
Myocardial infarction	1 (0.4%)	0	0	0

AE = Adverse Event; APTC = Antiplatelet Trialist's Collaboration; MI = Myocardial Infarction; MedDRA = Medical Dictionary for Regulatory Activities; NR = Not reported.
APTC events are defined as non-fatal strokes or non-fatal myocardial infarctions or vascular deaths (including deaths of unknown cause). If no events occurred for a certain category, the category are not presented. Investigator text for AEs encoded using MedDRA version 26.0. Percentages are based on N in the column headings. Part 2, for faricimab Q4W to faricimab PTI arm, includes AEs with onset on or after the Week 24 treatment or dose hold or if none onset on or after Day 168 through Week 72, or for the aflibercept Q4W to faricimab PTI arm, includes AEs with an onset on or after the date of the first faricimab dose through Week 72. For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

B.3.10.5 Non-ocular safety

B.3.10.5.1 Non-ocular adverse events

Study Part 2 (Week 24 through Week 72)

In BALATON, most of the non-ocular AEs that occurred from Week 24 until the first dose of faricimab were [redacted]

24 [redacted]

In COMINO, [redacted] and [redacted] experienced at least one non-ocular AE in the faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arms, respectively (Table 24). [redacted]

Table 24: Most common non-ocular AEs (≥ 2% in any treatment arm in Part 2) in study Part 2 (Week 24 through Week 72), safety-evaluable population

	BALATON		COMINO	
	Faricimab 6 mg Q4W to Faricimab 6 mg PTI Part 2 (N=270)	Aflibercept 2 mg Q4W to Faricimab 6 mg PTI Part 2 (N=267)	Faricimab 6 mg Q4W to Faricimab 6 mg PTI Part 2 (N=359)	Aflibercept 2 mg Q4W to Faricimab 6 mg PTI Part 2 (N=342)
Total number of patients with at least one AE	136 (50.4%)	126 (47.2%)	191 (53.2%)	174 (50.9%)
Total number of events	358	304	465	413
COVID-19	33 (12.2%)	25 (9.4%)	45 (12.5%)	46 (13.5%)
Hypertension	14 (5.2%)	8 (3.0%)	13 (3.6%)	8 (2.3%)
Nasopharyngitis	7 (2.6%)	10 (3.7%)	11 (3.1%)	16 (4.7%)
Upper respiratory tract infection	6 (2.2%)	9 (3.4%)	8 (2.2%)	8 (2.3%)
Fall	7 (2.6%)	5 (1.9%)	NR	NR
Hypercholesterolemia	6 (2.2%)	2 (0.7%)	NR	NR
Influenza	3 (1.1%)	6 (2.2%)	9 (2.5%)	10 (2.9%)
Back pain	NR	NR	10 (2.8%)	4 (1.2%)
Urinary tract infection	NR	NR	6 (1.7%)	8 (2.3%)
Arthralgia	NR	NR	9 (2.5%)	4 (1.2%)
Bronchitis	NR	NR	2 (0.6%)	7 (2.0%)

AE = Adverse Event; MedDRA = Medical Dictionary for Regulatory Activities; NR = Not reported.
Investigator text for AEs encoded using MedDRA version 26.0. Percentages are based on N in the column headings.
Part 2, for faricimab Q4W to faricimab PTI arm, includes AEs with onset on or after the Week 24 treatment or dose hold or if none onset on or after Day 168 through Week 72, or for the aflibercept Q4W to faricimab PTI arm, includes AEs with an onset on or after the date of the first faricimab dose through Week 72.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

B.3.10.6 Deaths

Study Part 2 (Week 24 through Week 72)

In BALATON, [redacted] (Table 25). [redacted]

In COMINO, [redacted] (Table 25). [redacted]

Table 25: Summary of patient deaths in study Part 2 (Week 24 through Week 72), safety-evaluable population

	BALATON		COMINO	
	Faricimab 6 mg Q4W to Faricimab 6 mg PTI (N=276)	Aflibercept 2 mg Q4W to Faricimab 6 mg PTI (N=274)	Faricimab 6 mg Q4W to Faricimab 6 mg PTI (N=365)	Aflibercept 2 mg Q4W to Faricimab 6 mg PTI (N=361)
Total number of deaths	2 (0.7%)	2 (0.7%)	5 (1.4%)	3 (0.8%)
Primary Cause of Death				
n	2	2	5	3
Cerebrovascular accident	1 (0.4%)	0	NR	NR
Coronary artery disease	0	1 (0.4%)	NR	NR
Death	0	1 (0.4%)	2 (0.5%)	0
Myocardial infarction	1 (0.4%)	0	0	2 (0.6%)
Aortic dissection	NR	NR	1 (0.3%)	0
Cardiac failure	NR	NR	0	1 (0.3%)
Pneumonia	NR	NR	1 (0.3%)	0

NR = Not Reported. Percentages for Total Number of Deaths are relative to total N. Include deaths that occur through the end of study.

B.3.11 Conclusions about comparable health benefits and safety

Despite the proven efficacy of anti-VEGF monotherapies for the treatment of RVO in controlled clinical trial settings, many patients fail to achieve and maintain similar outcomes in clinical practice (61-63). Furthermore, the frequent injections needed to maintain efficacy is a cause of stress and anxiety for patients (23), with the requirement for multiple clinic visits for treatment and/or monitoring to achieve optimal long-term outcomes resulting in a high burden for patients, caregivers, and healthcare professionals (12, 64-66). Therefore, there is a need for novel treatment options that can extend treatment intervals for longer, without compromising efficacy and safety.

Ang-2 and VEGF-A concentrations are elevated in RVO (16, 67) and both are key drivers of RVO, synergistically increasing vascular permeability and stimulating RVO neovascularisation (19, 20). Dual inhibition of these two distinct ligands, mediated through two distinct receptors (the VEG-F receptor and the Tie2 receptor), reduces vascular permeability and inflammation, inhibits pathological angiogenesis, and restores vascular stability. Faricimab is a first in class dual-pathway inhibitor of Ang-2 and VEGF, designed for ocular use (16). Faricimab's unique approach of targeting two very distinct and separate pathways is crucially different to the broad binding of existing anti-VEGF treatments to multiple members of the VEGF family of growth factors. This suggests faricimab will provide an effective and well-tolerated treatment option for patients with RVO which can be administered less frequently than current approved treatments, with comparable outcomes. Thereby, providing patients and the healthcare system with an opportunity to alleviate the substantial treatment burden associated with current anti-VEGF therapies and reducing overall costs, while improving independence for those living with RVO and their caregivers.

Treatment and dosing

The Phase III BALATON and COMINO trials were designed to primarily show non-inferiority of faricimab compared with aflibercept for the change in BCVA from baseline to Week 24 in the anti-VEGF treatment naïve ITT population. An additional objective was to assess the efficacy of faricimab to achieve dosing intervals up to Q16W (Weeks 24-72). Clinical experts concurred that the enrolled populations are reflective of patients seen in UK clinical practice (3).

To address heterogeneity of treatment response in RVO, BALATON and COMINO studies incorporated an innovative PTI dosing regimen based on the widely used T&E concept, which

allowed for incremental changes by 4 weeks up to a maximum of Q16W, with reductions by 4 weeks or back to a 4-week dosing interval if needed. The PTI design was informed by the DMO Phase 2 BOULEVARD trial (68), which demonstrated superior VA gains with faricimab compared to ranibizumab monotherapy at Week 24, and suggested that faricimab patients experienced greater durability of effect, with greater average times to disease reactivation in the off-treatment period.

The PTI design was validated in Phase III trials in nAMD patients (TENAYA and LUCERNE) (69, 70), and DMO patients (YOSEMITE and RHINE) (71, 72). These trials demonstrated that, compared to previous T&E regimens, PTI extensions of 4 weeks (compared to 2 weeks) and to a maximum Q16W interval (compared to Q12W) could help reduce the frequency of scheduled visits, with a reduced treatment burden helping to improve real-world outcomes.

Visual and anatomical outcomes

In both BALATON and COMINO, the pre-specified primary endpoint was met. These BCVA gains were maintained from Weeks 24–72, in both trials, when the faricimab PTI (Q4W up to Q16W) were investigated. This maintenance of vision was achieved with the extension of treatment intervals of up to Q16W; in BALATON, [redacted] of patients were on a dosing interval of ≥ 12 weeks and [redacted] > 16 weeks in the faricimab Q4W to faricimab PTI arm, and [redacted] ≥12 weeks and 47.5% of patients in the aflibercept Q4W to faricimab arm. In COMINO, [redacted] patients were on a dosing interval of ≥12 weeks and [redacted] on >16 weeks in the faricimab Q4W to faricimab PTI arm, and [redacted] on ≥12 weeks and [redacted] of patients in the aflibercept Q4W to faricimab arm.

Results from a Roche sponsored UK Medisoft study (47), showed that the percentage of BRVO patients achieving an average treatment interval of ≥Q12W with aflibercept was 6.47% and ≥Q16W, 1.89% 18 months after treatment initiation. With ranibizumab at 18 months, ≥Q12W, 9.48% and ≥Q16W, 3.05% (47). In CRVO patients, those achieving ≥Q12W with aflibercept was 7.24% and ≥Q16W, 1.36% and with ranibizumab, ≥Q12W, 6.83% and ≥Q16W, 1.40% (47). Even at 5 years post treatment, the percentage of individuals achieving ≥Q12W and ≥Q16W with either anti-VEGF, were still lower than that obtained with faricimab at 18 months.

The percentage of patients achieving Q4W to Q16W treatment intervals in BALATON and COMINO with faricimab, were higher than that those observed in the UK Medisoft study mentioned above, compared with both standards of care (aflibercept and ranibizumab), over

similar time periods, utilising a clinically relevant PTI T&E regime. This validates the trial design for extension of treatment intervals in increments of 4 weeks. The high proportion of faricimab patients achieving extended treatment intervals of at least Q12W represents a clinically meaningful reduction in the treatment burden in patients with RVO. This conclusion was confirmed by UK clinical experts (3).

The results of the anatomical outcomes in RVO, namely comparable reduction in CST, MO, SRF, IRF and a higher proportion of patients with resolution of macular leakage, taken together with the anatomical outcomes from YOSEMITE and RHINE (greater reduction in CST, greater reduction in macular leakage and absence of IRF and DMO) suggest a trend of improved vascular stability with faricimab PTI and provide robust evidence for the improved duration of treatment effect in vascular diseases. In totality, the anatomic outcomes observed with faricimab offer benefits to both physicians and patients in UK clinical practice given that the absence of MO, SRF and IRF are strong drivers for deciding when to treat. As such, the anatomical benefits observed with faricimab will allow physicians to achieve longer treatment intervals, in incremental extensions of 4 weeks, thereby reducing the frequency of injections and alleviating the burden on patients, caregivers and the healthcare system. Despite patients having attended monthly in BALATON and COMINO to maintain masking during treatment, the PTI algorithm only utilised data collected at dosing visits to guide changes to the treatment interval. Thus, in real-world practice there may be no requirement for monthly monitoring between treatment visits, which was confirmed with clinicians (3).

Safety profile

Safety data from BALATON and COMINO indicate that faricimab was generally well-tolerated as evidenced by the low incidence of serious ocular AEs, ocular AESIs and AEs leading to treatment withdrawal. No new or unexpected safety signals were identified in the clinical trial program compared with aflibercept up to Week 24 or further in the trials up to Week 72.

Discussion

Overall, UK clinical experts were encouraged by the efficacy, anatomical benefits and increased treatment intervals associated with faricimab initiation, adding that the Q12W and Q16W dosing would correspond well with routine monitoring for RVO, thereby foregoing the need for additional monitoring and treatment appointments (3).

An NMA was conducted to provide a robust and current analysis of comparative efficacy between faricimab and relevant comparators (see Appendix D). Results of the NMA

demonstrated faricimab to be associated with superior or comparable visual outcomes in terms of BCVA and superior or comparable anatomical outcomes in terms of decreasing retinal thickness with a similar or lower injection frequency than current standard of care. Adverse events were also found to be comparable for faricimab and relevant comparators.

A limitation of the current available evidence is that there was no comparator from Weeks 24 to 72. In Weeks 24 to 72 of the trials, all patients, including those previously on aflibercept, moved to faricimab PTI dosing. The decision to switch all aflibercept patients to faricimab PTI after the first 6 months was based on both faricimab's additional mechanism of action and the efficacy results of the phase III faricimab studies in DMO and nAMD (69, 71) which showed faricimab to be non-inferior to aflibercept, with comparable safety. Emerging data from the real world in nAMD and DMO patients, who have switched from prior anti-VEGF therapy to faricimab, is starting to report improvements in vision, CST, fluid resolution and treatment intervals, further validating the decision to switch all RVO patents to Faricimab in weeks 24-72 in BALATON and COMINO (55).

Conclusion

The results of the Phase III clinical trials provide strong evidence of the efficacy and safety, optimal treatment frequency of faricimab in patients with RVO with particular focus on the high percentage of patients achieving treatment intervals of ≥Q12W and Q16W. The pivotal studies BALATON and COMINO demonstrate that patients receiving faricimab up to Q16W via a PTI regimen can maintain vision gains over 72 weeks. Together with anatomical outcomes such as absence of MO, SRF, IRF and macular leakage, and the supporting data from the Phase III DMO trials, faricimab offers significant benefits to both physicians and patients in UK clinical practice as the extended injection intervals will result in fewer injections without compromising vision gains or safety.

With its unique dual mechanism of action, faricimab brings innovation to RVO treatment, providing patients with a much needed opportunity to improve the treatment burden (12, 64, 65) associated with current anti-VEGF therapies while optimising disease control for those living with RVO. Moreover, a longer-acting treatment option that reduces the need for future treatment and monitoring visits will also help to improve the burden on the healthcare system, ensuring patients retain continuity of treatment with the ultimate accolade of maintaining their vision.

B.3.12 Ongoing studies

There are no completed or ongoing studies expected to provide additional evidence for the indication being appraised in the next 12 months.

B.4 Cost-comparison analysis

B.4.1 Changes in service provision and management

Faricimab is anticipated to be used in the outpatient hospital setting, in line with currently licensed anti-VEGF therapies used for RVO, namely aflibercept and ranibizumab. There are no additional requirements anticipated in terms of service provision or disease management with the inclusion of faricimab in the treatment pathway.

It is anticipated that a substantial proportion of patients who receive faricimab will be able to have their treatment intervals extended out to Q16W, following the loading dose. The outputs of our analysis suggest that the number of injections required with faricimab versus aflibercept and ranibizumab will be much lower. Details of the resource consumption associated with the use of faricimab are provided in Section B.4.2 below.

- A comparison with the dexamethasone IVT implant was not considered in the analyses. The rationale for exclusion was similar to reasons stated in TA305 - dexamethasone was not considered a comparator to aflibercept because ranibizumab dominated dexamethasone for treating visual impairment caused by MO-RVO;

- Dexamethasone has potentially substantial side effects including increased intraocular pressure and cataract.

The EAG agreed with the manufacturer during scoping that ranibizumab is the main comparator and highlighted that dexamethasone may be used in patients who do not respond to anti-VEGF drugs. As ranibizumab dominated dexamethasone, it can be assumed that as faricimab possesses similar efficacy and safety, it will also dominate dexamethasone.

B.4.2 Cost-comparison analysis inputs and assumptions

B.4.2.1 Features of the cost-comparison analysis

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

Results from the BALATON and COMINO trials found comparable gains in BCVA from baseline at Week 24 observed in the faricimab Q4W and aflibercept Q4W treatment arms.

These gains were maintained over time through Week 72 on a faricimab PTI dosing regimen, and the results were supported by the supplementary analyses and anatomical outcomes. The potential to extend treatment intervals with faricimab up to Q16W was demonstrated, with approximately 48% of patients on an extended dosing interval of Q12W or Q16W at Week 68, resulting in approximately 5.5 mean injections in study Part 2.

The results of a network meta-analysis study also demonstrated that faricimab was non-inferior to aflibercept and ranibizumab.

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

An overview of the cost-comparison analysis is presented in Table 26.

Table 26: Summary of the cost-comparison analysis

Feature	Chosen approach
Population	Adults (aged ≥18 years) with RVO to reflect the populations included in the BALATON and COMINO trials.
Intervention	Faricimab
Comparator(s)	• Aflibercept • Ranibizumab
Outcomes	Mean incremental per-patient costs and total per-patient costs
Perspective	NHS and personal social services (PSS) in England and Wales
Time horizon	Lifetime – 25 Years (assuming maximum age of 100 Years)
Discounting	Costs discounted at 3.5% per annum
Technology acquisition cost	£857 (list Price) [redacted]

NHS: National Health Service; PSS: Personal Social Services; RVO: Retinal Vein Occlusion.

B.4.2.2 Model structure

A cost-comparison model was developed in Microsoft Excel ® 2016 using a Markov cohort approach to calculate the proportion of patients across three health states over time: On treatment; Off treatment (discontinued) and Death (Figure 22). It consists of a two-eye model where the disease progression of both eyes is independent from each other. There were no bilateral cases in the BALATON and COMINO trials. The prevalence and incidence of second eye involvement were assumed based on TA409 and TA305 (2, 38). The general modelling approach and inputs were cross referenced with previous technology appraisals and

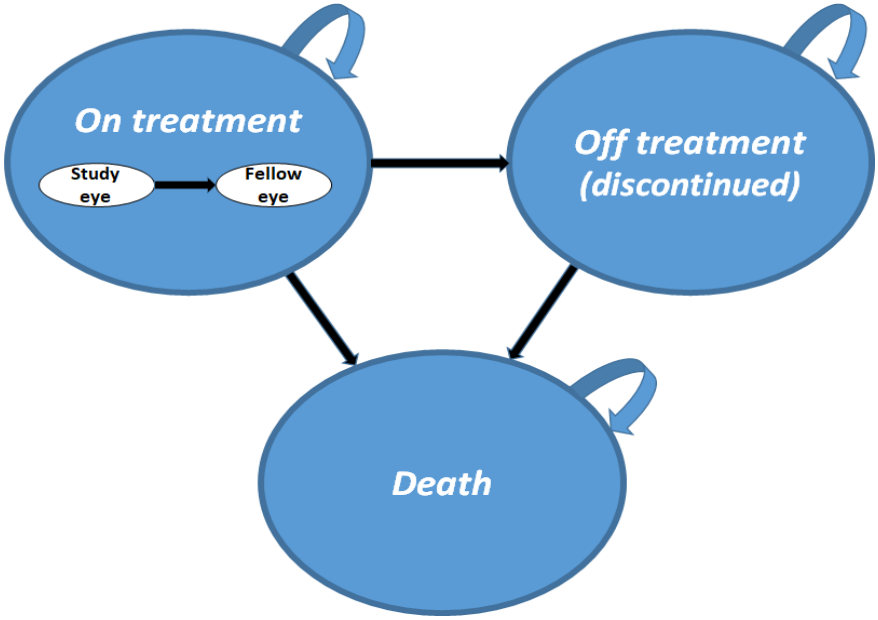
subsequently validated by external health economists and UK clinical experts. If patients discontinue, no switching to other therapies is assumed. Instead, disease progression on best standard of care (Bsc) is modelled, informed by the pattern typically observed in clinical trials with Sham arms (no initial gains in visual acuity and slow deterioration without appropriate treatment thereafter). The model differentiates three periods following the clinical pattern typically observed for RVO:

- **Initial treatment phase (6 months):** long loading phase where most vision improvements occur.
- **Maintenance phase:** characterised by a stabilisation of the disease and maintenance of vision gains previously achieved.
- **Rest of life phase:** the disease is assumed to resolve for a share of patients who can discontinue without loss of efficacy and potentially a share of patients who continue to require treatment.

A lifetime time horizon (25 years) was adopted in line with the NICE reference case (73). The time horizon was considered to be sufficiently long to reflect any differences in costs between the technologies being compared. A cycle length of 4-weeks was adopted, reflecting the shortest treatment period (Q4W) which could be applied in the model. In line with the NICE reference case (73) a discount rate of 3.5% was applied to costs and benefits in the model. The impact of the discount rate was explored in a scenario analysis by applying a discount rate of 1.5% Section B.4.4).

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

Figure 22: Cost-comparison model structure



B.4.2.3 Patient population

The patient population considered in the analysis was reflective of the anticipated marketing authorisation for faricimab and the populations evaluated in the BALATON and COMINO trials: adults aged ≥ 18 years with visual impairment due to MO secondary to branched and central retinal vein occlusion (B/CRVO).

BALATON and COMINO are identical in design, were conducted in parallel, and there are no relevant imbalances in key baseline characteristics between the patient populations (see section B.3.3.2). The main data sources used in the model are the pooled data covering the patient populations of BALATON and COMINO, and the populations of studies included in the network meta-analysis (see Sections B.3.6 and B.3.8).

In the base case analysis, baseline characteristics - including age and gender - were derived from the ITT populations of the BALATON and COMINO trials (Table 27). Estimates of the proportion of patients with unilateral or bilateral RVO at baseline, were informed by values used in previous appraisals for RVO (TA305 and TA409) (2, 38). Feedback from UK clinical experts agreed that the baseline characteristics of the model were generalisable to UK clinical practice (3).

Table 27: Modelled population baseline characteristics

Characteristic	Value (RVO)	Source
Age, mean (SD) at baseline	64.3 years (11) [CRVO] 65.6 years (13) [BRVO]	BALATON and COMINO trials
Percentage male	52.7% [CRVO] 51.8% [BRVO]	BALATON and COMINO trials
Prevalence of RVO in second eye at baseline	0.8% [CRVO] 6.1% [BRVO]	TA409 and TA305 assumption
Monthly incidence of RVO in second eye	0.6% [CRVO] 2.6% [BRVO]	TA409 and TA305 assumption

SE; standard error: SD; standard deviation.

B.4.2.4 Mortality

Mortality was modelled by applying general population all-cause mortality data obtained from England and Wales National Life Tables published by the Office for National Statistics (2019) based on 2020−2022 mortality data (74). To reflect the patient population in the model, age- and gender-specific mortality rates were combined into a single rate using the proportion of males and mean age set in the model to reflect the patient population in the BALATON and COMINO trials.

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

B.4.2.5 Intervention and comparators' acquisition costs

A summary of the acquisition costs for faricimab, aflibercept and ranibizumab is presented in Table 28 below. The drug acquisition costs for aflibercept and ranibizumab were based on the list price stated in the British National Formulary (75). Whilst confidential patient access scheme (PAS) discounts have been agreed with the Department of Health for aflibercept and ranibizumab, the size of these discounts is unknown to Roche and therefore the list price for each treatment was used in the base case cost comparison analyses. Scenario analyses exploring the impact of varying the discounts applied to the list price of aflibercept and ranibizumab have been conducted (see Section B.4.4).

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

Table 28: Acquisition costs of the intervention and comparator technologies

	Faricimab			Aflibercept			Ranibizumab		
Pharmaceutical formulation	120 mg/mL solution for injection vial			2 mg/50 µL solution for injection vial			1.65 mg/0.165 mL solution for injection in pre-filled syringe		
(Anticipated) care setting	Hospital			Hospital			Hospital		
Acquisition cost (excluding VAT) *	**Net price*** [redacted]			**NHS list price (75)** £816.00			**NHS list price (75)** £551.00		
Method of administration	Intravitreal injection			Intravitreal injection			Intravitreal injection		
Dose	6 mg			2 mg			0.5 mg		
Dosing regimen	6 LP → Q16/12W (T&E)			2 LP→ Q16/12W (T&E)			0.5 LP → Q16/12W (T&E)		
Administration frequency	**Phase**	**BRVO**	**CRVO**	**Phase**	**BRVO**	**CRVO**	**Phase**	**BRVO**	**CRVO**
	Treatment	5.91	5.84	Treatment	5.91	5.84	Treatment	5.91	5.84
	Maintenance	5.82	6.84	Maintenance	5.82	6.84	Maintenance	5.82	6.84
	Rest of life	5.82	6.84	Rest of life	5.82	6.84	Rest of life	5.82	6.84
Separate monitoring visits	Treatment Phase: 0 Maintenance Phase: 0 Rest of Life Phase: 0			Treatment Phase: 0 Maintenance Phase: 0 Rest of Life Phase: 0			Treatment Phase: 0 Maintenance Phase: 0 Rest of Life Phase: 0		

** Price listed includes an approved patient access scheme.*

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

B.4.2.6 Dosing regimens

In BALATON and COMINO, the dosing regimen consisted of a loading phase of six injections (once a month for 6 months), followed by a PTI dosing regimen in intervals between Q4W and Q16W

PTI is a protocol-driven treat-and-extend regimen in which treatment intervals are adjusted based on individualised treatment response, as measured by CST and visual acuity (see Section B.3.6.3). Dosing intervals in the PTI arm could be extended up to every 16 weeks (Q16w), in increments of 4 weeks. This is also in line with the anticipated marketing authorisation for faricimab (20). At faricimab dosing visits, treatment intervals were maintained or adjusted (i.e., increased by 4 weeks or decreased by 4, 8, or 12 weeks), based on CST and BCVA values.

Patients whose dosing interval had been previously extended and who experience disease worsening that triggered an interval reduction were not allowed to extend the interval again, with the exception of patients whose dosing intervals were reduced to Q4W; their interval could be extended again but only to an interval that was 4 weeks less than their original maximum extension. For example, a patient on a Q12W interval who required a 4-week interval reduction could not be extended beyond a Q8W interval for the remainder of the study.

Consultation with UK clinical experts confirmed that the PTI arm was reflective of T&E regimens, and if administering faricimab in clinical practice they would expect to follow a T&E regimen in the first years of treatment. Clinicians also confirmed the interval reduction performed within the study was overly conservative and would not be replicated in clinical practice (3). The algorithm used for PTI dosing is shown in Figure 4.

A range of dosing schedules are available for aflibercept and ranibizumab. In the base case analysis, it is assumed that aflibercept and ranibizumab are administered using T&E regimen. This was selected as the extended treatment intervals of a T&E regimen can lessen the treatment burden for patients and clinics by reducing the number of hospital visits and the overall number of injections. In PRN (as needed) regimens, patients receive treatment in response to disease activity. Whilst the risk of eye deterioration between intervals in RVO is less compared to nAMD and DMO and lends itself to PRN dosing, clinical experts agreed that PRN regimens are not regularly used in clinical practice for administering anti-VEGF therapies as this would interfere with future planning of administrations and consequently more likely to result in capacity constraints (3). The assumption made for the base case was equivalence in efficacy, as such; the frequency of injections for faricimab from BALATON and COMINO was

considered the same for the comparator arms. Individual studies from aflibercept and ranibizumab show that in reality, the interval does not extend as much as faricimab making this a conservative estimate. Injection frequencies from these studies were analysed in scenario analyses. UK clinical experts consulted by Roche were aligned with the approach taken in the base case analysis, and agreed that they expected to be able to extend treatment intervals more with faricimab than aflibercept and ranibizumab (3) (see Section B.4.2.11).

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

B.4.2.7 Treatment duration and discontinuation

Due to the resolving nature of RVO where the 5-year follow-up of the SCORE2 study (76) showed that 55% of patients did not have a visit at 5 years, it was assumed 55% would discontinue after 5 years. The remainder of patients were assumed to, still receive treatment and the injection numbers in years 2-5 (maintenance phase) were broadly stable. To account for this pattern of no disease worsening in the absence of treatment in case of disease resolution, disease progression for patients after they reach the maximum treatment duration (rest of life phase) will reflect general age related vision loss.

Treatment discontinuation probabilities are assumed to be similar across treatments for all comparators based on the findings of the network meta-analysis. Probabilities in the treatment and maintenance phase are based on the clinical trial results for faricimab and aflibercept in BALATON and COMINO (53, 54). In order to obtain the annual probability, total patient numbers in both trials divides patients discontinuing within the trials less the number of deaths. This is then annualised based on the regimen phase. The calculations are provided in Table 29. The rest of life phase is assumed to be equivalent to the maintenance phase.

Table 29: Treatment discontinuation probabilities

	Patients discontinuing BALATON and COMINO	Excluding deaths as this is accounted for separately in the model	N	Annualisation	Annualised discontinuation probability
Treatment phase (until week 24)	26+12	3+1	729+553	52/24	5.7%

Maintenance phase (week 24 - week 72)	52+48	4+3	729+553	52/48	7.9%

UK clinical experts consulted by Roche suggested that in the majority of cases RVO could be well controlled with treatment, and patients would no longer receive anti-VEGF injections after 5 years of treatment. For people who develop RVO in their second eye (bilateral or fellow eye involvement), a maximum treatment duration of 5 years is started from the point that RVO develops in the second eye. UK clinical experts agreed with the approach and assumptions in the base case analysis to model discontinuation.

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

In current UK clinical practice, patients are diagnosed using OCT. In the model, the cost of an OCT is applied across all patients at cycle one. It is also applied in the first model cycle after patients develop RVO in their second eye. The cost of OCT was sourced from the 2021/2022 NHS reference schedule (Table 30) (77). The assumption that OCT is used to diagnose RVO was validated in consultation with UK clinical experts (see Section B.4.2.11).

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

Table 30: Optical coherence tomography cost

Item	Unit cost	Source
OCT	£159.05	NHSE reference schedule 2021/22. Outpatient Procedure code for Retinal Tomography: BZ88A (ophthalmology) (77)

OCT: optical coherence tomography.

Injection administration visits

For the base case, the frequency of injection administrations is derived from data pooled across the BALATON and COMINO studies (see Sections B.3.6, B.4.2.1 and B.4.2.6) split by treatment, indication (CRVO and BRVO) as well as treatment phase (first 6 months & maintenance phase). This was applied to all arms in the analysis.

Alternative estimates of injection administration frequencies associated with different treatment regimens have been explored as scenario analyses (see Section B.4.4). The underlying calculations are presented in appendix K. The mean injection numbers were extracted and annualised based on the reported time period. Patients discontinuing/dying were accounted for, therefore, the annualised numbers were adjusted to account for

discontinuation within the time period, as likely not all patients will have experienced the full period. This adjustment was based on the exposure time observed in BALATON and COMINO.

Table 31 shows a scenario where for faricimab, as in the base case, the frequency of injection administrations is derived from data pooled across the BALATON and COMINO studies. For the comparator arms, values were identified in the systematic literature review for randomised clinical evidence as well as a targeted literature review to identify single arm trials. References to the studies are highlighted in Table 32. The underlying calculations are presented in Appendix K.

Table 31: Annual mean number of injection administration visits (observed in clinical trials and identified in SLR)

Treatment		Faricimab	Ranibizumab			Aflibercept		
Regimen		T&E	Q4W	PRN	T&E	Q4W	PRN	T&E
CRVO	First 6 months	5.84	Set to be similar to aflibercept Q4W based on BALATON & COMINO since no differences are expected for planned regimens	5.3	5.58	5.84	5.25	5.36
	Maintenance phase	6.84		8.78	10.92	12.71	4.99	8.78
BRVO	First 6 months	5.91		5	No evidence available, set to be similar to CRVO	5.86	No evidence available, set to be similar to CRVO	No evidence available, set to be similar to CRVO
	Maintenance phase	5.82		6.04		12.73		

Table 32: Source of annual mean number of injection administration visits (observed in clinical trials and identified in SLR)

Treatment		Faricimab	Ranibizumab			Aflibercept		
Regimen		T&E	Q4W	PRN	T&E	Q4W	PRN	T&E
CRVO	First 6 months	Based on COMINO	Set to be similar to Aflibercept Q4W based on BALATON & COMINO since no differences are expected for planned regimens	Weighted average of LEAVO (Hykin et al. 2019), SHORE (Campochiaro et al. 2014), and CRUISE (Brown et al. 2010)	Casselholm De Salles 2019	Based on COMINO	Weighted average of LEAVO and GALILEO	Weighted average of Casselholm De Salles 2019, CENTERA and SCORE2
	Maintenance phase							
BRVO	First 6 months	Based on BALATON		Weighted average of BLOSSOM (Wei et al 2020), BRIGHTER (Tadayoni et al. 2017), SHORE and BRAVO (Campochiaro et al. 2014)	No evidence available, set to be similar to CRVO	Based on BALATON	No evidence available, set to be similar to CRVO	No evidence available, set to be similar to CRVO
	Maintenance phase							

Proportionate interval dosing

Table 33 shows the dosing regimen titled “Planned # per regimen Q4-Q16” utilises the frequency of injections based on the number of loading doses and the proportion of patients on a Q4W – Q16W regimen. Table 33 below shows the distribution over treatment intervals in this scenario.

Table 33: Proportion of patients on Q4W – Q16W

	Number of 4-weekly loading doses	Q4	Q8	Q12	Q16	Reference
Faricimab (CRVO)	6	35%	20%	8%	37%	Based on COMINO
Faricimab (BRVO)	6	23%	13%	12%	52%	Based on BALATON
Ranibizumab	6	20%	80%	0%	no Q16W evidence	Based on Casselholm De Salles 2019
Aflibercept	6	3%	54%	44%	no Q16W evidence	Based on the CENTERA study (Korobelnik et al 2021)

The unit costs for injection administration visits were obtained from the NHS Reference Schedule 2021/2022 and the appraisal of aflibercept for DMO (TA346) (77, 78). It was assumed that IVT injections would be administered in consultant led outpatient appointments, following an assessment of retinal fluid using OCT. It was also assumed that there would be an additional resource use and cost associated with IVT injections which would apply at each injection administration visit. The cost of an IVT injection was estimated as the difference in costs between an injection administration visit and a monitoring visit as calculated by the evidence review group (ERG) in the appraisal of aflibercept for DMO (TA346) (78). In the base case analysis, in addition to treatment acquisition cost (see Table 28), the cost of an injection administration visit was assumed to comprise of an outpatient consultant-led visit (£143.93), an injection administration cost (£54.54), and an OCT procedure (£159.05) – see Table 30 and Table 34 (77). UK clinical experts agreed with this approach and the cost and resource use estimates (see Section B.4.2.11).

The proportion of outpatient consultant or non-consultant led (£105.46) and day case visits (£753.53) were explored in scenario analyses – see Table 34 (77).

Table 34: Resource use unit costs

Item	Unit cost	Source
Consultant led outpatient visit	£143.93	NHS reference costs 21/22: Consultant led non-admitted follow-up (ophthalmology) WF01A, service code 130
IVT injection	£54.54	Estimated from aflibercept for DMO EAG report (TA346)

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

Monitoring visits

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

Treat and extend is a proactive regimen that allows extension of treatment intervals in the absence of disease activity. If a sufficient number of injections administration visits are taking place, separate monitoring visits may not be required if following a T&E regimen. PRN, or "as required", regimens are considered reactive and involve frequent, often monthly visits where an injection is given only after the reoccurrence of disease activity.

For the T&E, it is assumed that no additional monitoring visits are required. This assumption applies in the model until discontinuation or death. These assumptions are consistent with the views of clinical experts consulted by Roche and in line with faricimab's anticipated marketing authorisation (20). Clinical experts agreed that the aim is to reduce additional monitoring visits whenever possible and that this could be achieved using T&E (see Section B.4.2.11).

In the base-case analysis, it is assumed that aflibercept and ranibizumab are administered using a T & E regimen, so additional monitoring visits are applied in all years of the model (see Table 28). This assumption was supported by the views of clinical experts who said that the overall aim is to avoid additional monitoring visits,

In the scenario analyses where PRN dosing regimens are explored, the minimum annual number of total monitoring visits can be seen in Table 35.

Table 35: Separate monitoring visits for faricimab, aflibercept and ranibizumab

Dosing regimen	Treatment phase		Maintenance phase		Rest of Life phase	
	BRVO	CRVO	BRVO	CRVO	BRVO	CRVO
Faricimab 6 LP → q16/12w (T&E)	0.00	0.00	0.00	0.00	0.00	0.00
Aflibercept 2 LP → PRN	2	2	8	8	8	8
Ranibizumab 0.5 LP → PRN	2	2	7	4	7	4

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

In the model, it is assumed that at each monitoring visit, retinal fluid would be assessed using OCT in a consultant led outpatient appointment. So, the cost of a separate monitoring visit comprised of an outpatient consultant-led visit and an OCT procedure (see Table 30 and Table 34). Feedback from UK clinical experts was aligned with the cost and resource assumptions adopted in the base case analysis (3).

B.4.2.9 Adverse reaction unit costs and resource use

The relative safety of faricimab and aflibercept was assessed in the safety-evaluable population defined as all patients in either study who received at least one injection of active study drug, grouped according to the actual treatment received. The safety results found that the incidence of AEs was generally comparable across treatment arms (Section B.3.10.2, Table 16).

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

B.4.2.10 Miscellaneous unit costs and resource use

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

B.4.2.11 Clinical expert validation

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

Clinical data have been incorporated into the model from BALATON and COMINO studies (53, 54), as well as other published clinical trials (see Section B.3.9). The general modelling approach and inputs were cross referenced with previous technology appraisals and subsequently validated by external health economists and UK clinical experts. To assess the generalisability of the evidence and plausibility of the model assumptions and predictions, clinical expert validation of the assumptions applied in the base case cost-comparison analysis

was sought from two leading UK clinical experts (3). A summary of the areas of feedback provided by the experts is below:

- Generalisability of the trial population to UK clinical practice (see Section B.4.2.3)
- Treatment injection frequencies and dosing regimens (see Sections B.4.2.6 and B.4.2.8)
- Treatment discontinuation patterns (see Section B.4.2.7)
- Healthcare resource use and costs (see Section B.4.2.8)

B.4.2.12 Uncertainties in the inputs and assumptions

A summary of the assumptions adopted in the base case cost-comparison analysis is presented in Table 36.

Table 36: Assumptions adopted in the base case cost-comparison analysis

Assumption	Description
Equivalent efficacy across treatments and regimens	The cost-comparison model assumes that the different treatments have equivalent efficacy and safety, regardless of the treatment regimens or injection frequencies. BALATON and COMINO demonstrate that faricimab is non-inferior to aflibercept in terms of outcomes and safety (B.3.6). Results from the NMA (Section B.3.8) also demonstrated that faricimab is associated with comparable efficacy in terms of BCVA and safety versus both aflibercept and ranibizumab.
Mortality	The cohort followed the age- and gender-adjusted mortality probabilities from published by the Office for National Statistics (2019) based on 2020−2022 mortality data (74).
Discontinuation probability	The annual probability of discontinuation was based on data pooled across the faricimab and aflibercept arms of BALATON and COMINO.
Treatment duration and discontinuation	A maximum treatment duration of 5 years from baseline was applied for 55% of patients. The remainder were assumed to, still receive treatment and the injection numbers in years 2-5 (maintenance phase). It was also assumed there was no disease worsening in the absence of treatment in case of disease resolution, disease progression for patients after they reach the maximum treatment duration (rest of life phase) will reflect general age related vision loss. Treatment discontinuation probabilities are assumed to be similar across treatments for all comparators.
Treatment switching	Patients were either on or off treatment and did not switch treatments.
Injection administration visits	Treatment frequency was derived from data pooled across the BALATON and COMINO studies (see Sections B.3.6 and B.4.2.6).

Monitoring visits	In the base case, it is assumed that people treated with any drug follow a T&E strategy and no monitoring visits in addition to administration injection visits are required. This assumption applies in the model until discontinuation or death.
Adverse event probability	The cost minimisation model assumes that the probability of adverse events was the same across all treatments and regimens, so safety is assumed to be equivalent. No adverse events are modelled in the base-case analysis.
Probability of developing bi-lateral disease	Estimates for the proportion of patients with fellow eye involvement (i.e. bilateral disease) at both baseline and monthly incidence, were informed by TA409 and TA305 (2, 38).
OCT	OCT is assumed to be undertaken at diagnosis (cycle one for treatment naive patients and in the first cycle after people develop bi-lateral disease), and at every injection administration and monitoring visit.
Consultant led appointments	It is assumed that all injection administration and monitoring visits are led by a consultant in an outpatient setting.

BCVA: best-corrected visual acuity; NMA: network meta-analysis; OCT: Optical coherence tomography; T&E: Treat and extend; TA: technology appraisal.

B.4.3 Base-case results

The results of the base case cost-comparison analysis are presented below (Table 37). The results presented to do not account for the patient access scheme discounts for aflibercept and ranibizumab, as these net prices are confidential. Therefore, the base case results presented below assume aflibercept and ranibizumab are provided at list price (75), while faricimab is provided at its confidential net price (see Section B.4.2.5).

Table 37: Base case results (faricimab at net price; aflibercept and ranibizumab at list price)

Cost	Faricimab 6mg LP→ T&E		Aflibercept 2mg LP → T&E		Ranibizumab 0.5mg LP → T&E	
	BRVO	**CRVO**	**BRVO**	**CRVO**	**BRVO**	**CRVO**
Drug cost	[redacted]	[redacted]	£35,856	£34,551	£24,228	£23,350
Administration cost	[redacted]	[redacted]	£15,543	£15,096	£15,553	£15,108
Additional monitoring cost	£0	£0	£0	£0	£0	£0
AE management cost	£0	£0	£0	£0	£0	£0
Costs of visual impairment	£1,313	£760	£1,313	£760	£1,313	£760
Mean total cost	[redacted]	[redacted]	£57,655	£52,290	£46,040	£41,137
Incremental cost vs faricimab	N/A		[redacted]	[redacted]	[redacted]	[redacted]

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

With similar results in BCVA outcomes, comparable safety and treatment durability to aflibercept and ranibizumab, faricimab represents a cost-effective alternative to currently licensed and NICE recommended anti-VEGF therapies (Table 37). This is a conservative estimate, as existing clinical experience for faricimab suggest treatment durability may be extended.

Acknowledging that aflibercept and ranibizumab are available to the NHS at a confidential discounted price, the impact of varying the level of discount to list price for aflibercept and ranibizumab was explored in a threshold analysis, presented in Table 38. When adopting the base case cost-comparison assumption, this analysis demonstrates that at the net price, faricimab remains [redacted] compared with aflibercept and ranibizumab up to a discount level of [redacted] and [redacted] respectively.

Table 38: Threshold analysis: incremental cost of faricimab compared with aflibercept and ranibizumab at varying list price discount levels

Discount	Aflibercept			Ranibizumab		
	Discounted aflibercept price	Incremental cost vs faricimab		Discounted ranibizumab price	Incremental cost vs faricimab	
		BRVO	CRVO		BRVO	CRVO
0%	£816.00	[redacted]	[redacted]	£551.00	[redacted]	[redacted]
10%	£734.40	[redacted]	[redacted]	£495.90	[redacted]	[redacted]
20%	£652.80	[redacted]	[redacted]	£440.80	[redacted]	[redacted]
30%	£571.20	[redacted]	[redacted]	£385.70	[redacted]	[redacted]
40%	£489.60	[redacted]	[redacted]	£330.60	[redacted]	[redacted]
50%	£408.00	[redacted]	[redacted]	£275.50	[redacted]	[redacted]
55%	£367.20	[redacted]	[redacted]	£248.00	[redacted]	[redacted]
60%	£326.40	[redacted]	[redacted]	£220.40	[redacted]	[redacted]
65%	£285.60	[redacted]	[redacted]	£192.90	[redacted]	[redacted]

B.4.4 Sensitivity and scenario analyses

B.4.4.1 Deterministic sensitivity analysis

A univariate deterministic sensitivity analysis (DSA) was conducted to assess which parameters have the greatest impact on incremental cost. In the absence of data on the

variability around parameter values, each was varied by ±20%. The parameter values used in the deterministic sensitivity analyses for BRVO and CRVO are presented in Table 39 and Table 40, respectively. Results of the DSA are displayed in Figure 23 and Figure 24 for BRVO and CRVO, respectively, where the 7 parameters that had the greatest impact on incremental costs are presented.

The results of the DSA (see Figure 23 and Figure 24) show that drug costs and model starting age have the biggest impact on incremental costs. All results remain consistent with the base case results, concluding that faricimab is overall [redacted].

Table 39: Parameter values used for DSA [BRVO]

Parameter	Base-case value	Lower value	Higher value	Variation
Drug cost for aflibercept (£)	816	653	979	± 20%
Drug cost for ranibizumab (£)	551	441	661	± 20%
Starting age of cohort (years)	66	52	79	± 20%
Administration cost for IVT injections	357	286	429	± 20%
Time horizon (years)	25	20	30	± 20%
Discount rate costs (%)	3.5	2.8	4.2	± 20%

DSA, deterministic sensitivity analysis; IVT, intravitreal injection.

Figure 23: Tornado plot (faricimab net price compared with aflibercept list price) [BRVO]

IVT, intravitreal injection.

Table 40: Parameter values used for DSA [CRVO]

Parameter	Base-case value	Lower value	Higher value	Variation
Drug cost for aflibercept (£)	816	653	979	± 20%
Drug cost for ranibizumab (£)	551	441	661	± 20%
Starting age of cohort (years)	64	51	77	± 20%
Administration cost for IVT injections	357	286	429	± 20%
Time horizon (years)	25	20	30	± 20%
Discount rate costs (%)	3.5	2.8	4.2	± 20%

DSA, deterministic sensitivity analysis; IVT, intravitreal injection.

Figure 24: Tornado plot (faricimab net price compared with aflibercept list price) [CRVO]

IVT, intravitreal injection.

Within BRVO, for the scenarios exploring alternative dosing regimens, the frequency of injection and monitoring visits varied; a summary of the injection and monitoring frequencies applied in the base-case analysis and in each scenario can be seen in Table 41.

Table 41: Annual mean number of injections and total visits per dosing regimen [BRVO]

Dosing regimen	Injections			Separate monitoring visits		
	Treatment phase	Maintenance phase	Rest of life phase	Treatment phase	Maintenance phase	Rest of life phase
Base-case						
Faricimab (6 LP → T&E	[redacted]	[redacted]	[redacted]	0	0	0
Aflibercept (2 LP → T&E)	[redacted]	[redacted]	[redacted]	0	0	0
Ranibizumab (0.5 LP → T&E)	[redacted]	[redacted]	[redacted]	0	0	0
Scenario analyses						
Trial-based Dosing Average						
Faricimab (6 LP → T&E	[redacted]	[redacted]	[redacted]	0	0	0
Aflibercept (2 LP → T&E)	5.36	8.78	8.78	0	0	0
Ranibizumab (0.5 LP → T&E)	5.58	10.92	10.92	0	0	0
Proportionate interval dosing						
Faricimab (6 LP → Q4W/Q8W/Q12W/Q16W) [T&E]	[redacted]	[redacted]	[redacted]	0	0	0
Aflibercept (2 LP → Q4W/Q8W/Q12W/Q16W) [T&E]	6.03	5.83	5.83	0	0	0
Ranibiumab (0.5 LP → Q4W/Q8W/Q12W/Q16W) [T&E]	6.20	7.89	7.89	0	0	0
PRN dosing						
Faricimab (6 LP → [T&E]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Aflibercept (2 LP → PRN	5.25	4.99	4.99	2	8	8
Ranibiumab (0.5 LP → PRN	5.00	6.04	6.04	2	7	7

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

Scenarios exploring alternative dosing regimens, frequency of injection and monitoring visits varied within the CRVO subgroup; a summary of the injection and monitoring frequencies applied in the base-case analysis and in each scenario can be seen in Table 42.

Table 42: Annual mean number of injections and total visits per dosing regimen [CRVO]

Dosing regimen	Injections			Separate monitoring visits		
	Treatment phase	Maintenance phase	Rest of life phase	Treatment phase	Maintenance phase	Rest of life phase
Base-case						
Faricimab (6 LP → T&E	[redacted]	[redacted]	[redacted]	0	0	0
Aflibercept (2 LP → T&E)	[redacted]	[redacted]	[redacted]	0	0	0
Ranibizumab (0.5 LP → T&E)	[redacted]	[redacted]	[redacted]	0	0	0
Scenario analyses						
Trial-based Dosing Average						
Faricimab (6 LP → T&E	[redacted]	[redacted]	[redacted]	0	0	0
Aflibercept (2 LP → T&E)	5.36	8.78	8.78	0	0	0
Ranibizumab (0.5 LP → T&E)	5.58	10.92	10.92	0	0	0
Proportionate Interval Dosing						
Faricimab (6 LP → Q4W/Q8W/Q12W/Q16W) [T&E]	[redacted]	[redacted]	[redacted]	0	0	0
Aflibercept (2 LP → Q4W/Q8W/Q12W/Q16W) [T&E]	6.03	5.83	5.83	0	0	0
Ranibiumab (0.5 LP → Q4W/Q8W/Q12W/Q16W) [T&E]	6.20	7.89	7.89	0	0	0
PRN Dosing						
Faricimab (6 LP → [T&E]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Aflibercept (2 LP → PRN	5.25	4.99	4.99	2	8	8
Ranibiumab (0.5 LP → PRN	5.30	8.78	8.78	2	4	4

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

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

Table 43: Scenario analyses results (with faricimab at net prices; aflibercept and ranibizumab at list price) [BRVO]

Scenario	Base-case	Scenario	Incremental cost vs aflibercept	% change from base case incremental cost	Incremental cost vs ranibizumab	% change from base case incremental cost
Base-case	-	-	[redacted]	N/A	[redacted]	N/A
Model starting age	66 years	50 years	[redacted]	[redacted]	[redacted]	[redacted]
		75 years	[redacted]	[redacted]	[redacted]	[redacted]
Discount rate	3.5%	1.5%	[redacted]	[redacted]	[redacted]	[redacted]
Aflibercept dosing regimen	LP → T&E	LP → Q4W/Q8W/Q12W/ Q16W) [T&E]	[redacted]	[redacted]	N/A	N/A
		LP → PRN (TD)	[redacted]	[redacted]	N/A	N/A
		LP → T&E (TD)	[redacted]	[redacted]	N/A	N/A
Ranibizumab dosing regimen	LP → T&E	LP → Q4W/Q8W/Q12W/ Q16W) [T&E]	N/A	N/A	[redacted]	[redacted]
		LP → PRN (TD)	N/A	N/A	[redacted]	[redacted]
		LP → T&E (TD)	N/A	N/A	[redacted]	[redacted]

LP, loading phase; T&E, treat and extend; QXW, one injection every X weeks; TD, Trial-based dosing

Table 44: Scenario analyses results (with faricimab at net prices; aflibercept and ranibizumab at list price) [CRVO]

Scenario	Base-case	Scenario	Incremental cost vs aflibercept	% change from base case incremental cost	Incremental cost vs ranibizumab	% change from base case incremental cost
Base-case	-	-	[redacted]	N/A	[redacted]	N/A
Model starting age	64 years	50 years	[redacted]	[redacted]	[redacted]	[redacted]
		75 years	[redacted]	[redacted]	[redacted]	[redacted]
Discount rate	3.5%	1.5%	[redacted]	[redacted]	[redacted]	[redacted]
Aflibercept dosing regimen	LP → T&E	LP → Q4W/Q8W/Q12W/ Q16W) [T&E]	[redacted]	[redacted]	N/A	N/A

		LP → PRN (ITD)	[redacted]	[redacted]	N/A	N/A
		LP → T&E (ITD)	[redacted]	[redacted]	N/A	N/A
Ranibizumab dosing regimen	LP → T&E	LP → Q4W/Q8W/Q12W/ Q16W) [T&E]	N/A	N/A	[redacted]	[redacted]
		LP → PRN (ITD)	N/A	N/A	[redacted]	[redacted]
		LP → T&E (ITD)			[redacted]	[redacted]

LP, loading phase; T&E, treat and extend; QXW, one injection every X weeks, TD, Trial-based dosing

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

B.4.5 Subgroup analysis

Economic subgroup analyses for CRVO and BRVO have been conducted for the purposes of this appraisal within the base case results.

B.4.6 Interpretation and conclusions of economic evidence

This economic evaluation focused on comparing the cost of faricimab with aflibercept and ranibizumab for the treatment of patients with macular oedema caused by retinal vein occlusion, from a UK health system perspective. The results of the economic evaluation show that faricimab is highly likely to be [redacted] for the NHS in comparison to aflibercept and ranibizumab with extensive scenario and sensitivity analyses demonstrating consistent results providing further certainty.

Previous Phase III trials (TENAYA and LUCERNE) demonstrated vision benefits and anatomic outcomes seen in faricimab, administered at up to Q16W, comparable with Q8W aflibercept. This, along with inferences validated by clinical experts based on their experience of faricimab in nAMD and DMO would suggest the dual mechanism of action of faricimab provides comprehensive disease control allowing physicians to extend treatment intervals up to every 16 weeks (4 months), while maintaining vision gains resulting in fewer injections and easing burden on the NHS with patient capacity.

The model draws upon clinical data from the BALATON and COMINO studies, the baseline characteristics of the patients in both trials have been validated by clinical experts and can be considered broadly representative of the corresponding population in the UK. This evaluation can therefore be considered relevant to clinical practice in England and Wales.

In-line with the cost comparison appraisal framework, evidence was presented to demonstrate that faricimab provides similar or greater health benefits to NICE recommended technologies (ranibizumab and aflibercept) (2, 38). As demonstrated in the results from BALATON and COMINO and the network meta-analysis (see Sections B.3.6 and B.3.9.4) the efficacy of faricimab is similar to aflibercept and ranibizumab, and safety is comparable. Furthermore, the

results in line with those seen in nAMD and DMO as well as clinician experience demonstrate that faricimab is a more durable treatment than aflibercept and ranibizumab, with greater intervals between injections being possible on faricimab.

A UK NHS perspective was taken with respect to the costs and resource use quantified in the model. All costs were taken from published UK sources or previous NICE technology appraisals in this disease area. This methodology is in accordance with that of the NICE Reference Case (73).

The base case results from the cost comparison show that faricimab is [redacted] compared to aflibercept and ranibizumab – see Table 37. Although current IVT anti-VEGF therapies are efficacious for most patients with MO secondary to RVO, best achievable responses to anti-VEGF treatment require frequent injections and clinic visits. Real-world data in patients with MO secondary to RVO suggest that the need for frequent monitoring and injections creates a barrier to optimal anti-VEGF treatment, leading to a decrease in the vision gains initially achieved during clinical trials (47). Additionally, MO secondary to RVO is a multifactorial disease and anti-VEGF treatments alone do not completely address it.

The better vascular stability afforded by the unique dual mechanism of action of faricimab provides comprehensive disease control, allowing physicians to extend treatment intervals up to every 16 weeks, while maintaining vision gains and safety comparable to aflibercept Q4W.

Results from Phase III clinical trials demonstrate that patients receiving faricimab can maintain vision gains comparable to every 4 weeks (bimonthly) aflibercept with the longest possible treatment intervals (up to every 16 weeks). At Week 68 (the last treatment interval decision time point in the study), approximately, 60% of patients in BALATON and 48% of patients in COMINO were on a dosing interval of Q12W or Q16W, highlighting the increased durability of effect. By helping patients regain and maintain vision with fewer injections compared with current IVT anti-VEGF therapy, faricimab supports patient, caregiver, and healthcare professional (HCP) priorities of reduced treatment burden showing an added clinical benefit to the NHS.

The results presented in this submission compare faricimab PAS price, to aflibercept and ranibizumab at list price, so should be interpreted with caution. Nevertheless, when varying the prices of aflibercept and ranibizumab, faricimab remains a cost effective option up to a discount of [redacted] and [redacted] for aflibercept and ranibizumab respectively.

Extensive sensitivity and scenario analyses have been conducted to test the robustness of model results when parameter values were manipulated, alternative approaches implemented, and different data sources utilised. Complete results of these analyses can be found in Section B.4.4.

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

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

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

With similar efficacy in terms of

- Improvement in BCVA,
- Impact on vision-related HRQoL,

as well as potential superior treatment durability and less frequent injections, the results of the economic analysis indicate that faricimab is the most cost-effective treatment option for RVO versus currently licensed anti-VEGF therapies and results in cost savings to the NHS over a lifetime time horizon up to discounts of [redacted] and [redacted] (vs aflibercept and ranibizumab respectively). Therefore, faricimab meets the cost-comparison criteria to be recommended as an option for the treatment of RVO.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Cost comparison appraisal

Faricimab for treating macular oedema caused by retinal vein occlusion [ID6197]

Summary of Information for Patients (SIP)

March 2024

File name	Version	Contains confidential information	Date
ID6197_Faricimab for RVO_SIP [REDACTED]	**1.0**	**Yes**	**11 March 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):

Generic name: Faricimab **Brand name:** Vabysmo®

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

Adult patients with visual impairment due to macular oedema secondary to branched and central retinal vein occlusion.

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.

European Union (EU): A marketing authorisation application (MAA) was submitted to the European Medicines Agency (EMA) in [redacted]; regulatory approval is anticipated in [redacted]. **United Kingdom (UK):** A submission for marketing authorisation was made to the Medicines and Healthcare Products Regulatory Agency (MHRA) in [redacted], via the MHRA ACCESS route; approval is anticipated [redacted].

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:

The following grants were provided to patient groups by Roche relevant to ophthalmology (i.e. not RVO disease specific):

- [redacted]
- [redacted]

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.

Condition that the medicine plans to treat:

Faricimab is a treatment intended for macular oedema caused by retinal vein occlusion (MO-RVO), a condition where the veins in the retina get may become blocked. This blockage can lead to swelling in the macula of the eye, the central part of the retina which is crucial for clear, detailed central vision. RVO can occur in various parts of the retina, including the central, hemi-central, or branch retinal veins, leading to different subtypes of the condition, such as central retinal vein occlusion (CRVO) and branch retinal vein occlusion (BRVO) (1).

Symptoms of disease:

Patients with MO-RVO often experience sudden and significant changes in their vision. The primary symptom is a decrease in central vision, which is crucial for activities like reading, driving, and recognising faces. The vision loss or blurring occurs because the swollen macula cannot function properly. Unlike some other eye conditions, the vision loss associated with MO-RVO is typically not painful, which can sometimes delay diagnosis and treatment.

How many people have the condition:

RVO is a widespread condition that affects millions globally. As of 2015, an estimated 28 million people had been diagnosed with RVO (2). The number of people with this condition is expected to increase, especially among those over 60 years old (3). In England and Wales, it is estimated that each year, about 11,600 people with MO-BRVO and 5,700 people with MO-CRVO experience visual problems. Within 2 months of being diagnosed, 85% of

those with BRVO and 75% with CRVO develop MO. Additionally, 50% of BRVO patients and all CRVO patients may suffer from vision loss due to MO (4).

Effects on quality of life on patients, families and carers:

The impact of MO-RVO on the quality of life is profound and multifaceted. For patients, the sudden loss of central vision significantly impacts their ability to perform daily tasks, leading to a loss of independence and potential unemployment (5, 6). This can cause emotional distress, depression, and social isolation (5). Families and carers also face a heavy burden. The necessity for frequent treatments, including monthly injections, places a considerable time and emotional burden on carers, who often must take time off work and bear the stress of supporting their loved ones through a challenging treatment regimen (6). The condition and its treatment can also lead to financial strain due to high healthcare costs, the need for frequent treatments, and ongoing patient monitoring. This adds further stress to healthcare systems already at full capacity and can hinder the delivery of timely care.

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?

How the condition is diagnosed:

Potential RVO patients can present with a wide variety of visual changes. Eye examination and retinal imaging are the standard of care techniques for diagnosis. Optical coherence tomography (OCT) is a widely used imaging technique providing quick and useful imaging of the macula. In RVO, OCT is recommended in the diagnosis, monitoring and assessing treatment response of MO-RVO. Common signs include intraretinal (within the retina) and subretinal (beneath the retina) fluid, and an increase in central subfield thickness (a thicker central part of the retina). Tests such as fluorescein angiography and OCT angiography can help give a clearer picture of the condition.

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.

What treatment are currently used:

Anti-vascular endothelial growth factor (VEGF) therapy, specifically aflibercept and ranibizumab, is the standard of care for treating MO-RVO. VEGF is a protein in the body that stimulates blood vessels to grow. If blood vessels are produced that are immature and

nascent, they may be incomplete and leak retinal fluid. If this occurs in the eye, this leaked fluid may create problems in one's vision, resulting in swelling, bleeding, or damage to the retina.

[redacted]. These treatments have acceptable, similar safety profiles.

Faricimab is being compared to these existing treatments, both of which have been officially evaluated and endorsed by NICE for RVO treatment in various guidelines published between 2013 and 2016 (8-10).

In addition to the licensed anti-VEGF treatments, there are other options like laser, dexamethasone, and bevacizumab, but they are less commonly used. Laser, which seals the leaking blood vessels, has been mostly replaced by the more effective intravitreal injections (IVT; injection into the eye) (11, 12). Dexamethasone implants, recommended for certain BRVO cases, release steroids to reduce swelling but carry risks like increased eye pressure and cataracts (1). Bevacizumab, an anti-VEGF used in treating certain cancers and that is not licenced for use in the eye, is rarely used in practice. These alternatives are generally secondary to the preferred licensed anti-VEGF therapies due to their limited applicability, potential side effects, or lower efficacy.

Limitations of current treatments and unmet need:

Current treatments for MO-RVO, like frequent anti-VEGF injections, place a heavy burden on patients, carers and family members, resulting in poorer vision outcomes over time.
Current anti-VEGFs only target one protein involved in the growth of immature blood vessels. Current literature has suggested that the targeting of new novel proteins, with VEGF, such as ANG2, may provide additional control of the disease (13, 14). Furthermore, the stress of regular eye injections significantly affects patients' quality of life, causing fear, stress, and anxiety. Many patients report feeling anxious, losing sleep, and having trouble concentrating before their treatments. The burden on family members and carers is substantial. Carers accompany the RVO patients for their treatment, impinging on their own time and responsibilities especially if they are employed or have their own family commitments.

Additionally, there is an unmet need on the current healthcare system. Frequent treatment patterns and the sheer number of patients have left little capacity spare to either introduce new patients or to offer the necessary support for individuals, particularly those with complex conditions. There is a clear need for novel treatment options that require fewer injections but still maintain or improve vision, reducing the emotional and physical strain on patients and carers.

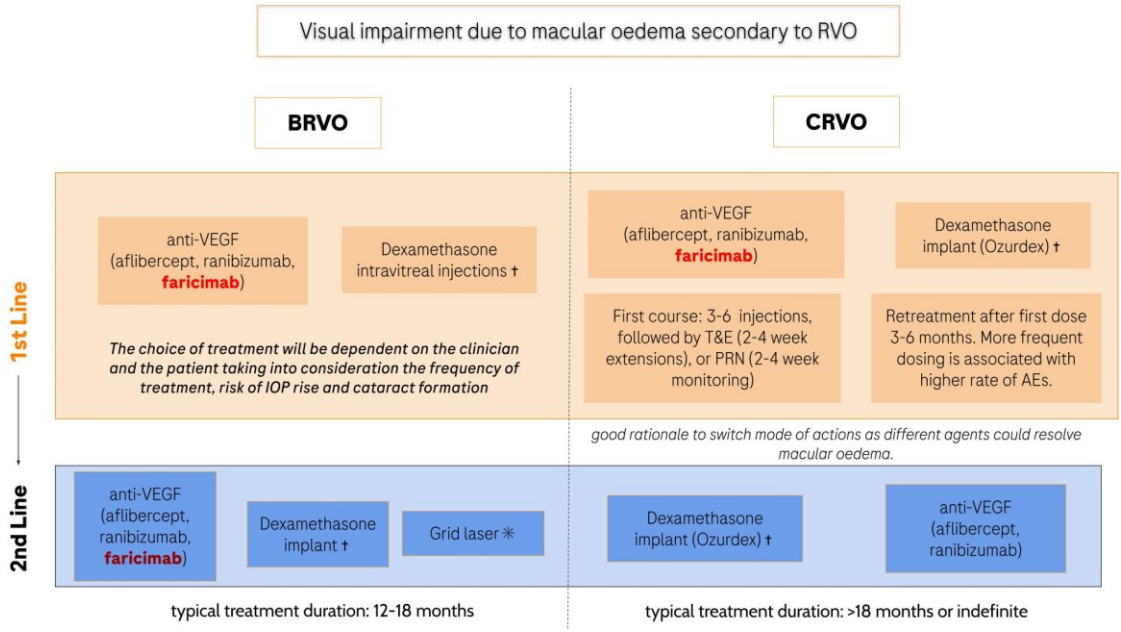
Proposed position for faricimab in the RVO treatment pathway:

Faricimab, which targets VEGF and ANG2, is expected to be approved for the same patient group as current treatments aflibercept and ranibizumab. It offers a new option for treating

adults with vision problems caused by MO-RVO, providing an alternative to these existing treatments. The proposed treatment pathway for faricimab is summarised below (

Figure *1*).

Figure 1: Proposed positioning of faricimab in treatment pathway for RVO



† Dexamethasone intravitreal implant is a NICE approved treatment but not considered a relevant comparator, as it is used for BRVO only after laser photocoagulation has been tried, or is deemed not suitable (1). ✳ Laser photocoagulation is not considered a relevant comparator as it is no longer the standard of care for RVO, with the exception of CRVO with ischaemic features.

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.

A. A survey with 131 European retinal patients with diabetic macular oedema (DMO) or RVO was conducted to understand their treatment burden, treatment-related anxiety and worry, and practical issues such as appointment attendance and work absence in patients receiving injection therapy (6). 45 patients with RVO were interviewed. A summary of their findings is presented below.

<u>For RVO patients:</u>

- 33% were still in employment and 53% were retired.
- 86% were initiated on a monthly regimen. Of this, 73% remained on monthly intervals, 13% moved to less frequent injections, and 13% received injections every 4–6 months.
- Each injection appointment took ~4.5 hours, comprising an average of 79 minutes of travel time and 188 minutes of appointment time. For the patients still in employment, ~50% needed to take 1 day off per appointment.
- The majority of patients required a carer's assistance around the time of the injection appointment, which totalled 6.3 hours of a carer's time per injection. Furthermore, 50% of carers were employed themselves, and of those, the majority needed to take time off to provide support to the patient.
- Over a six month period, patients had an average of ~9.2 appointments with retina specialists and ophthalmologists averaging 13.5 hours per patient.
- Emotional and physical effects: 18% of patients reported that their sleep was affected, 4% had reduced concentration and 50% reported being uptight.
- More than 55% reported 'moderate to large' impact on their quality of life (QOL). This is a greater impact compared to other chronic conditions such as diabetes, asthma, glaucoma, hypertension, thyroid conditions.

<u>For patients with DMO and RVO:</u>

- 75% experienced anxiety about their most recent injection, with 54% reporting that they were anxious for ~2 days prior to treatment.
- ~ 20% of patients had anxiety about their appointment.
- 47% of patients reported having had adverse physical effects from the anxiety experienced around the injection (such as exhaustion) as well as from the procedure itself (such as red eyes and blurry vision).
- 58% of patients reported that they were uptight and/or could not relax.
- 46% reported that they found it difficult to think of anything but the injection.
- The one improvement that patients wished for was to have fewer injections to achieve the same visual results (42%).

B. In-depth semi-structured interviews were conducted with 17 Australian patients with RVO (15). These investigated six main QOL themes: concerns about the disease progression and treatment outcome (health concerns), emotional responses to the disease (emotional), experiencing a range of symptoms (symptoms), inability to do things as before (activity limitation), adapting to the visual loss (coping), and inconveniences due to RVO (convenience). The results are summarised as follows:

<u>Theme 1: concerns about the disease progression and treatment outcome (health concerns)</u>

- This was the major concern for RVO patients.
- Treatments improved their clinical symptoms but did not restore the lost vision.
- That they might continue to lose their eyesight or go blind especially if the vision loss was progressive or those with treatment failures.
- The possibility of second eye involvement.

- Recurrence of their eye disease.
- People living on their own and those who did not have support of their family members and friends were concerned about their future.

Theme 2: emotional responses to the disease (emotional)

- Feeling frustration due to their eye condition.
- Feeling scared, depressed, anxious, shocked, sad or low.
- Feeling depressed because of the sudden loss of vision or the progressive deterioration of the vision.
- Frequent follow-ups caused anxiety in some participants.
- Felt sad or low when their test results were not good or when they had to go for their injections.

Theme 3: experiencing a range of symptoms (symptoms)

- Symptoms that varied from overall blurring of vision, difficulty in focusing, loss of central vision, double vision, seeing floaters and difficulty in light and dark adaptation, to complete loss of sight.
- Ocular pain, discomfort, and blood-shot eyes in patients receiving intravitreal injections.

Theme 4: inability to do things as before (activity limitation)

- Difficulty reading small print, driving at night, seeing at a distance and engaging in leisure activities.
- Driving was more difficult at night than during the day.
- Being more careful with driving in general.
- Giving up their driver's license as they felt it was not safe for others
- Seeing objects clearly at a distance such as seeing bus numbers, recognising people's faces across the street, and identifying street signs.

Theme 5: adapting to the visual loss (coping)

- Having to adopt several coping strategies to manage their visual loss such as praying, meditation and putting faith in God helped some participants to navigate the difficult journey.
- Positive strategies included acceptance, self-distraction, trying to be positive and trusting God.
- Staying positive and believing that their eye condition will not worsen, or will become stabilised.
- Negative strategies included disengagement, venting and substance abuse. Acceptance, disengagement, self-distraction, venting and trusting God.
- Self-distraction by engaging in leisure activities and spending time with friends and family members.

Theme 6: inconveniences due to the eye condition (convenience)

- Having to attend frequent eye appointments and have regular ocular treatment.

- Waiting long hours in the clinic.
- Travelling a long way to have treatment.
- Having to carry glasses all the time.

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

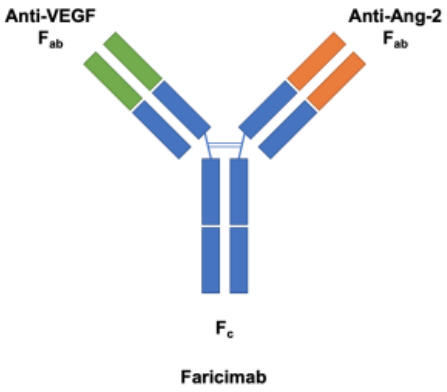
Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

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.

Faricimab's key features and how it works:

Faricimab is an antibody treatment being considered for RVO. It functions by binding to two specific proteins, Ang-2 and VEGF-A, that act independently and contribute to the condition (Figure 2) (14). This unique dual-action approach helps to decrease blood vessel leakage and swelling, stop harmful blood vessel growth, and bring back normal blood vessel function in the eye. Since faricimab is effective, doctors might be able to increase the length of time between each treatment, possibly going as long as 16 weeks between doses, without losing any of the benefits for vision. This could mean fewer hospital or clinic visits and injections for patients, easing the burden on both individuals, their carers and the healthcare systems. Additionally, with fewer treatments needed, eye care clinics could help more patients, especially as more people need treatment for eye conditions like RVO.

Figure 2: Structure of faricimab



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.
Faricimab is not used in combination with other medicines.

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?
How much and how often faricimab will be given (16, 17): The recommended dose of faricimab is 6 mg (0.05 mL solution), administered by IVT every 4 weeks (monthly). Patients may need three or more of these monthly injections at the start. After this initial phase, treatment may be adjusted using a “treat -and-extend” approach, based on how the patient is responding. The interval between doses could be potentially extended in 4 weeks intervals if the patient is doing well. However, if there is any sign of the patient's condition worsening, the time between injections may need to be shortened. It is important to note that treatment intervals less than 4 weeks or more than 16 weeks have not been tested. Regular check-ups are essential, though they do not have to be monthly unless deemed necessary by the doctor. Faricimab is designed for ongoing use, but if it is clear that a patient is not benefiting from the treatment, treatment should be stopped. **How faricimab is given and monitoring (16, 17):** Faricimab comes in a vial meant for a one-off IVT use only. It must be given by a qualified healthcare professional trained in IVTs. The vial should be inspected for any particles or colour changes, and if present, the vial should not be used. The injection must be carried out under aseptic conditions, including the use of surgical hand sanitiser, sterile gloves, a sterile drape covering, and a sterile eyelid speculum to keep the eye open. The patient’s medical history for allergic reactions should be carefully evaluated before the injection. Immediately following the injection, the patient's eye pressure should be monitored to make sure it is not elevated. Patients will be told to report any symptoms suggesting signs of eye infection, such as vision loss, eye pain, eye redness, sensitivity to light, or blurry vision.

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.

The **BALATON** [NCT04740905 (18)] and **COMINO** [NCT04740931 (19)] studies were global, multicentre Phase III clinical trials, conducted in 22 countries, designed to assess the effectiveness and safety of faricimab in treating MO-RVO. The studies aimed to demonstrate that faricimab was as effective as aflibercept, the current standards of care for RVO, by comparing improvements in vision up to week 24. Initially, patients received monthly injections for 24 weeks. A total of 570 patients in BALATON and 750 patients in COMINO were enrolled and randomly assigned to one of two treatment groups in each trial. One group received faricimab, and the other received aflibercept. After week 24, the studies transitioned into a phase where faricimab's treatment intervals could be personalised (personalised treatment interval [PTI] regimen), extending up to every 16 weeks based on patient response. This approach allowed for a more tailored treatment plan, potentially reducing the number of injections needed and maintaining the effectiveness of the therapy over a longer period. The structure of these studies ensured that treatment adjustments were made objectively, based on the patient's progress, while maintaining regular check-ups throughout the 72-week study period.

Key inclusion criteria:

- Adults aged 18 or older at the time of signed the informed consent form.
- People diagnosed with BRVO in the BALATON study, or CRVO/HRVO in the COMINO study.
- Vision measured by a special eye chart (ETDRS), should be within a certain range.
- The thickness of the retina, measured by an eye scan (SD-OCT), needs to be above a certain thickness, showing significant swelling.

Key exclusion criteria:

- People with very high blood pressure measured when resting on the first day.
- People who have had a stroke or heart attack in the last 6 months.
- Women who are pregnant, breastfeeding, or planning to get pregnant during the study.
- People who had MO-RVO before or has had it for over 4 months without getting better.
- People with certain serious eye problems like a detached retina or a large hole in the macula.
- People who have already received treatments for MO-RVO, including other drugs injected into the eye.
- People who had specific laser treatments for their eyes.
- People treated for other eye diseases that can cause similar swelling.
- People with major illness or surgery in the last month.
- People with another eye condition that could cause vision loss not related to the vein blockage.

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.

Faricimab efficacy:

Faricimab was investigated in the BALATON (18) and COMINO (19) studies to see whether it was effective with an acceptable safety profile in treating patients with MO-RVO. Data pooling was not conducted across the studies as each type of RVO - BRVO and CRVO - affects the retina in different ways. The main analyses of how well faricimab worked were carried out on all the patients who were treated, based on the treatment group they were initially assigned.

Primary outcome measure:

In the BALATON and COMINO studies, faricimab was shown to be just as effective as aflibercept in improving vision in the study eye by the 24th week, which was the primary outcome measure of the studies. By week 24 in BALATON, patients treated with faricimab improved their vision by an average of 16.9 letters, while those treated with aflibercept improved by 17.5 letters, a minor difference of 0.6 letters. In COMINO, the improvement was 16.9 letters for faricimab and 17.3 for aflibercept, a difference of just 0.4 letters. These small differences show that faricimab is as effective as aflibercept in treating vision problems caused by RVO, staying within the acceptable range of less than a 4-letter difference in vision improvement.

Secondary outcome measures:

In the BALATON and COMINO studies, faricimab showed consistent effectiveness with aflibercept up to Week 24 and maintained this through Week 72. By Weeks 64, 68 and 72, over 60% of patients in both studies had significant vision improvement with faricimab. The studies also noted that a similar number of patients avoided major vision loss over time, with nearly all patients in both studies preventing a loss of 15 or more letters in their vision score by Weeks 64, 68 and 72.

The reduction in central retinal thickness (CRT) which is an indicator of swelling reduction, and the absence of MO are both key indicators of disease improvement. They were maintained in a significant proportion of patients through Week 72 under the faricimab PTI regimen.

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.

In the BALATON (18) and COMINO (19) studies, patient-reported outcomes were measured by the National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25), a questionnaire assessing vision-related quality of life. Results showed that both faricimab and aflibercept significantly improved patients' vision-related quality of life from the start of the study through Week 72. Initially, the average scores for patients in both studies were in the low 80s out of a possible 100, indicating a relatively high quality of life at the start.

By Week 24, patients in both the faricimab and aflibercept groups saw similar improvements in their NEI VFQ-25 scores, demonstrating that both treatments effectively enhanced patients' perception of their vision quality. These improvements were sustained through Week 72, indicating long-term benefits in vision-related quality of life for patients under the faricimab (PTI) dosing regimen.

Specifically, by Week 72 in BALATON, the improvement in the NEI VFQ-25 score was around 6 points for the faricimab group and 7.8 points for the aflibercept group. In COMINO, the improvement was around 7.8 points for the faricimab group and 8.5 points for the aflibercept group. These results highlight the positive impact of both treatments on the daily lives of patients with MO-RVO, maintaining significant quality of life improvements over the long term.

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.

In the BALATON (18) and COMINO (19) studies, the safety of faricimab was closely monitored and compared to aflibercept. Initially, both treatments showed a similar safety profile, with few adverse events (AEs) causing patients to stop treatment. As expected, there were more AEs and serious AEs (SAEs) reported in the later part of the studies (Week 24 to Week 72) due to the longer follow-up period, but the safety results for faricimab remained consistent and the treatment was still well received with few discontinuations due to AEs.

Ocular AEs, or eye-related side effects, were similar across both treatment groups and both study phases. In the first 24 weeks, 16.3% to 27.7% of participants experienced ocular AEs, depending on the study and treatment group, with serious ocular AEs being rare. From Week 24 to Week 72, the rate of ocular AEs increased slightly to 28.1% to 36.2%, but most were mild to moderate in severity and not serious. Notably, COMINO saw a slightly higher incidence of serious ocular AEs in the later part of the study within the faricimab group, though these events were not considered related to the treatment and were mostly resolved by the study's end.

Overall, the safety findings from these studies suggest that faricimab is well-tolerated, with a safety profile comparable to aflibercept and other similar treatments for RVO, even when dosing intervals are adjusted in the later part of the studies.

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

Faricimab offers a new mode of action:

While anti-VEGF treatments have shown effectiveness in clinical trials for RVO, many patients fail to achieve and maintain similar outcomes in clinical practice. The frequent injections required for these treatments also contribute to patient stress and anxiety, and the necessity for regular clinic visits places a significant burden on patients, caregivers, and healthcare professionals.

Faricimab introduces a new mode of action as a dual-action antibody, targeting both Ang-2 and VEGF, which are crucial in the development of RVO. Its unique mechanism of blocking two different pathways - helps reduce swelling, inflammation, and unwanted blood vessel growth while stabilising the blood vessels in the eye. This dual action of faricimab sets it apart from existing treatments that mainly target the VEGF pathway, offering the potential for extended treatment intervals without compromising on the treatment's effectiveness or safety.

Faricimab is effective and well-tolerated in clinical trials:

In the BALATON (18) and COMINO (19) studies, faricimab was found to be as effective as aflibercept in improving vision by Week 24. This effectiveness was sustained through Week 72, with over 60% of patients experiencing significant vision improvement. The studies also showed that nearly all patients prevented major vision loss over time, and key indicators of disease improvement, such as reduced retinal thickness and absence of MO and intraretinal fluid, were maintained.

Safety profiles for faricimab and aflibercept were similar, with a low incidence AEs leading to treatment discontinuation. Although more AEs were reported in the later study phase, faricimab remained well-tolerated. Ocular AEs were comparable across treatment groups and study phases, with most being non-serious and of mild to moderate severity.

These results indicate faricimab's potential as a safe, effective treatment for RVO, with the added benefit of possibly longer intervals between treatments.

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

A key limitation in the BALATON (18) and COMINO (19) studies is the lack of a comparator group from Weeks 24 to 72. During this period, all participants, including those initially treated with aflibercept, were transitioned to a PTI dosing regimen with faricimab. This shift was influenced by faricimab's unique dual mechanism of action targeting not only VEGF but also ANG2 as well as its demonstrated non-inferiority to aflibercept in treating other eye conditions like DMO and neovascular age-related macular degeneration (nAMD), coupled with similar safety profiles.

Emerging real-world data from patients with nAMD and DMO transitioning from other anti-VEGF therapies to faricimab indicate potential benefits in vision improvement, reduction in CST, fluid resolution, and extended treatment intervals. These findings support the decision to switch RVO patients to faricimab in the later stages of the BALATON and COMINO studies.

The studies further reinforce faricimab's ability to enhance retinal stability and maintain efficacy over time. The PTI dosing strategy, which allows for extended intervals between treatments (up to 16 weeks), aims to lessen the frequency of clinic visits and injections, thereby potentially reducing the overall treatment burden for patients and healthcare systems. This approach is facilitated by pre-defined criteria for adjusting treatment intervals based on objective measures of disease activity, offering a tailored treatment plan that can adapt to each patient's individual response.

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.

How the model reflects the condition:

- The economic case presented in this submission is based on an analysis assessing the use of faricimab compared with aflibercept and ranibizumab for the treatment of adult patients with macular oedema caused by retinal vein occlusion
- The approach taken is a cost comparison assuming equal efficacy between all technologies, with differentiation based on acquisition. To model costs and health benefits is done by three periods following the clinical pattern typically observed for RVO **Initiation** (loading phase, **maintenance phase** (characterised by a stabilisation of the disease and maintenance of vision gains previously achieved) and **Rest of life phase,** where the disease is assumed to resolve for a share of patients who can discontinue without loss of efficacy and potentially a share of patients who continue to require treatment.
- The data used to predict how long patients treated with each treatment would remain in each health state, which informs the amount of costs and health gains they would accrue, is based on data from the faricimab and comparator studies.

Modelling how much a treatment improves quality of life:

- As the analysis used for assessing faricimab was a cost comparison, it is assumed the efficacy of all treatments is similar.

Modelling how the costs of treatment differ with the new treatment:

- The analysis in the submission assumed equal durability and treatment interval between all technologies. However, as seen in nAMD and DMO it is anticipated faricimab could allow greater extension in treatment intervals due to its dual mechanism of action. This would mean in reality, the total costs of treatment related to faricimab is anticipated to be less as less frequent monitoring and hospital visits will be required.

Uncertainty:

- Due to limited data availability, there is some uncertainty regarding the treatment extension estimates included within the economic model. These are common obstacles and as equivalence is assumed with all treatments has negligible impact.

Cost-minimisation results:

In the company's base-case analysis, faricimab is cost-saving compared to aflibercept and ranibizumab. These results do not take into account any confidential commercial discounts for the comparator treatments, or the committee's preferred assumptions which may differ to those applied in the base-case analysis.

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)

Faricimab's unique dual mechanism of action supports the increased durability of effect, providing patients with a much needed opportunity to alleviate the treatment burden (20-22) associated with current anti-VEGF therapies. Faricimab brings innovation to RVO, while optimising disease control for those living with RVO. Additionally, a longer-acting treatment option that reduces the need for future treatment and monitoring visits will also help to alleviate the burden on the healthcare system, ensuring patients retain continuity of treatment and ultimately maintain their vision.

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

If a person is registered as blind or partially sighted they are considered disabled, as stated in the Equality Act 2010 (23). Therefore, the patient population addressed in this submission is a protected group under this act.

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.

- The Royal College of Ophthalmologists Retinal Vein Occlusion (RVO) Clinical Guidelines https://www.rcophth.ac.uk/wp-content/uploads/2015/07/Retinal-Vein-Occlusion-Guidelines-2022.pdf

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

BCVA	best corrected visual acuity
BRVO	branch retinal vein occlusion
CRT	central retinal thickness
CRVO	central retinal vein occlusion
CST	central subfield thickness
DMO	diabetic macular oedema
EMA	European Medicines Agency
ETDRS	Early Treatment Diabetic Retinopathy Study
HRVO	hemiretinal vein occlusion
IVT	intravitreal injection
MAA	marketing authorisation application
MHRA	Medicines and Healthcare products Regulatory Agency
nAMD	neovascular age-related macular degeneration
NEI-VFQ-25	National Eye Institute Visual Function Questionnaire – 25
NICE	National Institute For Health And Care Excellence
OCT	optical coherence tomography
PTI	personalised treatment interval
RVO	retinal vein occlusion
SAE	serious adverse event
VEGF	vascular endothelial growth factor

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:

1. Ophthalmologists RCo. Retinal Vein Occlusion (RVO) Clinical Guidelines [Accessed on 12/Feb/24]. 2022.
2. Song P, Xu Y, Zha M, Zhang Y, Rudan I. Global epidemiology of retinal vein occlusion: a systematic review and meta-analysis of prevalence, incidence, and risk factors. Journal of global health. 2019;9(1):010427.
3. Organisation WH. Ageing and health [Accessed on 20/Feb/2022]. 2022.

4. NICE. Ranibizumab (Lucentis®) for the treatment of visual impairment due to macular edema secondary to retinal vein occlusion (RVO) [Accessed 13/Feb/24]. 2011.
5. Sabel BA, Wang J, Cárdenas-Morales L, Faiq M, Heim C. Mental stress as consequence and cause of vision loss: the dawn of psychosomatic ophthalmology for preventive and personalized medicine. The EPMA journal. 2018;9(2):133-60.
6. Sivaprasad S, Oyetunde S. Impact of injection therapy on retinal patients with diabetic macular edema or retinal vein occlusion. Clinical ophthalmology (Auckland, NZ). 2016;10:939-46.
7. Healthcare W. Wilmington Heathcare Report National Summary September to December 2022 [data on file]. 2022.
8. NICE. Aflibercept for treating visual impairment caused by macular oedema after branch retinal vein occlusion [TA409] [Accessed on 13/Feb/2024]. 2016.
9. NICE. Aflibercept for treating visual impairment caused by macular oedema secondary to central retinal vein occlusion [TA305] [Accessed on 12/Feb/24]. 2014.
10. NICE. Ranibizumab for treating visual impairment caused by macular oedema secondary to retinal vein occlusion [TA283] [Accessed on 13/Feb/2024]. 2013.
11. Tan MH, McAllister IL, Gillies ME, Verma N, Banerjee G, Smithies LA, et al. Randomized controlled trial of intravitreal ranibizumab versus standard grid laser for macular edema following branch retinal vein occlusion. American journal of ophthalmology. 2014;157(1):237-47.e1.
12. Clark WL, Boyer DS, Heier JS, Brown DM, Haller JA, Vitti R, et al. Intravitreal Aflibercept for Macular Edema Following Branch Retinal Vein Occlusion: 52-Week Results of the VIBRANT Study. Ophthalmology. 2016;123(2):330-6.
13. Khanani AM, Russell MW, Aziz AA, Danzig CJ, Weng CY, Eichenbaum DA, et al. Angiopoietins as Potential Targets in Management of Retinal Disease. Clinical ophthalmology (Auckland, NZ). 2021;15:3747-55.
14. Regula JT, Lundh von Leithner P, Foxton R, Barathi VA, Cheung CM, Bo Tun SB, et al. Targeting key angiogenic pathways with a bispecific CrossMAb optimized for neovascular eye diseases. EMBO molecular medicine. 2016;8(11):1265-88.
15. Prem Senthil M, Khadka J, Gilhotra JS, Simon S, Fenwick EK, Lamoureux E, et al. Understanding quality of life impact in people with retinal vein occlusion: a qualitative inquiry. Clinical and Experimental Optometry. 2019;102(4):406-11.
16. USPI VP. Vabysmo Proposed USPI [Roche data on file].
17. SmPC VP. Vabysmo Proposed SmPC [Roche data on file].
18. Clinicaltrials.gov. A Study to Evaluate the Efficacy and Safety of Faricimab in Participants With Macular Edema Secondary to Branch Retinal Vein Occlusion (BALATON) [Accessed on 13/Feb/2024]. 2024.
19. Clinicaltrials.gov. A Study to Evaluate the Efficacy and Safety of Faricimab in Participants With Macular Edema Secondary to Central Retinal or Hemiretinal Vein Occlusion (COMINO) [Accessed on 13/Feb/2024]. 2024.
20. Gale R, Gill C, Pikoula M, Lee AY, Hanson RLW, Denaxas S, et al. Multicentre study of 4626 patients assesses the effectiveness, safety and burden of two categories of treatments for central retinal vein occlusion: intravitreal anti-vascular endothelial growth factor injections and intravitreal Ozurdex injections. The British journal of ophthalmology. 2021;105(11):1571-6.

21. Romano F, Lamanna F, Gabrielle PH, Teo KYC, Battaglia Parodi M, Iacono P, et al. Update on Retinal Vein Occlusion. Asia-Pacific journal of ophthalmology (Philadelphia, Pa). 2023;12(2):196-210.
22. Laouri M, Chen E, Looman M, Gallagher M. The burden of disease of retinal vein occlusion: review of the literature. Eye (London, England). 2011;25(8):981-8.
23. Office GE. Equality Act 2010: guidance [Accessed on 12/Feb/2024]. 2010.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Cost-comparison appraisal

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

Company Response to Clarification Questions

April 2024

File name	Version	Contains confidential information	Date
ID6197_Faricimab for RVO_EAG clarification response [redacted]	**1.0**	**Yes**	**12 April 2024**

Content

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Section A : Clarification on effectiveness data 7
Literature searches 7
A 1. Appendix D states that the searches were updated in December 2023 but no details (i.e. strategies, hits per resource) are given, nor do they appear in the PRISMA flow diagram. Please provide full details of all update searches and an updated PRISMA flowchart. 7
A 2. Appendices D and I both mention searches of grey literature resources including the websites of individual country specific HTA bodies, ClinTrial.gov and the websites of the FDA, UK government and European Medicines Agency (EMA) and specialist resources such as CEA and RePEc. Whilst full list of resources including web addresses and date of searching were provided in tables 6-9 (Appendix D) and tables 35-38 (Appendix I), there was no information given on keywords used for the searches or the number of hits retrieved. It is unclear if these are what is referred to in the PRISMA flow chart as hand searching (App D Fig.1 & App I, Fig 18). Please provide full details for each resource including keywords used and hits per resource. 14
A 3. Please confirm whether any additional searches, other than those reported in Appendix D section D.1.4, were conducted to retrieve information regarding adverse events (AEs) for Faricimab and, if so, provide full details including date, resource names and search strategies used. 20
A 4. Unlike Appendix D, Appendix I only reports a single set of searches conducted in April 2023. However, Table 35 reported a search of conference proceedings held between January 2019 - June 2023, which does not match the April 23 search date. Please confirm if any update searches were conducted, and if the date span reported for the conference searches is correct. 35
Decision problem 35
Systematic review 35
A 5. Please clarify the approach taken to conduct data extraction, specifically: 35
A 6. Section D.1.7 of Appendix D mentions that 166/240 records were excluded during full text screening however, no further details are provided. Please provide a list of the excluded references, together with reasons for exclusion. 35
Clinical effectiveness evidence 86

A 7. Appendix L provides details of a real-world data study. Please explain how this study contributed to the submission. 86

A 8. Appendix M lists the questions used during a clinical expert elicitation exercise. 86

Indirect treatment comparison (ITC) 87

A 9. Priority question. The Network Meta-analysis (NMA) presented in Appendix D contains a section referred to as "*Feasibility Assessment*". However, the only mention of heterogeneity is that it has a *"high likelihood"* and, on this basis, a random effects model was chosen (see Technical Support Document (TSD) 3. There is no mention of consistency (see TSD 4). Therefore, please conduct a full feasibility assessment that systematically examines variation between trials in clinical and methodological characteristics, any potential treatment modifying effect and thus the implications for the network for any methods to mitigate heterogeneity or inconsistency with reference to TSD 3 and TSD 4. 87

A 10. Priority question: Aside from the BALATON and COMINO RCTs, few details are provided of the trials used to populate the NMA. 87

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Model structure 88

B 1. Priority question: On page 88 of the CS it is mentioned that patients cannot switch to another therapy if they discontinue their current treatment. Please explain to what extent this is a realistic assumption and what would happen to the results if patients could switch to another treatment. 88

B 2. Please provide a rationale for the cut-off points used in the definition of the health states. 89

Clinical input parameters 89

B 3. Priority question: Page 93 of the CS states that: "patients whose dosing interval had been previously extended and who experience disease worsening that triggered an interval reduction were not allowed to extend the interval again, with the exception of patients whose dosing intervals were reduced to Q4W; their interval could be extended again but only to an interval that was 4 weeks less than their original maximum extension." 89

B 4. Priority question: In section B.4.2.4 of the CS it is mentioned that: "as there was no evidence to suggest that mortality rates would differ across treatments, the annual rate of mortality was assumed to be equivalent for faricimab, aflibercept and ranibizumab." Please explain if this statement implies that disease-specific mortality rate has been included in the model in addition to background mortality and set equal between treatments; or if this statement means that only background mortality has been included in the model. In case

disease-specific mortality rate (or excess risk of death due to the disease) is included in the model please provide details on the value(s) used and comment on the validity exercises that have been conducted for the elevated risk input(s). 92

B 5. Priority question: Table 29 of the CS presents the annual treatment discontinuation probabilities that were estimated for the treatment phase and the maintenance phase based on data from the BALATON and COMINO trials. According to the text of the CS, these annual probabilities were implemented for all treatments in the model and for the rest of life phase the respective probability was set equal to the probability estimated for the maintenance phase. However, the company also assumed that 55% would have discontinued after 5 years. 93

B 6. On page 93 of the CS, the algorithm used for PTI dosing is mentioned. In Figure 4, it can be seen that for improving CST (-10% to –20%) and a BCVA worsening between 0 and –10, the interval is maintained (yellow) whereas for the same BCVA range and a worse CST (-10% to +10%) the interval is extended by 4 weeks (green). Could you please provide the rationale for this? 95

B 7. The dosing schedule of faricimab (and the comparators) is based on a T&E regimen as according to clinical feedback is most likely to be used in clinical practice. However, the CS reported that the risk of eye deterioration between intervals in RVO is smaller compared to nAMD and DMO and may require an PRN dosing (as needed regimens based on response to disease activity) and this is the reason the company included this option as a scenario analysis. Please also include the PRN option in the model as currently in the drop-down option defining treatment regimen only the T&E is included (on the Cost inputs sheet). 96

B 8. The sheet ‘Model inputs’ of the electronic model includes inputs on the proportion of patients across health states and 2nd eye involvement. However, the % used for the baseline distribution of the first eye at baseline and second eye with and without disease at baseline are not described in the CS document. Please provide a detailed description of the inputs, how they have been used in the model and how have they been validated. 96

B 9. On page 89 of the company submission, the company states that the main data sources used in the model are the pooled data covering the patient populations of BALATON and COMINO, and the populations of studies included in the network meta-analysis. Please explain how the data were pooled, i.e., were data treated as if from one study, or was a form of meta-analysis applied? In addition, please provide an overview of all model inputs based on pooled RCT data versus input based on the indication-specific RCT. 97

Cost inputs..... 98

B 10. Priority question: The cost of an injection was estimated as the difference in costs between an injection administration visit and a monitoring visit based on the calculations performed by the evidence review group (ERG) in the appraisal of aflibercept for DMO (TA346). As the TA346 guidance was published in 2015, please explain if these costs are still considered relevant to be used in the current setting, if and how they were validated, and if (and how) they were adjusted for inflation or if they were updated using more recent available sources (NHS costing manual or any other source). 98

Company results 98

B 11. Priority question: Please confirm if the proportionate interval dosing presented in Table 33 has only been included in the scenario analyses. Please explain how the values in Table 33 have been used to derive the values (for the injection frequencies in the treatment, maintenance and rest of life phases) presented in Table 41 and Table 42 for the proportionate interval dosing scenario analyses. Please give a detailed explanation of the computations. 98

B 12. Priority question: The total costs presented in the CS seem to be accounting for informal care costs and travel costs which does not match to the company's description of the cost items included in the base case results. In Table 37 for instance, the mean total costs are not equal to the sum of the drug acquisition and administration costs, and the costs of visual impairment. Based on the model, it seems that the mean total costs presented throughout the submission consider travel and informal care costs. If this is an error, please update all results accordingly. 99

B 13. Priority question: Please include all the scenario analyses presented in the CS in the macro in the Excel models that automates the running of scenarios. 101

Section C : Textual clarification and additional points 101

C 1. On page 94 of the CS it is mentioned that: "In order to obtain the annual probability, total patient numbers in both trials divides patients discontinuing within the trials less the number of deaths." It seems like this sentence is incomplete. Please edit accordingly. 101

C 2. Several documents are missing from the submission reference pack. These include the following as referenced in Document B: 102

References 103

Tables and figures

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: Clarification on effectiveness data

Literature searches

A 1. Appendix D states that the searches were updated in December 2023 but no details (i.e. strategies, hits per resource) are given, nor do they appear in the PRISMA flow diagram. Please provide full details of all update searches and an updated PRISMA flowchart.

Please see Table 1, Table 2 and Table 3 below for the detailed search strategy for the updated Dec 2023 search. As with the original search, the database search strings identified all relevant studies (full papers or abstracts from any conference) indexed in Embase and were modified for performing searches in MEDLINE and Cochrane, to account for differences in syntax and thesaurus headings. Searches included terms for free text and Medical Subject Heading (MeSH) terms.

Table 1: Embase <1980 to 2023 Week 48>: accessed 06/12/2023

#	Searches	Results
1	retina vein occlusion/	6,231
2	((retina* vein* or retina*venous or retinal branch vein* or hemiretina* vein* or hemiretina* venous* or hemiretinal vein* or hemi-retinal vein* or hemi-retina* vein* or hemiretina* venous*) adj4 (thrombos* or occlu*)).ab,ti.	8,508
3	(rvo or crvo or hrvo or brvo).ab,ti.	4,718
4	1 or 2 or 3	11,165
5	exp macular edema/ or exp retina macula edema/ or exp retina macula cystoid edema/ or exp Cystoid Macular Edema/	21,766
6	maculopath$.tw.	6,866
7	(macula$ adj3 (edema or oedema)).tw.	21,254
8	((cystoid or clinically significant) adj2 macular adj2 (edema or oedema)).tw.	5,791
9	(CME or CSME or CMO or CSMO).tw.	17,483
10	5 or 6 or 7 or 8 or 9	49,231
11	4 and 10	4,462
12	exp faricimab/	318
13	(faricimab or RG 7716 or RO 6867461).mp.	344
14	exp Ranibizumab/	12,800
15	(ranibizumab or Lucentis or RG3645 or rhufab V2 or 347396-82-1 or "347396821" or 347396-821 or 347-396-821 or 3473-96-821 or ((PDS or port delivery system) adj2 ranibizumab)).mp.	13,216
16	exp Aflibercept/	9,262
17	(Aflibercept or Eylea or zaltrap or AVE0005 or Bay 86-5321 or HSDB 8258 or VEGF Trap* or 862111-32-8 or "862111328" or 8621-11-328 or 862111-328 or 862-111-328 or trapeye$ or trap-eye$).mp.	9,825
18	exp Bevacizumab/	75,496

19	(bevacizumab or Avastin or rhuMAb-VEGF or L01XC07 or 216974-75-3 or "216974753" or 216974-753 or 216-974-753 or 2169-74-753 or Mvasi or altuzan or kyomarc).mp.	77,997
20	exp laser coagulation/	23,515
21	(laser adj2 (therapy or treatment or strateg$ or photocoagulation or surgery)).tw.	41,524
22	dexamethasone/ or dexamethasone.mp.	201,825
23	exp tarcocimab tedromer/ or (KSI-301 or KSI 301 or tarcocimab).mp.	54
24	exp *vasculotropin inhibitor/ or exp vascular endothelial growth inhibitor/	82,047
25	*angiogenesis inhibitors/	7,632
26	((("Vascular Endothelial Cell Growth Factor*" or "Vascular Endothelial Growth Factor*" or vasculotropin* or VEGF* or "Vascular Permeability Factor*") adj3 (block* or inhibit* or antagoni*)) or anti-vegf or (anti adj2 VEGF*)).ti,ab.	36,754
27	exp 'biosimilar agent'/ or 'biosimilar agent'.mp. or (('biosimilar'.mp. or exp 'biosimilar'/ or biosimilar.mp.) and pharmaceuticals.mp.) or ('follow on'.mp. and ('biologics'.mp. or exp 'biologics'/ or biologics.mp.)) or ((subsequent and entry).mp. and ('biologics'.mp. or exp 'biologics'/ or biologics.mp.)) [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]	7,829
28	12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27	379,532
29	exp clinical trial/	1,847,395
30	exp randomized controlled trial/ or exp "randomized controlled trial (topic)"/	1,052,884
31	exp controlled clinical trial/ or exp "controlled clinical trial (topic)"/	1,255,467
32	exp controlled study/	10,144,678
33	exp multicenter study/	378,657
34	exp phase 2 clinical trial/	109,194
35	exp phase 3 clinical trial/	71,868
36	exp phase 4 clinical trial/	6,418
37	exp randomization/	98,965
38	exp single blind procedure/	52,482
39	exp double blind procedure/	209,927
40	exp crossover Procedure/	75,871
41	exp placebo/	391,572
42	randomi?ed controlled trial$.tw.	331,143
43	rct.tw.	55,046
44	(random$ adj2 allocat$).tw.	55,203
45	single blind$.tw.	31,822
46	double blind$.tw.	239,586
47	((treble or triple) adj blind$).tw.	1,947
48	placebo$.tw.	364,796
49	exp prospective study/	892,873
50	29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49	11,610,131
51	exp animal/ not (exp human/ and exp animal/)	4,781,997
52	((p?ediatr* or child or children or infant or adolescent) not ((p?ediatr* or child or children or infant or adolescent) and adult)).mp.	2,555,132
53	exp comment/ or exp note/ or exp editorial/ or exp letter/ or exp case reports/ or exp Case study/ or exp Abstract report/	3,084,787
54	51 or 52 or 53	10,086,755
55	50 not 54	8,537,394
56	11 and 28 and 55	1,461
57	4 and 28 and 55	1,902

58	limit 57 to yr="2023 -Current"	131
59	limit 57 to dd=20230403-20231206	54
60	(Apr* 2023 or May* 2023 or Jun* 2023 or Jul* 2023 or Aug* 2023 or Sep* 2023 or Oct* 2023 or Nov* 2023 or Dec* 2023).dp.	565,269
61	58 and 60	70
62	58 or 59 or 61	142

Table 2: Ovid MEDLINE(R) and Epub ahead of print, in-process, in-data-review & other non-indexed citations and daily <1946 to December 05, 2023>: accessed 06/12/2023

#	Searches	Results
1	retinal vein occlusion.mp. or retina vein occlusion/	7,163
2	retinal vein obstruction.mp.	119
3	(Retinal Vein Thromboses or Retinal Vein Thrombosis or Retinal Vein Occlusions).mp.	787
4	((retina* vein* or retina*venous or retinal branch vein* or hemiretina* vein* or hemiretina* venous* or hemiretinal vein* or hemi-retinal vein* or hemi-retina* vein* or hemiretina* venous*) adj4 (thrombos* or occlu*)).ab,ti.	6,600
5	(rvo or crvo or hrvo or brvo).ab,ti.	3,277
6	1 or 2 or 3 or 4 or 5	7,968
7	faricimab.mp.	104
8	(RG 7716 or RO 6867461).mp.	1
9	exp Ranibizumab/	4,827
10	(ranibizumab or Lucentis or RG3645 or rhufab V2 or 347396-82-1 or "347396821" or 347396-821 or 347-396-821 or 3473-96-821 or ((PDS or port delivery system) adj2 ranibizumab)).mp.	6,537
11	(Aflibercept or Eylea or zaltrap or AVE0005 or Bay 86-5321 or HSDB 8258 or VEGF Trap* or 862111-32-8 or "862111328" or 8621-11-328 or 862111-328 or 862-111-328 or trapeye$ or trap-eye$).mp.	3,689
12	exp Bevacizumab/	14,503
13	(bevacizumab or Avastin or rhuMAb-VEGF or L01XC07 or 216974-75-3 or "216974753" or 216974-753 or 216-974-753 or 2169-74-753 or Mvasi or altuzan or kyomarc).mp.	23,534
14	exp laser coagulation/	8,256
15	laser coagulation.mp. or Laser Coagulation/	9,092
16	(laser adj2 (therapy or treatment or strateg$ or photocoagulation or surgery)).tw.	31,817
17	dexamethasone/ or dexamethasone.mp.	81,672
18	exp tarcocimab tedromer/ or (KSI-301 or KSI 301 or tarcocimab).mp.	11
19	vascular endothelial growth inhibitor.mp.	69
20	*angiogenesis inhibitors/	18,562
21	((("Vascular Endothelial Cell Growth Factor*" or "Vascular Endothelial Growth Factor*" or vasculotropin* or vegf* or "Vascular Permeability Factor*") adj3 (block* or inhibit* or antagoni*)) or anti-vegf or (anti adj2 VEGF*)).ti,ab.	23,067
22	exp 'biosimilar agent'/ or 'biosimilar agent'.mp. or (('biosimilar'.mp. or exp 'biosimilar'/ or biosimilar.mp.) and pharmaceuticals.mp.) or ('follow on'.mp. and ('biologics'.mp. or exp 'biologics'/ or biologics.mp.)) or ((subsequent and entry).mp. and ('biologics'.mp. or exp 'biologics'/ or biologics.mp.)) [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word]	3,679

23	7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22	174,597
24	exp clinical trial/ or exp Clinical Trials as Topic/	1,290,208
25	exp randomized controlled trial/ or exp Randomized controlled trials as Topic/	767,328
26	exp controlled clinical trial/ or exp "controlled clinical trial (topic)"/	696,650
27	exp multicenter study/	340,699
28	exp randomization/ or exp Random allocation/	107,042
29	randomi?ed controlled trial$.tw.	258,236
30	(clinic$ adj trial$1).tw.	494,192
31	(random$ adj2 allocat$).tw.	45,059
32	exp single blind method/ or single blind$.tw.	43,719
33	exp Double blind method/ or double blind$.tw.	228,670
34	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.	201,242
35	exp Placebos/ or placebo$.tw.	268,731
36	phase 4 clinical trial.mp.	44
37	exp prospective study/	674,267
38	or/24-37	2,488,537
39	exp animal/ not (exp human/ and exp animal/)	5,176,539
40	((p?ediatr* or child or children or infant or adolescent) not ((p?ediatr* or child or children or infant or adolescent) and adult)).mp.	2,567,586
41	exp comment/ or exp note/ or exp editorial/ or exp letter/ or exp case reports/ or exp Case study/ or exp Abstract report/ or exp Historical article/ or case report.tw.	4,799,719
42	39 or 40 or 41	11,797,117
43	6 and 23 and 38	748
44	43 not 42	704
45	limit 44 to yr="2023 -Current"	32
46	limit 44 to dt=20230403-20231206	20
47	(2023 Apr* or 2023 May* or 2023 Jun* or 2023 Jul* or 2023 Aug* or 2023 Sep* or 2023 Oct* or 2023 Nov* or 2023 Dec*).dp.	746,447
48	44 and 47	14
49	45 or 46 or 48	34

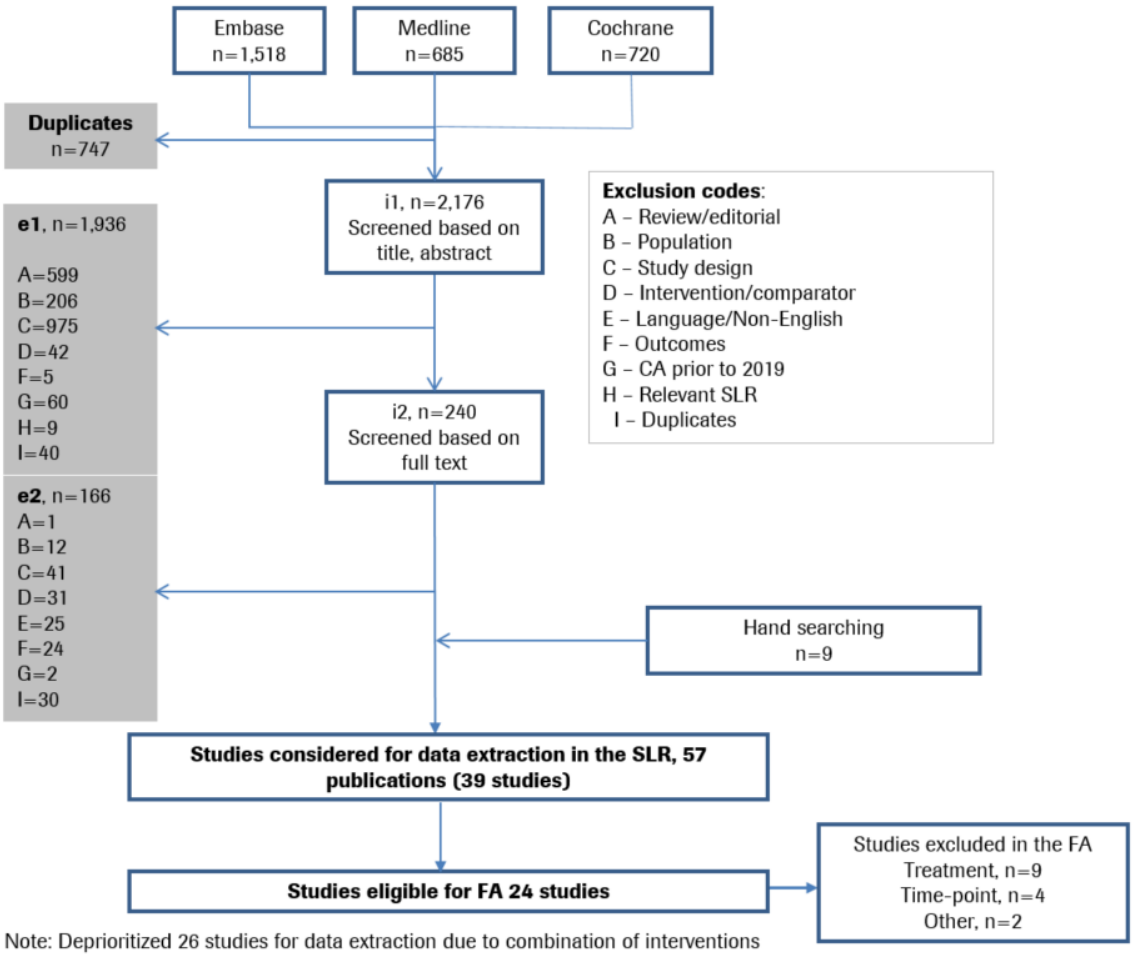
Table 3: The Cochrane Library including CENTRAL, CDSR and DARE: accessed 06/12/2023

#	Searches	Results
1	retinal vein occlusion.mp. or retina vein occlusion/	981
2	retinal vein obstruction.mp.	9
3	(Retinal Vein Thromboses or Retinal Vein Thrombosis or Retinal Vein Occlusions).mp.	71
4	((retina* vein* or retina*venous or retinal branch vein* or hemiretina* vein* or hemiretina* venous* or hemiretinal vein* or hemi-retinal vein* or hemi-retina* vein* or hemiretina* venous*) adj4 (thrombos* or occlu*)).ab,ti.	958
5	(rvo or crvo or hrvo or brvo).ab,ti.	650
6	1 or 2 or 3 or 4 or 5	1,089
7	(faricimab or RG 7716 or RO 6867461).mp.	60
8	(ranibizumab or Lucentis or RG3645 or rhufab V2 or 347396-82-1 or "347396821" or 347396-821 or 347-396-821 or 3473-96-821 or ((PDS or port delivery system) adj2 ranibizumab)).mp.	2,364

9	(Aflibercept or Eylea or zaltrap or AVE0005 or Bay 86-5321 or HSDB 8258 or VEGF Trap* or 862111-32-8 or "862111328" or 8621-11-328 or 862111-328 or 862-111-328 or trapeye$ or trap-eye$).mp.	1,216
10	(bevacizumab or Avastin or rhuMAb-VEGF or L01XC07 or 216974-75-3 or "216974753" or 216974-753 or 216-974-753 or 2169-74-753 or Mvasi or altuzan or kyomarc).mp.	7,764
11	exp laser coagulation/	748
12	laser coagulation.mp. or Laser Coagulation/	1,267
13	(laser adj2 (therapy or treatment or strateg$ or photocoagulation or surgery)).tw.	7,914
14	dexamethasone/ or dexamethasone.mp.	15,018
15	exp tarcocimab tedromer/ or (KSI-301 or KSI 301 or tarcocimab).mp.	16
16	vascular endothelial growth inhibitor.mp.	4
17	angiogenesis inhibitors/	1,678
18	((("Vascular Endothelial Cell Growth Factor*" or "Vascular Endothelial Growth Factor*" or vasculotropin* or vegf* or "Vascular Permeability Factor*") adj3 (block* or inhibit* or antagoni*)) or anti-vegf or (anti adj2 VEGF*)).ti,ab.	2,945
19	exp 'biosimilar agent'/ or 'biosimilar agent'.mp. or (('biosimilar'.mp. or exp 'biosimilar'/ or biosimilar.mp.) and pharmaceuticals.mp.) or ('follow on'.mp. and ('biologics'.mp. or exp 'biologics'/ or biologics.mp.)) or ((subsequent and entry).mp. and ('biologics'.mp. or exp 'biologics'/ or biologics.mp.))	426
20	or/7-19	34,989
21	exp animal/ not (exp human/ and exp animal/)	2,948
22	((p?ediatr* or child or children or infant or adolescent) not ((p?ediatr* or child or children or infant or adolescent) and adult)).mp.	180,554
23	exp comment/ or exp note/ or exp editorial/ or exp letter/ or exp case reports/ or exp Case study/ or exp Abstract report/ or exp Historical article/ or case report.tw.	3,946
24	21 or 22 or 23	186,909
25	6 and 20	737
26	25 not 24	730
27	limit 26 to yr="2023 -Current" [Limit not valid in DARE; records were retained]	16

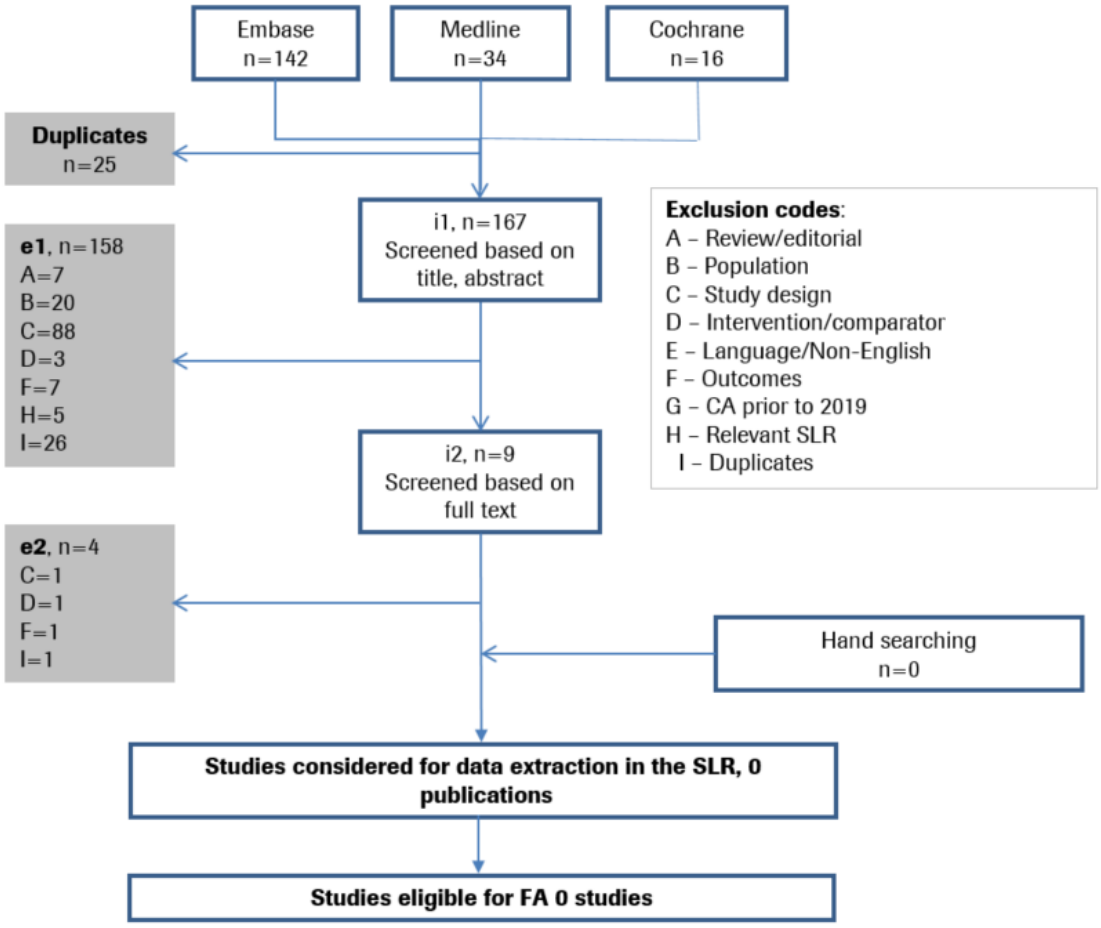
The updated set of PRISMA flow diagrams can be found in Figure 1, Figure 2 and Figure 3 below.

Figure 1: PRISMA flow diagram for the original clinical SLR review (Apr 2023)



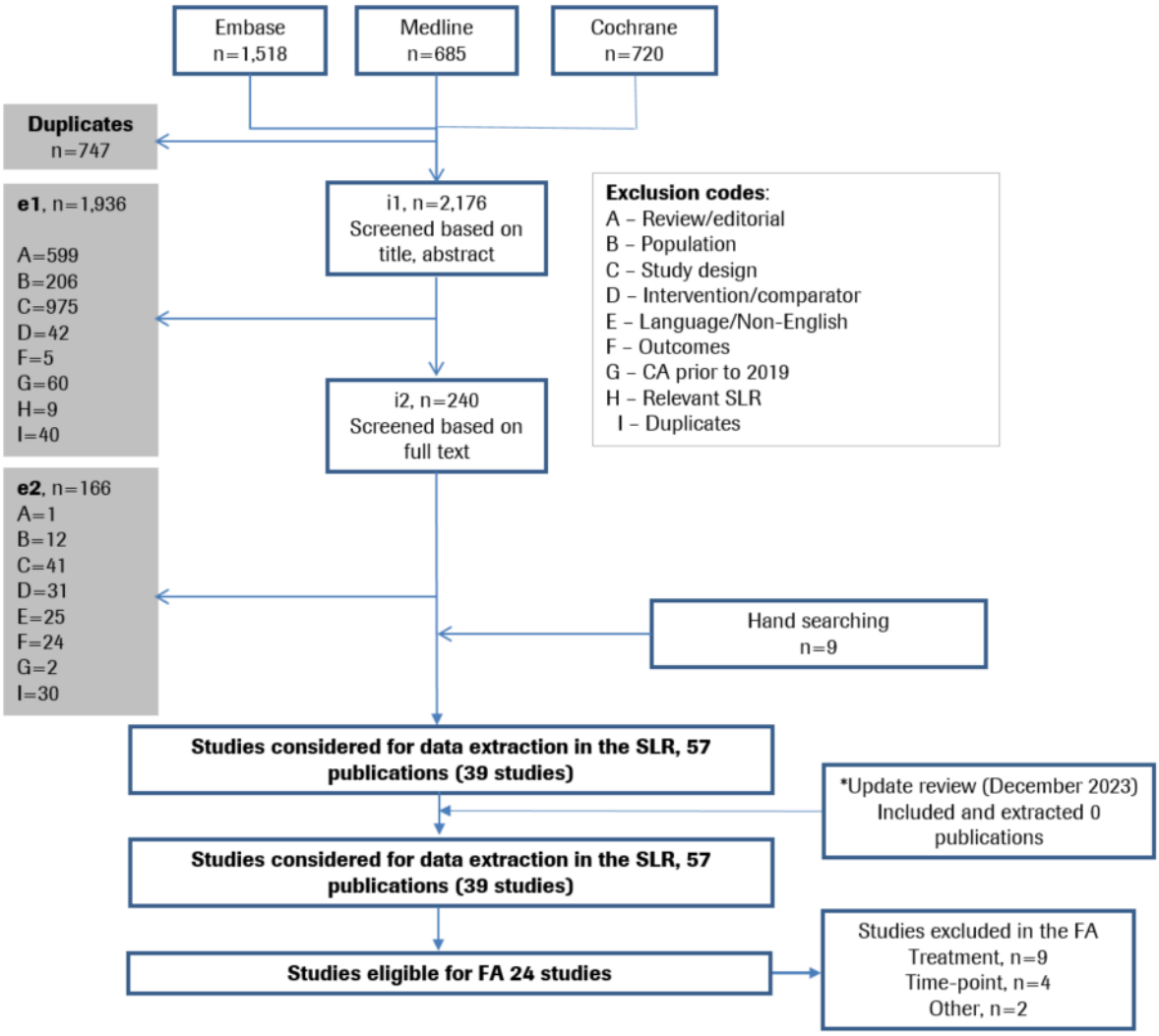
Note: Deprioritized 26 studies for data extraction due to combination of interventions

Figure 2: PRISMA flow diagram for the updated clinical SLR review (Dec 2023)



Note: Deprioritized 5 studies for data extraction due to combination of interventions

Figure 3: Overall PRISMA flow diagram for clinical SLR review



As mentioned in Appendix D.1.7, the updated search carried out in Dec 2023 had identified five additional publications. However, upon thorough review, these publications were considered irrelevant as they had been deprioritised, or were not feasible for inclusion in the subsequent network meta-analysis (NMA). Please see Appendix D, Table 10 for the list of publications identified in the Dec 2023 search.

A 2. Appendices D and I both mention searches of grey literature resources including the websites of individual country specific HTA bodies, ClinTrial.gov and the websites of the FDA, UK government and European Medicines Agency (EMA) and specialist resources such as CEA and RePEc. Whilst full list of resources including web addresses and date of searching were provided in tables 6-9 (Appendix D) and tables 35-38 (Appendix I), there was no information given on keywords used for the searches or the number of hits retrieved. It is unclear if these are what is referred to in the

PRISMA flow chart as hand searching (App D Fig.1 & App I, Fig 18). Please provide full details for each resource including keywords used and hits per resource.

The Company can confirm that the term "hand-searching" as mentioned in the PRISMA flow charts for Appendix D (Figure 1) and Appendix I (Figure 18) refers to the grey literature searches. Please see below for the full details of the hand-searching results for Appendix D and Appendix I.

For Appendix D: Hand-searching results for the original clinical SLR review (Apr 2023)

Table 4: Conference abstracts searched: accessed 11/04/23

Conference	Website	Date of the Search	Search terms	No. of hits	No. of relevant records
European Society of Retina Specialists (Euretina)	https://euretina.softr.app/vilnius	11-04-2023	Retinal vein occlusion, RVO	379	0
The Association for Research and Vision in Ophthalmology (ARVO)	https://www.arvo.org/	20-04-2023	Retinal vein occlusion, RVO	342	0
American Academy of Ophthalmology (AAO)	https://www.aao.org/	13-04-2023	Retinal vein occlusion, RVO	253	
The Retina International World Congress of Ophthalmology	https://retinaworldcongress.org/	20-04-2023	Retinal vein occlusion, RVO	0	0
The Royal Australian and New Zealand College of Ophthalmologists (RANZCO)	https://apaophth.org/the-royal-australian-and-new-zealand-college-of-ophthalmologists/	20-04-2023	Retinal vein occlusion, RVO	59	0

Table 5: HTA agency websites searched: accessed 20/04/23

HTA agencies	Website	Date of the Search	Search terms	No. of hits	No. of relevant records
National Institute for Health and Care Excellence (NICE)	https://www.nice.org.uk/	20-04-2023	Retinal vein occlusion, RVO	14	0
Scottish medical consortium (SMC)	https://www.scottishmedicines.org.uk/	21-04-2023	Retinal vein occlusion, RVO	8	0

Pharmaceutical Benefits Advisory Committee (PBAC)	https://pbac.pbs.gov.au/	21-04-2023	Retinal vein occlusion, RVO	12	0
Canadian Agency for Drugs and Technologies in Health (CADTH)	https://www.cadth.ca/	21-04-2023	Retinal vein occlusion, RVO	48	0

Table 6: Key government/international bodies searched: accessed 21/04/23

Key government/international bodies	Website	Date of the Search	Search terms	No. of hits	No. of relevant records
Gov.UK	https://www.gov.uk/	21/04/2023	Retinal vein occlusion, RVO	129	0
FDA	https://www.fda.gov/	21/04/2023	Retinal vein occlusion, RVO	46	0
EMA	http://www.ema.europa.eu/ema/	21/04/2023	Retinal vein occlusion, RVO	20	0

Table 7: Clinical trial registries searched: accessed 21/04/23

Source name	Website	Date of the Search	Search terms	No. of hits	No. of relevant records
ClinicalTrial.gov	https://classic.clinicaltrials.gov/	21-04-2023	Retinal vein occlusion, RVO	68	7

Table 8: Additional sources searched: accessed 21/04/23

Source name	Website	Date of the Search	Search terms	No. of hits	No. of relevant records
CSR reports	-	21-04-2023	Retinal vein occlusion, RVO	2	2

For Appendix D: Hand-searching results for the updated clinical SLR review (Dec 2023)

Table 9: HTA agency websites searched: accessed 08/12/23

HTA agencies	Website	Date of the Search	Search terms	No. of hits	No. of relevant records
National Institute for Health and Care Excellence (NICE)	https://www.nice.org.uk/	08-12-2023	Retinal vein occlusion, RVO	13	0
Scottish medical consortium (SMC)	https://www.scottishmedicines.org.uk/	08-12-2023	Retinal vein occlusion, RVO	8	0
Pharmaceutical Benefits Advisory Committee (PBAC)	https://pbac.pbs.gov.au/	08-12-2023	Retinal vein occlusion, RVO	9	0
Canadian Agency for Drugs and Technologies in Health (CADTH)	https://www.cadth.ca/	08-12-2023	Retinal vein occlusion, RVO	42	0

Table 10: Key government/international bodies searched: accessed 08/12/23

Key government/international bodies	Website	Date of the Search	Search terms	No. of hits	No. of relevant records
Gov.UK	https://www.gov.uk/	08-12-2023	Retinal vein occlusion, RVO	144	0
FDA	https://www.fda.gov/	08-12-2023	Retinal vein occlusion, RVO	62	0
EMA	http://www.ema.europa.eu/ema/	11-12-2023	Retinal vein occlusion, RVO	20	0

Table 11: Clinical trial registries searched: accessed 11/12/23

Source name	Website	Date of the Search	Search terms	No. of hits	No. of relevant records
ClinicalTrial.gov	https://classic.clinicaltrials.gov/	11-12-2023	Retinal vein occlusion, RVO	0	0

For Appendix I: Hand-searching results for the economic SLR review

Table 12: Conference abstracts searched: accessed 21/04/23

Conference	Website	Date of the Search	Search terms	No. of hits	No. of relevant records
European Society of Retina Specialists (Euretina)	https://euretina.softr.app/vilnius	21-04-2023	Retinal vein occlusion, RVO	379	0
The Association for Research and Vision in Ophthalmology (ARVO)	https://www.arvo.org/	21-04-2023	Retinal vein occlusion, RVO	342	0
American Academy of Ophthalmology (AAO)	https://www.aao.org/	21-04-2023	Retinal vein occlusion, RVO	253	
The Retina International World Congress of Ophthalmology	https://retinaworldcongress.org/	21-04-2023	Retinal vein occlusion, RVO	0	0
The Royal Australian and New Zealand College of Ophthalmologists (RANZCO)	https://apaophth.org/the-royal-australian-and-new-zealand-college-of-ophthalmologists/	21-04-2023	Retinal vein occlusion, RVO	59	0

Table 13: HTA agency websites searched: accessed 21/04/23

HTA agencies	Website	Date of the Search	Search terms	No. of hits	No. of relevant records
National Institute for Health and Care Excellence (NICE)	https://www.nice.org.uk/	21-04-2023	Retinal vein occlusion, RVO	14	4
Scottish medical consortium (SMC)	https://www.scottishmedicines.org.uk/	21-04-2023	Retinal vein occlusion, RVO	8	4
Pharmaceutical Benefits Advisory Committee (PBAC)	https://pbac.pbs.gov.au/	21-04-2023	Retinal vein occlusion, RVO	12	4
Canadian Agency for Drugs and Technologies in Health (CADTH)	https://www.cadth.ca/	21-04-2023	Retinal vein occlusion, RVO	48	5

Table 14: Key government/international bodies searched: accessed 21/04/23

Key government/international bodies	Website	Date of the Search	Search terms	No. of hits	No. of relevant records
Gov.UK	https://www.gov.uk/	21/04/2023	Retinal vein occlusion, RVO	129	0
FDA	https://www.fda.gov/	21/04/2023	Retinal vein occlusion, RVO	46	0
EMA	http://www.ema.europa.eu/ema/	21/04/2023	Retinal vein occlusion, RVO	20	0

Table 15: Additional sources searched: accessed 21/04/23

Source name	Website	Date of the Search	Search terms	No. of hits	No. of relevant records
International Network of Agencies for Health Technology Assessment (INAHTA)	https://www.inahta.org/	21-04-2023	Retinal vein occlusion, RVO	0	0
National Institute for Health Research Health Technology Assessment (NIHR HTA)	https://www.nihr.ac.uk/	21-04-2023	Retinal vein occlusion, RVO	0	0
University of York Centre for Reviews and Dissemination	https://www.york.ac.uk/crd/	21-04-2023	Retinal vein occlusion, RVO	0	0
The Cost-Effectiveness Analysis (CEA) Registry	https://cevr.tuftsmedicalcenter.org/databases/cea-registry	21-04-2023	Retinal vein occlusion, RVO	8	0

EconPapers within Research Papers in Economics (RePEc)	http://repec.org/	21-04-2023	Retinal vein occlusion, RVO	36	0

A 3. Please confirm whether any additional searches, other than those reported in Appendix D section D.1.4, were conducted to retrieve information regarding adverse events (AEs) for Faricimab and, if so, provide full details including date, resource names and search strategies used.

As mentioned in Appendix D, a total of 57 publications (describing 39 studies) met the inclusion criteria of the SLR. Of the 39 studies included (Appendix D, Table 11), 20 studies were integrated into a general network for the NMA feasibility assessment.

Please see Table 16 and Table 17 for safety outcomes captured as part of the SLR, reported for the 6-month time point when data are available. For the sake of readability and ease of consultation, only the outcome results reported for studies that are part of the base case (general) network are presented.

Table 16: Treatment discontinuation / withdrawals

Study details	Intervention	Time point	Sample size, n	Withdrawals / discontinuations, n (%)					
				Due to any cause	Due to adverse events	Due to lack of efficacy	Lost to follow-up	Due to death	Due to any other reason
BALATON (GR41984) (3) Phase 3 International N=553	FAR 6 mg Q4W	24 weeks	276	4 (1.4)	1 (0.4)	0 (0)	2 (0.7)	0 (0)	Withdrawal by subject: 1 (0.4)
	AFL 2 mg Q4W		277	3 (1.1)	0 (0)	0 (0)	0 (0)	0 (0)	Protocol deviation: 3 (1.1)
BLOSSOM (NCT0197633) Wei 2019 (4) Phase 3 N=283	RAN 0.5 mg PRN	6 months	190	5 (2.6)	2 (1.1)	0 (0)	1 (0.5)	0 (0)	Subject withdrew consent: 2 (1.1)
	Sham		93	2 (2.2)	1 (1.1)	0 (0)	0 (0)	0 (0)	Physician's decision: 1 (1.1)
BRAVO (NCT00486018) Campochiaro 2010 (5) Phase 3	RAN 0.3 mg Q4W	6 months	134	6 (4.5)	NR	NR	NR	NR	Patient decision was common reason for discontinuation

USA N=398	RAN 0.5 mg Q4W		131	6 (4.6)	NR	NR	NR	NR	
	Sham		132	9 (6.8)	NR	NR	NR	NR	
BRIGHTER (NCT01599650) Tadayoni, 2016, 2017 (7, 8) Phase 3b International N=455	RAN 0.5 mg PRN	6 months	180	9 (4.9)	1 (0.5)	0 (0)	1 (0.5)	1 (0.5)	Withdrawal of consent: 5 (2.7) Physicians decision: 1 (0.5)
	RAN 0.5 mg PRN + laser		183	10 (5.6)	4 (2.2)	0 (0)	0 (0)	0 (0)	Withdrawal of consent: 4 (2.2) Protocol deviation: 2 (1.1)
	Laser montherapy		92	12 (13.0)	3 (3.3)	0 (0)	0 (0)	0 (0)	Withdrawal of consent: 3 (3.3) Physicians decision: 6 (6.5)
BRVO (NCT01635803) Vader 2020 (9) Phase 2/3 Netherlands N=286	BEV 1.25 mg Q4W	6 months	139	4 (2.9)	NR	NR	NR	NR	NR

	RAN 0.5 mg Q4W		138	8 (5.8)	NR	NR	NR	NR	NR
COMINO (15) (GR41986) Phase 3 International N=729	FAR 2 mg Q4W	24 weeks	366	6 (1.6)	1 (NR)	0 (0)	0	1 (NR)	Non-compliance with study drug: 2 (0.5) Other: 2 (0.5)
	AFL 2 mg Q4W		363	10 (2.8)	1 (NR)	0 (0)	1 (0.3)	2 (NR)	Withdrawal by subject: 4 (1.1) Physician decision: 1 (0.3) Protocol deviation: 1 (0.3)
COMRADE-B (NCT01396057) Hattenbach 2018 (17) Phase 3b International N=244	RAN 0.5 mg PRN	6 months	115	11 (8.7)	2 (1.6)	2 (1.6)	0 (0)	0 (0)	Protocol violation: 4 (3.2) Subject withdrew consent: 3 (2.4)
	DEX 0.7 mg SD		100	18 (15.3)	6 (5.1)	6 (5.1)	0 (0)	0 (0)	Protocol violation: 4 (3.4) Subject withdrew consent: 2 (1.7)

COMRADE-C (NCT01396083) Hoerauf 2016 2016 (18) Phase 3b International N=243	RAN 0.5 mg PRN	6 months	124	11 (8.9)	2 (1.6)	2 (1.6)	1 (0.8)	0 (0)	Abnormal laboratory value(s): 1 (0.8) Subject withdrew consent: 4 (3.2) Administrative problems: 1 (0.8)
	DEX 0.7 mg SD		119	47 (39.5)	28 (23.5)	13 (10.9)	0 (0)	0 (0)	Protocol violation: 1 (0.8) Subject withdrew consent: 5 (4.2)
COPERNICUS (NCT00943072) Boyer 2012 (19) Phase 3 International N=187	AFL 2 mg Q4W	24 weeks	114	5 (4.3)	0 (0)	0 (0)	1 (0.9)	0 (0)	Withdrawal of consent: 3 (2.6) Other: 1 (0.9)
	Sham		74	14 (18.9)	3 (4.1)	0 (0)	2 (2.7)	2 (2.7)	Withdrawal of consent: 1 (1.4) Protocol deviation: 1 (1.4) Treatment failure: 4 (5.4)
CRAVE (NCT01428388) Rajagopal 2015 (22) USA N=98	BEV 1.25 mg Q4W	6 months	49	12 (NR)	NR	NR	NR	NR	No baseline OCT scan: 1

	RAN 0.5 mg Q4W		49	11 (NR)	NR	NR	NR	NR	No baseline OCT scan: 2
CRUISE (NCT00485836) Brown, 2010 (23) Phase 3 USA N=392	RAN 0.5 mg Q4W	6 months	130	11 (8.5)	NR	NR	NR	NR	NR
	RAN 0.3 mg Q4W		132	3 (2.3)	NR	NR	NR	NR	NR
	Sham		130	15 (11.5)	NR	NR	NR	NR	NR
GALILEO (NCT01012973) Holz 2013 (26) Phase 3 Europe N=171	AFL 2 mg Q4W	Before week 24	106	10 (9.4)	0 (0)	0 (0)	1 (0.9)	NR	Protocol violation: 5 (4.7) Withdrawal of consent: 3 (2.8) Other: 1 (0.9)
	Sham		71	15 (21.1)	4 (5.6)	5 (7)	0 (0)	NR	Protocol violation: 2 (2.8) Withdrawal of consent: 3 (4.2) Other: 1 (1.4)

GENEVA Trial (NCT00168324 and NCT00168298) Haller 2010 (29) Phase 3 International N=1267	DEX 0.7 mg SD	Prior to day 180	427	NR	8 (NR)	0 (0)	2 (NR)	NR	Personal reasons: 7 Protocol violation: 4 Other: 3
	DEX 0.35 mg SD		414	NR	8 (NR)	3 (3.6)	NR	NR	Personal reasons: 3 Protocol violation: 1 Other: 4
	Sham		426	NR	9 (NR)	4 (4.2)	3 (NR)	NR	Personal reasons: 4 Protocol violation: 2 Other: 7
Li 2018 (33) (NCT01660802) Phase 3 China N=262	DEX 0.7 mg SD	6 months	129	3 (2.3)	NR	NR	NR	NR	NR
	Sham		130	7 (5.4)	1 (NR)	NR	NR	NR	NR
ROCC (NCT00567697) Kinge 2010 (44) Phase 3 Norway	RAN 0.5 mg PRN	6 months	15	1 (NR)	1 (NR)	0 (0)	0 (NR)	0 (NR)	One patient developed retinal artery thrombosis and was withdrawn from the study shortly after the first injection

N=29	Sham		14	2 (NR)	1 (NR)	0 (0)	0 (0)	0 (0)	Two patients were withdrawn from the study, 1 for planned surgery because of cholecystitis and the other following a diagnosis of AMD, a protocol violation
SCORE 2 (NCT01969708) Scott 2017 (45) Phase 3 USA N=362	AFL 2 mg Q4W	6 months	180	5 (2.8)	2 (NR)	0 (0)	0 (0)	1 (NR)	Withdrew consent: 2
	BEV 1.25 mg Q4W		182	9 (4.9)	2 (NR)	0 (0)	0 (0)	1 (NR)	Withdrew consent: 6
VIBRANT (NCT01521559) Campochiaro 2015 (55) Phase 3 International N=181	AFL 2 mg Q4W	24 weeks		6 (6.6)	3 (3.3)	NR	0 (0)	0 (0)	NR
	Laser			9 (9.8)	0 (0)	NR	1 (1.1)	1 (1.1)	NR

Table 17: Summary of adverse events occurring in RVO studies

Study details	Study arm	Time point / Subgroup, if any	N	Ocular AEs	Ocular SAEs	Nonocular AEs	Nonocular SAEs	Conjunctival hemorrhage	Traumatic cataract	IOP elevation	Eye pain	VA reduced	Retinal detachment	Retina ischemia	Retinal tear
BALATON (GR41984) (3) Phase 3 International N=553	FAR 6 mg Q4W	BRVO	276	45 (16.3)	3 (1.1)	90 (32.6)	9 (3.3)	8 (2.9)	3 (1.1)	1 (0.4)	0 (0)	NR (NR)	3 (1.1)	NR (NR)	NR (NR)
	AFL 2 mg Q4W	BRVO	274	56 (20.4)	2 (0.7)	97 (35.4)	16 (5.8)	10 (3.6)	1 (0.4)	7 (2.6)	4 (1.5)	NR (NR)	3 (1.1)	NR (NR)	NR (NR)
BLOSSOM (NCT0197633) Wei 2019 (4) Phase 3 N=283	RAN 0.5 mg PRN	BRVO	190	NR (NR)	0 (0)	67 (35.3)	4 (NR)	13 (6.8)	NR (NR)	5 (2.6)	9 (4.7)	1 (0.5)	NR (NR)	4 (2.1)	NR (NR)
	Sham		92	NR (NR)	0 (0)	32 (34.8)	2 (NR)	2 (2.2)	NR (NR)	0 (0)	1 (1.1)	2 (2.2)	NR (NR)	2 (2.2)	NR (NR)

BRAVO (NCT00486018) Campochiaro 2010 (5) Phase 3 USA N=398	RAN 0.3 mg Q4W	BRVO	134	NR (NR)	NR (NR)	2 (1.5)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	1 (0.7)	NR (NR)	1 (0.7)
	RAN 0.5 mg Q4W	BRVO	131	NR (NR)	NR (NR)	1 (0.8)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)
	Sham	BRVO	132	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)
BRIGHTER (NCT01599650) Tadayoni, 2016 (7, 8) Phase 3b International N=455	RAN 0.5 mg PRN	BRVO	180	51 (28.3)	NR (NR)	NR (NR)	NR (NR)	11 (6.1)	NR (NR)	5 (2.8)	8 (4.4)	NR (NR)	NR (NR)	NR (NR)	NR (NR)
	RAN 0.5 mg PRN + laser	BRVO	183	68 (37.2)	2 (1.1)	NR (NR)	NR (NR)	12 (6.6)	NR (NR)	8 (4.4)	10 (5.5)	NR (NR)	NR (NR)	NR (NR)	NR (NR)
	Laser monotherapy	BRVO	88	12 (13.6)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)
BRVO (NCT01635803) Vader 2020 (9)	BEV 1.25 mg Q4W	BRVO	140	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	2 (1.4)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)

Phase 2/3 Netherlands N=286	RAN 0.5 mg Q4W		140	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	2 (1.4)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)
COMINO (15) (GR41986) Phase 3 International N=729	FAR 6 mg Q4W	CRVO, HRVO	365	84 (23)	9 (2.5)	121 (33.2)	1 (0.3)	NR (NR)	NR (NR)	0 (0)	NR (NR)	1 (0.3)	NR (NR)	1 (0.3)	0 (0)
	AFL 2 mg Q4W	CRVO, HRVO	361	100 (27.7)	12 (3.3)	143 (37.1)	1 (0.3)	NR (NR)	NR (NR)	1 (0.3)	NR (NR)	0 (0)	NR (NR)	2 (0.6)	1 (0.3)
COMRADE-B (NCT01396057) Hattenbach 2018 (17) Phase 3b International N=244	RAN 0.5 mg PRN	BRVO	126	61 (48.4)	NR (NR)	NR (NR)	7 (5.6)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)
	DEX 0.7 mg SD	BRVO	118	74 (62.7)	NR (NR)	NR (NR)	8 (6.8)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)
COMRADE-C (NCT01396083) Hoerauf 2016 (18) Phase 3b	RAN 0.5 mg PRN	CRVO	124	69 (55.6)	1 (0.8)	72 (58.1)	9 (7.3)	16 (12.9)	NR (NR)	7 (5.6)	15 (12.1)	8 (6.5)	NR (NR)	1 (0.8)	NR (NR)

International N=243	DEX 0.7 mg SD + sham		119	103 (86.6)	9 (7.6)	65 (54.6)	9 (7.6)	13 (10.9)	NR (NR)	38 (31.9)	15 (12.6)	22 (18.5)	NR (NR)	6 (5)	NR (NR)
COPERNICUS (NCT00943072) Boyer 2012 (19, 20) Phase 3 International N=187	AFL 2 mg Q4W	CRVO	114	NR (68.4)	4 (3.5)	NR (NR)	NR (5.3)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	1 (0.9)	NR (NR)	NR (NR)	0 (0)
	Sham	CRVO	74	NR (68.9)	10 (13.5)	NR (NR)	NR (8.1)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	1 (1.4)	NR (NR)	NR (NR)	1 (1.4)
CRAVE (NCT01428388) Rajagopal 2015 (22) USA N=98	BEV 1.25 mg Q4W	BRVO, CRVO, HRVO	49	NR (NR)	0 (0)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	0 (0)
	RAN 0.5 mg Q4W	BRVO, CRVO, HRVO	49	NR (NR)	0 (0)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	0 (0)
CRUISE (NCT00485836)	RAN 0.5 mg Q4W	CRVO	129	2 (1.6)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	0 (0)	NR (NR)	0 (0)

Brown, 2010 (23) Phase 3 USA N=392	RAN 0.3 mg Q4W		132	3 (2.3)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	0 (0)	NR (NR)	0 (0)
	Sham	CRVO	129	5 (3.9)	2 (NR)	NR (NR)	NR (NR)	1.6 (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	0 (0)	NR (NR)	0 (0)
GALILEO (NCT01012973) Holz 2013 (26) Phase 3 Europe N=171	AFL 2 mg Q4W	CRVO	104	NR (54.8)	2 (1.9)	NR (45.2)	NR (5.8)	NR (8.7)	NR (NR)	3 (2.9)	NR (11.5)	1 (1.5)	NR (NR)	NR (NR)	1 (1)
	Sham	CRVO	68	NR (64.7)	5 (7.4)	NR (54.4)	NR (7.4)	NR (4.4)	NR (NR)	2 (2.9)	NR (4.4)	NR (NR)	NR (NR)	NR (NR)	0 (0)
GENEVA Trial (NCT00168324 and NCT00168298) Haller 2010 (29) Phase 3 International N=1267	DEX 0.7 mg SD	BRVO, CRVO	427	NR (62.9)	NR (NR)	NR (NR)	NR (NR)	85 (20.2)	NR (NR)	109 (25.9)	31 (7.4)	7 (1.7)	NR (NR)	NR (NR)	NR (NR)
	DEX 0.35 mg SD	BRVO, CRVO	412	NR (61.9)	NR (NR)	NR (NR)	NR (NR)	72 (17.5)	NR (NR)	103 (25)	17 (4.1)	7 (1.7)	NR (NR)	NR (NR)	NR (NR)
	Sham	BRVO, CRVO	423	NR (42.8)	NR (NR)	NR (NR)	NR (NR)	63 (14.9)	NR (NR)	6 (1.4)	16 (3.8)	9 (2.1)	NR (NR)	NR (NR)	NR (NR)

Li 2018 (33) (NCT01660802) Phase 3 China N=262	DEX 0.7 mg SD	BRVO, CRVO	129	NR (NR)	NR (NR)	NR (NR)	NR (NR)	24 (18.6)	NR (NR)	38 (29.5)	3 (2.3)	4 (3.1)	NR (NR)	NR (NR)	NR (NR)
	Sham	BRVO, CRVO	130	NR (NR)	NR (NR)	NR (NR)	NR (NR)	5 (3.8)	NR (NR)	4 (3.1)	3 (2.3)	6 (4.6)	NR (NR)	NR (NR)	NR (NR)
MARVEL (36) (CTRI/2012/01/003120) Narayanan 2017 Phase 3 India N=75	RAN 0.5 mg PRN	BRVO	37	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	1 (0)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)
	BEV 1.25 mg PRN	BRVO	38	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	0 (0)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)
ROCC (NCT00567697) Kinge 2010 (44)	RAN 0.5 mg PRN	CRVO	15	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	0 (0)	NR (NR)	NR (NR)

Phase 3 Norway N=29	Sham		14	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	1 (NR)
SCORE 2 (NCT01969708) Scott 2017 (45) Phase 3 USA N=362	AFL 2 mg Q4W	CRVO, HRVO	180	2 (1.1)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	>35 mm Hg 0 (0)	NR (NR)	NR (NR)	0 (0)	NR (NR)	NR (NR)
	BEV 1.25 mg Q4W		182	6 (3.3)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	>35 mm Hg 2 (1.1)	NR (NR)	NR (NR)	1 (0.5)	NR (NR)	NR (NR)
VIBRANT (NCT01521559) Campochiaro 2015 (55) Phase 3 North America & Japan N=181	AFL 2 mg Q4W	BRVO, HRVO	91	NR (37.4)	1 (NR)	NR (47.3)	NR (8.8)	NR (19.8)	NR (NR)	NR (NR)	NR (4.4)	NR (NR)	NR (NR)	NR (NR)	NR (NR)
	Laser	BRVO, HRVO	92	NR (27.2)	1 (NR)	NR (50)	NR (9.8)	NR (4.3)	NR (NR)	NR (NR)	NR (5.4)	NR (NR)	NR (NR)	NR (NR)	NR (NR)

A 4. Unlike Appendix D, Appendix I only reports a single set of searches conducted in April 2023. However, Table 35 reported a search of conference proceedings held between January 2019 - June 2023, which does not match the April 23 search date. Please confirm if any update searches were conducted, and if the date span reported for the conference searches is correct.

The Company can confirm that the discrepancy noted was an error. Only one set of searches was conducted in April 2023, as reflected in Appendix I, Table 35. The mention of a broader time span for conference proceedings searches does not correspond to additional searches but was mistakenly stated.

Decision problem

No questions.

Systematic review

A 5. Please clarify the approach taken to conduct data extraction, specifically:

a) How were disagreements and discrepancies resolved between the first reviewer and the senior reviewer who checked data extractions?

b) Please explain what is meant by "*quality checked by a senior reviewer*", in Appendix D.1.6?

Data extraction was conducted by one reviewer. Extractions were verified by a second independent reviewer for 100% of the data elements, and any disputes were referred to a senior strategic advisor to reconcile.

A 6. Section D.1.7 of Appendix D mentions that 166/240 records were excluded during full text screening however, no further details are provided. Please provide a list of the excluded references, together with reasons for exclusion.

Please see Table 18 below for the 166 excluded studies with reasons for exclusion.

Table 18: List of excluded studies and rationale

Authors	Title	Journal	Year	Volume	Page no	DOI	Second pass (Include/Exclude)	Exclusion reason
Anonymous	A randomized clinical trial of early panretinal photocoagulation for ischemic central vein occlusion. The Central Vein Occlusion Study Group N report	Ophthalmology	1995	102	1434-44		Exclude	Intervention/comparator
Anonymous	Evaluation of grid pattern photocoagulation for macular edema in central vein occlusion. The Central Vein Occlusion Study Group M report	Ophthalmology	1995	102	1425-33		Exclude	Intervention/comparator
Battaglia Parodi, M. S., S.; Bergamini, L.; Ravalico, G.	Grid laser treatment of macular edema in macular branch retinal vein occlusion	Documenta Ophthalmologica	1999	97(3-4)	223-227		Exclude	Intervention/comparator
Battaglia Parodi, M. S., S.; Ravalico, G.	Grid laser treatment in macular branch retinal vein occlusion	Graefe's Archive for Clinical and Experimental Ophthalmology	1999	237(12)	1024-1027	https://dx.doi.org/10.1007/s004170050339	Exclude	Intervention/comparator

Callizo, J. A., A.; Striebe, N. A.; Bemme, S.; Feltgen, N.; Hoerauf, H.; Bertelmann, T.	Bevacizumab versus bevacizumab and macular grid photocoagulation for macular edema in eyes with non-ischemic branch retinal vein occlusion: results from a prospective randomized study	Graefe's Archive for Clinical and Experimental Ophthalmology	2019	257(5)	913-920	https://dx.doi.org/10.1007/s00417-018-04223-9	Exclude	Study design
Campochiaro, P. A. H., G.; Channa, R.; Shah, S. M.; Nguyen, Q. D.; Ying, H.; Do, D. V.; Zimmer-Galler, I.; Solomon, S. D.; Sung, J. U.; Syed, B.	Antagonism of vascular endothelial growth factor for macular edema caused by retinal vein occlusions: Two-year outcomes	Ophthalmology	2010	117(12)	2387-2394.e5	https://dx.doi.org/10.1016/j.ophtha.2010.03.060	Exclude	Study design
Feltgen, N. H., L. O.; Bertelmann, T.; Callizo, J.; Rehak, M.; Wolf, A.; Berk, H.; Eter, N.; Lang, G. E.; Pielen, A.; Schmitz-Valckenberg, S.; Quiering, C.; Rose, U.; Hoerauf, H.	Comparison of ranibizumab versus dexamethasone for macular oedema following retinal vein occlusion: 1-year results of the COMRADE extension study	Acta Ophthalmologica	2018	96(8)	e933-e941	https://dx.doi.org/10.1111/aos.13770	Exclude	Study design

Feltgen, N. O., Y.; Boscia, F.; Holz, F. G.; Korobelnik, J. F.; Brown, D. M.; Heier, J. S.; Stemper, B.; Rittenhouse, K. D.; Asmus, F.; Ahlers, C.; Vitti, R.; Saroj, N.; Mitchell, P.	Impact of Baseline Retinal Nonperfusion and Macular Retinal Capillary Nonperfusion on Outcomes in the COPERNICUS and GALILEO Studies	Ophthalmology Retina	2019	3(7)	553-560	https://dx.doi.org/10.1016/j.oret.2019.02.010	Exclude	Study design
Huang, J. M. K., R. N.; Ghanekar, A.; Wang, P. W.; Day, B. M.; Blodi, B. A.; Domalpally, A.; Quezada-Ruiz, C.; Ip, M. S.	Disease-modifying effects of ranibizumab for central retinal vein occlusion	Graefe's Archive for Clinical and Experimental Ophthalmology	2022	260(3)	799-805	https://dx.doi.org/10.1007/s00417-021-05224-x	Exclude	Study design
McAllister, I. L. S., L. A.; Chen, F. K.; Mackey, D. A.; Sanfilippo, P. G.	Functional benefits of a chorioretinal anastomosis at 2 years in eyes with a central retinal vein occlusion treated with ranibizumab compared with ranibizumab monotherapy	BMJ open ophthalmology	2021	6(1)	e000728	https://dx.doi.org/10.1136/bmjophth-2021-000728	Exclude	Study design

Murata, T. K., M.; Inoue, M.; Nakao, S.; Osaka, R.; Shiragami, C.; Sogawa, K.; Mochizuki, A.; Shiraga, R.; Kaneko, T.; Chandrasekhar, C.; Tsujikawa, A.; Kamei, M.	Estimating ranibizumab injection numbers and visual acuity at 12 months based on 2-month data on branch retinal vein occlusion treatment	Scientific reports	2022	Vol.12	7661p	https://doi.org/10.1038/s41598-022-11113-y	Exclude	Study design
Murata, T. K., M.; Inoue, M.; Nakao, S.; Osaka, R.; Shiragami, C.; Sogawa, K.; Mochizuki, A.; Shiraga, R.; Ohashi, Y.; Kaneko, T.; Tsujikawa, A.; Kamei, M.	Comparison of ranibizumab with or without focal/grid laser for macular edema secondary to branch retinal vein occlusion: 12-month results from the ZIPANGU study	Investigative ophthalmology & visual science		Vol.61	2020-05-03 to 2020-05-07. 2020 Annual Meeting Association for Research in Vision and Ophthalmology		Exclude	Study design
Parodi, M. B. D. S., G.; Ravalico, G.	Grid laser treatment for exudative retinal detachment secondary to ischemic branch retinal vein occlusion	Retina	2008	28(1)	97-102	https://dx.doi.org/10.1097/IAE.0b013e318074bc1d	Exclude	Intervention/comparator

Pielen, A. F., N.; Hattenbach, L. O.; Hoerauf, H.; Bertelmann, T.; Quiering, C.; Vogeler, J.; Priglinger, S.; Lang, G. E.; Schmitz-Valckenberg, S.; Wolf, A.; Rehak, M.	Ranibizumab Pro Re nata versus Dexamethasone in the Management of Ischemic Retinal Vein Occlusion: Post-hoc Analysis from the COMRADE Trials	Current eye research	2019		01-Nov	https://dx.doi.org/10.1080/02713683.2019.1679839	Exclude	Study design
Sadda, S. D., R. P.; Pappuru, R. R.; Keane, P. A.; Jiao, J.; Li, X. Y.; Whitcup, S. M.	Vascular changes in eyes treated with dexamethasone intravitreal implant for macular edema after retinal vein occlusion	Ophthalmology	2013	120(7)	1423-1431	https://dx.doi.org/10.1016/j.ophtha.2012.12.021	Exclude	Study design
Sophie, R. H., G.; Scott, A. W.; Zimmer-Galler, I.; Nguyen, Q. D.; Ying, H.; Do, D. V.; Solomon, S.; Sodhi, A.; Gehlbach, P.; Duh, E.; Baranano, D.; Campochiaro, P. A.	Long-term outcomes in ranibizumab-treated patients with retinal vein occlusion; the role of progression of retinal nonperfusion	American Journal of Ophthalmology	2013	156	693-705	https://dx.doi.org/10.1016/j.ajo.2013.05.039	Exclude	Study design

Tang, W. G., J.; Xu, G.; Liu, W.; Chang, Q.	Three Monthly Injections Versus One Initial Injection of Ranibizumab for the Treatment of Macular Edema Secondary to Branch Retinal Vein Occlusion: 12-Month Results of a Prospective Randomized Study	Ophthalmology and Therapy	2022	11(6)	2309-2320	https://dx.doi.org/10.1007/s40123-022-00588-7	Exclude	Study design
Thach, A. B. Y., L.; Hoang, C.; Tuomi, L.	Time to clinically significant visual acuity gains after ranibizumab treatment for retinal vein occlusion: BRAVO and CRUISE trials	Ophthalmology	2014	121	1059-66	https://dx.doi.org/10.1016/j.ophtha.2013.11.022	Exclude	Study design
Yiu, G. W., R. J.; Wang, Y.; Wang, Z.; Wang, P. W.; Haskova, Z.	Spectral-Domain OCT Predictors of Visual Outcomes after Ranibizumab Treatment for Macular Edema Resulting from Retinal Vein Occlusion	Ophthalmology Retina	2020	4(1)	67-76	https://dx.doi.org/10.1016/j.oret.2019.08.009	Exclude	Study design
Scott, I. U. O., N. L.; VanVeldhuisen, P. C.; Ip, M. S.; Blodi, B. A.	SCORE2 Report 20: Relationship of Treatment Discontinuation With Visual Acuity and Central Subfield Thickness Outcomes	American Journal of Ophthalmology	2023	248	157-163	https://dx.doi.org/10.1016/j.ajo.2022.12.026	Exclude	Intervention/comparator

Karimi, S. N., H.; Nafisi, H.; Nouri, H.; Ansari, I.; Barkhordari, S.; Samnejad, S.; Abtahi, S. H.	Acetazolamide and bevacizumab combination therapy versus bevacizumab monotherapy in macular edema secondary to retinal vein occlusion	Journal francais d'ophtalmologie.	2023	2		https://dx.doi.org/10.1016/j.jfo.2022.09.025	Exclude	Intervention/comparator
Singer, M. A. B., D. S.; Williams, S.; McKee, H.; Kerr, K.; Pegoraro, T.; Trevino, L.; Kopczynski, C. C.; Hollander, D. A.	Phase 2 Randomized Study (Orion-1) of a Novel, Biodegradable Dexamethasone Implant (Ar-1105) for the Treatment of Macular Edema Due to Central or Branch Retinal Vein Occlusion	Retina	2023	43(1)	25-33	https://dx.doi.org/10.1097/IAE.0000000000003632	Exclude	Study design
Moreno-Lopez, M. d.-A.-P., P.; de-Arriba-Palomero, F.; Ituruburu, F. P.; Dompablo, E.; Negrete, F. J. M.	Prospective evaluation of the effectiveness of combined treatment of macular edema secondary to retinal vein occlusion with intravitreal bevacizumab and dexamethasone implants	Arquivos brasileiros de oftalmologia.	2022	21		https://dx.doi.org/10.5935/0004-2749.20230040	Exclude	Study design
Xuehui Shi, Wenbin We	The efficacy and safety of Conbercept in Macular Edema secondary to Branch Retinal Vein Occlussion	European Society of Retina Specialists (Euretina)	2022			https://euretina.softr.app/abstract?recordId=receA5AavImnw6gvI	Exclude	Intervention/comparator

Gu, S. Z. N., O.; Bressler, S. B.; Du, W.; Amer, F.; Moini, H.; Bressler, N. M.	Correlation between change in central subfield thickness and change in visual acuity in macular edema due to retinal vein occlusion: post hoc analysis of COPERNICUS, GALILEO, and VIBRANT	Graefe's Archive for Clinical and Experimental Ophthalmology	2022	260(12)	3799-3807	https://dx.doi.org/10.1007/s00417-022-05697-4	Exclude	Outcomes
Scott, I. U. O., N. L.; Vanveldhuisen, P. C.; Ip, M. S.; Blodi, B. A.	Baseline Characteristics and Outcomes After Anti-Vascular Endothelial Growth Factor Therapy for Macular Edema in Participants With Hemiretinal Vein Occlusion Compared With Participants With Central Retinal Vein Occlusion: Study of Comparative Treatments for Retinal Vein Occlusion 2 (SCORE2) Report 18	JAMA Ophthalmology	2022	140(5)	458-464	https://dx.doi.org/10.1001/jamaophthalmol.2022.0352	Exclude	Outcomes
Wang, X. B. W., G. J.; Liu, C.	Efficacy of Dexamethasone intravitreal implant combined with anti-VEGF drug in the treatment of retinal vein occlusion. [Chinese]	International Eye Science	2022	22(10)	1717-1721	https://dx.doi.org/10.3980/j.issn.1672-5123.2022.10.24	Exclude	Duplicate

Liang, X. S., B.; Ou, Z.; An, H.; Li, L.	Comparison of intravitreal ranibizumab monotherapy vs. ranibizumab combined with dexamethasone implant for macular edema secondary to retinal vein occlusion	Frontiers in Medicine	2022	9 (no pagination)		https://dx.doi.org/10.3389/fmed.2022.930508	Exclude	Study design
Frederiksen, K. H. V., J. P.; Pedersen, F. N.; Vergmann, A. S.; Sorensen, T. L.; Laugesen, C. S.; Kawasaki, R.; Peto, T.; Grauslund, J.	Navigated laser and aflibercept versus aflibercept monotherapy in treatment-naive branch retinal vein occlusion: A 12-month randomized trial	Acta Ophthalmologica	2022	100(7)	e1503-e1509	https://dx.doi.org/10.1111/aos.15182	Exclude	Duplicate
Avitabile, T. L., A.; Reibaldi, A.	Intravitreal triamcinolone compared with macular laser grid photocoagulation for the treatment of cystoid macular edema	American Journal of Ophthalmology	2005	140(4)	e1-695	https://dx.doi.org/10.1016/j.ajo.2005.05.021	Exclude	Population
Gurudas, S. P., N.; Nicholson, L.; Sen, P.; Ramu, J.; Sivaprasad, S.; Hykin, P.	Visual Outcomes Associated with Patterns of Macular Edema Resolution in Central Retinal Vein Occlusion Treated with Anti-Vascular Endothelial Growth Factor Therapy: A Post Hoc Analysis of the Lucentis, Eylea, Avastin in Vein Occlusion (LEAVO) Trial	JAMA Ophthalmology	2022	140(2)	143-150	https://dx.doi.org/10.1001/jamaophthalmol.2021.5619	Exclude	Study design

Wykoff, C. C. A., F.; Adamis, A. P.; Basu, K.; Eichenbaum, D. A.; Haskova, Z.; Lin, H.; Loewenstein, A.; Mohan, S.; Pearce, I. A.; Sakamoto, T.; Schlottmann, P. G.; Silverman, D.; Sun, J. K.; Wells, J. A.; Willis, J. R.; Tadayoni, R.; Aaberg, T.; Abbey, A.; Abdulaeva, E.; Abengoechea, S.; Abraham, P.; Ach, T.; Adams, S.; Adan Civera, A.; Adrean, S.; Agostini, H.; Alam, S.; Alezzandrini, A.; Alfaro, V.; Aliseda, D.; Almony, A.; Amat, P.; Amini, P.; Antoszyk, A.; Arias, L.; Asaria, R.; Avila, M.; Awh, C. C.; Bafalluy, J.; Baker, C.; Bandello, F.; Barakat, M.; Barraza, K.; Bator, G.; Baumal, C.; Belfort Jr, R.; Bergstrom, C.; Bertolucci, G.; Bochow, T.; Bolz, M.; Borcz, E.; Bordon, A.; Boyer, D.; Bratko, G.; Brent, M.; Brown, J.; Brown, D. M.; Budzinskaya, M.; Buffet, S.; Burgess, S.; Burton,	Efficacy, durability, and safety of intravitreal faricimab with extended dosing up to every 16 weeks in patients with diabetic macular oedema (YOSEMITE and RHINE): two randomised, double-masked, phase 3 trials	The Lancet	2022	399(10326)	741-755	https://dx.doi.org/10.1016/S0140-6736%2822%2900018-6	Exclude	Population

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Garcia, R.; Garcia-Layana, A.; Gawecki, M.; George, S.; Ghanchi, F.; Ghorayeb, G.; Goldberg, R.; Goldstein, M.; Gomes, N.; Gomez Ulla, F.; Gonzalez, V.; Greven, C.; Gupta, S.; Guzman, M.; Harris, M.; Hatz, K.; Hau, V.; Hayashi, K.; Heier, J.; Herba, E.; Hershberger, V.; Higgins, P.; Hirakata, A.; Ho, A.; Holekamp, N.; Honda, S.; Hsu, J.; Hu, A.; Hurcikova, M.; Ikeda, Y.; Isernhagen, R.; Ito, Y.; Jackson, T.; Jacoby, R.; Jafree, A.; Javey, G.; Javid, C.; Jhaveri, C.; Johnson, M.; Kacerik, M.; Kaluzny, J.; Kampik, D.; Kang, S. W.; Kapoor, K.; Karabas, L.; Kawasaki, T.; Kerenyi, A.; Khanani, A.; Khurana, R.; Kim, B.; Kimura, K.; Kishino, G.; Kitano, S.; Klein-Mascia, K.; Kokame, G.; Korobelnik, J. F.; Kulikov, A.; Kuriyan, A.; Kwong, H.; Kwun, R.; Lai, T.; Lai, C. C.; Laird, P.; Lalonde, L.; Lanzetta, P.; Larsen, M.; Laugesen, C.;								

Lavinsky, D.; Lebreton, O.; Lee, S.; Levy, J.; Lipkova, B.; Liu, M.; Liu, J.; Lohmann, C. P.; London, N.; Lorenz, K.; Lotery, A.; Lozano Rechy, D.; Lujan, S.; Ma, P.; Maeno, T.; Mahmood, S.; Makkouk, F.; Malik, K.; Marcus, D.; Margherio, A.; Mastropasqua, L.; Maturi, R.; McCabe, F.; McKibbin, M.; Mehta, H.; Menon, G.; Mentes, J.; Michalska-Malecka, K.; Misheva, A.; Mitamura, Y.; Mitchell, P.; Modi, Y.; Mohamed, Q.; Montero, J.; Moore, J.; Morales Canton, V.; Morori-Katz, H.; Morugova, T.; Murakami, T.; Muzyka-Wozniak, M.; Nardi, M.; Nemcansky, J.; Nester-Ostrowska, K.; Neto, J.; Newell, C.; Nicolo, M.; Nielsen, J.; Noda, K.; Obana, A.; Ogata, N.; Oh, H.; Oh, K.; Ohr, M.; Oleksy, P.; Oliver, S.; Olivier, S.; Osher, J.; Ozcaliskan, S.; Ozturk, B.; Papp, A.; Park, K. H.; Parke, D. W.; Parravano, M. C.; Patel,								

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Scott, I. U. O., N. L.; VanVeldhuisen, P. C.; Ip, M. S.; Blodi, B. A.	SCORE2 Report 17: Macular thickness fluctuations in anti-VEGF-treated patients with central or hemiretinal vein occlusion	Graefe's Archive for Clinical and Experimental Ophthalmology	2022	260(5)	1491-1500	https://dx.doi.org/10.1007/s00417-021-05494-5	Exclude	Duplicate
Chanthowong, K. S., S.; Yoipaiboon, Y.; Hemanak, S.	Comparison of ziv-aflibercept and bevacizumab for treatment of naive central retinal vein occlusion with macular edema: interim analysis of a randomized noninferiority trial	Investigative Ophthalmology and Visual Science	2022	63(7)	3743-F0164		Exclude	Duplicate
Gordon, C.	Poor response to anti-VEGF treatment in macular edema secondary to central retinal vein occlusion and its baseline predictors: a post hoc analysis of COPERNICUS and GALILEO	Investigative Ophthalmology and Visual Science	2022	63(7)	1757-F0217		Exclude	Study design
Frederiksen, K. H. V., J.; Pedersen, F. N.; Vergmann, A. S.; Sorensen, T. L.; Laugesen, C.; Kawasaki, R.; Peto, T.; Grauslund, J.	Navigated laser and aflibercept in treatment of branch retinal vein occlusion and macular edema: a 12 months randomized clinical trial	Investigative Ophthalmology and Visual Science	2022	63(7)	1728-F0188		Exclude	Study design

Park, D. G. J., W. J.; Park, J. M.; Kim, J. Y.; Ji, Y. S.; Sagong, M.	Prospective trial of treat-and-extend regimen with aflibercept for branch retinal vein occlusion: 1-year results of the PLATON trial	Graefe's archive for clinical and experimental ophthalmology = Albrecht von Graefes Archiv fur klinische und experimentelle Ophthalmologie.	2021	29		https://dx.doi.org/10.1007/s00417-021-05150-y	exclude	Study design
Korobelnik, J. F. L., M.; Eter, N.; Bailey, C.; Wolf, S.; Schmelter, T.; Allmeier, H.; Chaudhary, V.	Efficacy and Safety of Intravitreal Aflibercept Treat-and-Extend for Macular Edema in Central Retinal Vein Occlusion: The CENTERA Study	American journal of ophthalmology.	2021	5		https://dx.doi.org/10.1016/j.ajo.2021.01.027	exclude	Study design
Bai, S.	Efficacy of intravitreal ranibizumab or Conbercept combined with laser photocoagulation for macular edema secondary to branch retinal vein occlusion. [Chinese]	International Eye Science	2017	17(4)	648-651	https://dx.doi.org/10.3980/j.issn.1672-5123.2017.4.14	Exclude	Non-english

Murata, T. K., M.; Inoue, M.; Nakao, S.; Osaka, R.; Shiragami, C.; Sogawa, K.; Mochizuki, A.; Shiraga, R.; Ohashi, Y.; Kaneko, T.; Chandrasekhar, C.; Tsujikawa, A.; Kamei, M.	The randomized ZIPANGU trial of ranibizumab and adjunct laser for macular edema following branch retinal vein occlusion in treatment-naive patients	Scientific reports	2021	11(1)	551	https://dx.doi.org/10.1038/s41598-020-79051-1	exclude	Duplicate
Sen, P. G., S.; Ramu, J.; Patrao, N.; Chandra, S.; Rasheed, R.; Nicholson, L.; Peto, T.; Sivaprasad, S.; Hykin, P.	Predictors of Visual Acuity Outcomes after Anti-Vascular Endothelial Growth Factor Treatment for Macular Edema Secondary to Central Retinal Vein Occlusion	Ophthalmology Retina	2021	5(11)	1115-1124	https://dx.doi.org/10.1016/j.oret.2021.02.008	exclude	Study design
Hendrick, A. V., P. C.; Scott, I. U.; King, J.; Blodi, B. A.; Ip, M. S.; Khurana, R. N.; Oden, N. L.	SCORE2 Report 13: Intraretinal Hemorrhage Changes in Eyes With Central or Hemiretinal Vein Occlusion Managed With Aflibercept, Bevacizumab or Observation. Secondary Analysis of the SCORE and SCORE2 Clinical Trials	American Journal of Ophthalmology	2021	222	185-193	https://dx.doi.org/10.1016/j.ajo.2020.08.030	Exclude	Study design

Velasque, L. B., S. N.; Streho, M.; Allmeier, H.; Machewitz, T.; Rittenhouse, K. D.	Intravitreal aflibercept in routine clinical practice: 12-month results from the French cohort of treatment-naive patients with macular edema secondary to retinal vein occlusion in the AURIGA study Audrey Giocanti-Auregan France	Ophthalmologica. Conference: European Society of Retina Specialists Congress, EURETINA	2021	244			Exclude	Study design
Fursova, A. A., H.; Machewitz, T.; Molina, D.	Intravitreal aflibercept in routine clinical practice: 12-month results from the Russian cohort of treatment-naive patients with diabetic macular edema in the AURIGA study	Ophthalmologica. Conference: European Society of Retina Specialists Congress, EURETINA	2021	244			Exclude	Study design
Li, Y. S., V.; Benmansour, F.; Friesenhahn, M.; Haskova, Z.	Prediction of ranibizumab injection frequency in patients with macular edema due to retinal vein occlusion during asneeded dosing period of BRAVO and CRUISE Phase 3 trials	Investigative Ophthalmology and Visual Science. Conference: Annual Meeting Association for Research in Vision and Ophthalmology, ARVO	2021	62			Exclude	Study design

Nourinia, R. E., M.; Ramezani, A.; Amizadeh, Y.; Khorshidifar, M.; Behnaz, N.; Safi, S.	Peripheral Ischemic Retinal Photocoagulation in Addition to Intravitreal Bevacizumab Versus Intravitreal Bevacizumab Alone for the Treatment of Macular Edema Secondary to Central Retinal Vein Occlusion	Retina	2020	40(6)	1110	https://dx.doi.org/10.1097/IAE.0000000000002573	exclude	Duplicate
Michl, M. F., M.; Seebock, P.; Sadeghipour, A.; Najeeb, B. H.; Bogunovic, H.; Schmidt-Erfurth, U. M.; Gerendas, B. S.	Automated quantification of macular fluid in retinal diseases and their response to anti-VEGF therapy	British Journal of Ophthalmology	2020	(no pagination)		https://dx.doi.org/10.1136/bjophthalmol-2020-317416	Exclude	Outcomes
Prasanna, P. B., V.; Figueiredo, N.; Sevgi, D. D.; Lu, C.; Braman, N.; Alilou, M.; Sharma, S.; Srivastava, S. K.; Madabhushi, A.; Ehlers, J. P.	Radiomics-based assessment of ultra-widefield leakage patterns and vessel network architecture in the PERMEATE study: insights into treatment durability	The British journal of ophthalmology.	2020	19		https://dx.doi.org/10.1136/bjophthalmol-2020-317182	Exclude	Study design
Giuffre, C. C., M. V.; Marchese, A.; Coppola, M.; Parodi, M. B.; Bandello, F.	Simultaneous intravitreal dexamethasone and aflibercept for refractory macular edema secondary to retinal vein occlusion	Graefe's archive for clinical and experimental ophthalmology = Albrecht von Graefes Archiv	2020	2		https://dx.doi.org/10.1007/s00417-019-04577-8	Exclude	Study design

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Ziemssen, F. H., T.; Grueb, M.; Mueller, B.; Berk, H.; Gamulescu, M. A.; Voegeler, J.; Wachtlin, J.; Ocean Study, Group	Reporting of Safety Events during Anti-VEGF Treatment: Pharmacovigilance in a Noninterventional Trial	Journal of Ophthalmology	2020	2020 (no pagination)		https://dx.doi.org/10.1155/2020/8652370	Exclude	Study design
Byeon, S. H. K., O. W.; Song, J. H.; Kim, S. E.; Park, Y. S.	Prolongation of activity of single intravitreal bevacizumab by adjuvant topical aqueous depressant (Timolol-Dorzolamide)	Graefe's Archive for Clinical and Experimental Ophthalmology	2009	247(1)	35-42	https://dx.doi.org/10.1007/s00417-008-0917-1	Exclude	Intervention/comparator
Gabriel, J. A., J. R.; Wykoff, C. C.; Brown, D. M.; Lunasco, L.; Arepalli, S.; Srivastava, S. K.; O'Connell, M.; Le, T. K.; Sevgi, D. D.; Biehl, S.; Rentz, O.; Berlon, M.; Hu, M.; Reese, J.; Ehlers, J. P.	Correlation of intraocular cytokine expression with higher order OCT features in retinal venous occlusive disease	Investigative Ophthalmology and Visual Science. Conference	2020	61			Exclude	Outcomes

Braimah, I. Z. K., E.; Amissah-Arthur, K. N.; Akafo, S.; Kwarteng, K. O.; Amoaku, W. M.	Safety of intravitreal ziv-aflibercept in choroido-retinal vascular diseases: A randomised double-blind intervention study	PLoS ONE	2019	14(10) (no pagination)		https://dx.doi.org/10.1371/journal.pone.0223944	exclude	Population
Guo, S. R., J.; Li, Z.; Fan, X.; Qin, L.; Li, J.	Aqueous semaphorin 3A level correlates with retinal macular oedema and ganglion cell degeneration in patients with retinal vein occlusion	Acta Ophthalmologica	2019	97(3)	273-278	https://dx.doi.org/10.1111/aos.14079	Exclude	Study design
Campochiaro, P. A. S., S. M.; Hafiz, G.; Quinlan, E.; Zimmer-Galler, I.; Nguyen, Q. D.; Do, D. V.; Ying, H.; Sung, J. U.; Wilmer Retinal Research, Group	Ranibizumab for Macular Edema Due to Retinal Vein Occlusions	Iovs	1545	48			exclude	Duplicate

Vader, M. J. C. S., A. M. E.; Verbraak, F. D.; Dijkman, G.; Hooymans, J. M. M.; Los, L. I.; Zwinderman, A. H.; Peto, T.; Hoyng, C. B.; Van Leeuwen, R.; Vingerling, J. R.; De Jong-Hesse, Y.; Van Lith-Verhoeven, J. J. C.; Dijkgraaf, M. G. W.; Schlingemann, R. O.	Comparing the efficacy of bevacizumab to ranibizumab in patients with retinal vein occlusion. the BRVO study	Acta Ophthalmologica	2019	97(Supplement 262)	39-40	https://dx.doi.org/10.1111/aos.14061	Exclude	Superceded by full paper
Campochiaro, P. A. W., C. C.; Brown, D. M.; Boyer, D. S.; Barakat, M.; Taraborelli, D.; Noronha, G.	Suprachoroidal Triamcinolone Acetonide for Retinal Vein Occlusion: Results of the Tanzanite Study	Ophthalmology Retina	2018	2(4)	320-328	https://dx.doi.org/10.1016/j.oret.2017.07.013	Exclude	Intervention/comparator
Wang, G. P. S., Y. H.; Han, L. F.; Ding, H.; Wang, X. H.; Jin, H. L.; Liu, J.; Ji, F.	Intravitreal injection of Ranibizumab combined with laser photocoagulation for macular edema secondary to BRVO. [Chinese]	International Eye Science	2018	18(3)	563-567	https://dx.doi.org/10.3980/j.issn.1672-5123.2018.3.39	Exclude	Duplicate

Channa, S. M., A. A.; Al-Swailmi, F. K.	Comparative study of bevacizumab and triamcenolone in macular edema secondary to branch retinal vein occlusion	Medical forum monthly	2017	Vol.28	15-18p		exclude	Study design
Chen, B. C., F.	Comparison of the therapeutic effect and safety of anti-VEGF drugs on macular edema secondary to non-ischemic retinal vein occlusion	International eye science	2019	Vol.19	426-429p	https://doi.org/10.3980/j.issn.1672-5123.2019.3.18	Exclude	Non-english
Chen, S. J. Y., Z. Q.; Yang, H.; Wu, N.; Li, S. Y.; Meng, X. H.	Effect of triamcinolone acetonide and laser photocoagulation for macular edema of retinal vein occlusion. [Chinese]	International Eye Science	2012	12(11)	2154-2156	https://dx.doi.org/10.3969/j.issn.1672-5123.2012.11.32	Exclude	Non-english
Chen, S. M. W., H.; Zheng, X. N.	Clinical observation of laser photocoagulation combined with Compound Xueshuantong capsule on the treatment of retinal vein occlusion	International eye science	2015	Vol.15	1826-1827p	https://doi.org/10.3980/j.issn.1672-5123.2015.10.44	Exclude	Non-english
Narayanan, R. S., M. W.; Chhablani, J.; Panchal, B.; Pappuru, R. R.; Das, T.; Jalali, S.; Ali, M. H.	Baseline morphological characteristics as predictors of final visual acuity in patients with branch retinal vein occlusions: MARVEL report no. 3	Indian journal of ophthalmology	2018	66(9)	1291-1294	https://dx.doi.org/10.4103/ijo.IJO_342_18	Exclude	Outcomes

Scott, I. U. F., M. J.; Oden, N. L.; Ip, M. S.; Blodi, B. A.; VanVeldhuisen, P. C.	SCORE2 Report 5: Vision-Related Function in Patients With Macular Edema Secondary to Central Retinal or Hemiretinal Vein Occlusion	American Journal of Ophthalmology	2017	184	147-156	https://dx.doi.org/10.1016/j.ajo.2017.10.008	Exclude	Outcomes
Eibenberger, K. S., L.; Rezar-Dreindl, S.; Wozniak, P.; Told, R.; Mylonas, G.; Krall, C.; Schmidt-Erfurth, U.; Sacu, S.	Effects of intravitreal dexamethasone implants on retinal oxygen saturation, vessel diameter, and retrobulbar blood flow velocity in ME secondary to RVO	Investigative Ophthalmology and Visual Science	2017	58(12)	5022-5029	https://dx.doi.org/10.1167/iovs.17-22229	Exclude	Study design
Feng, J. W.	Intravitreal injection of triamcinolone acetonide combined with retinal photocoagulation for cystoid macular edema associated with nonischemic central retinal vein occlusion. [Japanese]	International Journal of Ophthalmology	2010	10(7)	1365-1367	https://dx.doi.org/10.3969/j.issn.1672-5123.2010.07.044	Exclude	Non-english
Gong, J. F. W., X. L.; Sun, T.; Xu, C. L.	Shuxuetong injection combined with intravitreal injection of Ranibizumab and laser photocoagulation in the treatment of BRVO with macular edema. [Chinese]	International Eye Science	2017	17(11)	2112-2115	https://dx.doi.org/10.3980/j.issn.1672-5123.2017.11.29	Exclude	Duplicate

Miwa, Y. M., Y.; Osaka, R.; Ooto, S.; Murakami, T.; Suzuma, K.; Takahashi, A.; Iida, Y.; Yoshimura, N.; Tsujikawa, A.	Ranibizumab for macular edema after branch retinal vein occlusion: One initial injection versus three monthly injections	Retina	2017	37(4)	702-709	https://dx.doi.org/10.1097/IAE.0000000000001224	Exclude	Study design
Scott, I. U. V. V., P. C.; Ip, M. S.; Blodi, B. A.; Oden, N. L.; King, J.; Antoszyk, A. N.; Peters, M. A.; Tolentino, M.	Baseline factors associated with 6-month visual acuity and retinal thickness outcomes in patients with macular edema secondary to central retinal vein occlusion or hemiretinal vein occlusion SCORE2 Study Report 4	JAMA Ophthalmology	2017	135(6)	639-649	https://dx.doi.org/10.1001/jamaophthalmol.2017.1141	Exclude	Outcomes
Bell, K. J. L. H., A.; Glasziou, P.; Mitchell, A. S.; Farris, M.; Wright, J.; Duerr, H. P.; Mitchell, P.; Irwig, L.	Early CRT monitoring using time-domain optical coherence tomography does not add to visual acuity for predicting visual loss in patients with central retinal vein occlusion treated with intravitreal ranibizumab a secondary analysis of trial data	Retina	2017	37(3)	509-514	https://dx.doi.org/10.1097/IAE.0000000000001207	Exclude	Outcomes

Gao, H. L., H. L.; Pang, R.	Clinical efficacy of compound anisodine injection combined with anti-VEGF in the treatment of macular edema due to branch retinal vein occlusion. [Chinese]	International Eye Science	2019	19(2)	323-325	https://dx.doi.org/10.3980/j.issn.1672-5123.2019.2.33	Exclude	Non-english
Scott, I. U. V., P. C.; Ip, M. S.; Blodi, B. A.; Oden, N. L.; Figueroa, M.; Dugel, P. U.	SCORE2 Report 2: Study Design and Baseline Characteristics	Ophthalmology	2017	124(2)	245-256	https://dx.doi.org/10.1016/j.ophtha.2016.09.038	Exclude	Outcomes
Georgopoulos, M. S., S.; Vecsei, P. V.; Michels, S.; Kiss, C.; Scholda, C.; Schmidt-Erfurth, U.	Therapy of macular edema with an intravitreal dexamethasone implant. [German]	Spektrum der Augenheilkunde	2006	20(5)	231-233	https://dx.doi.org/10.1007/bf03163806	Exclude	Non-english
Li, Q. Z., S. W.; Zhang, D. N.	Intravitreal injection of Conbercept combined with 532-laser retinal photocoagulation for retinal vein occlusion. [Chinese]	International Eye Science	2017	17(2)	284-287	https://dx.doi.org/10.3980/j.issn.1672-5123.2017.2.23	Exclude	Duplicate
Ziemssen, F. F., N.; Holz, F. G.; Guthoff, R.; Ringwald, A.; Bertelmann, T.; Wiedon, A.; Korb, C.	Demographics of patients receiving Intravitreal anti-VEGF treatment in real-world practice: healthcare research data versus randomized controlled trials	BMC ophthalmology	2017	17(1)	7	https://dx.doi.org/10.1186/s12886-017-0401-y	Exclude	Outcomes

Gong, J. F. W., X. L.; Sun, T.; Xu, C. L.	Shuxuetong injection combined with intravitreal injection of Ranibizumab and laser photocoagulation in the treatment of BRVO with macular edema	International eye science	2017	Vol.17	2112-2115p	https://doi.org/10.3980/j.issn.1672-5123.2017.11.29	Exclude	Non-english
Gu, S. Z. N., O.; Bressler, S. B.; Du, W.; Moini, H.; Bressler, N. M.	Correlation between change in central subfield thickness and change in visual acuity in eyes with macular edema due to branch retinal vein occlusion receiving fixed-dosing intravitreal aflibercept regimens: a post hoc analysis of the VIBRANT clinical trial	Investigative ophthalmology & visual science		Vol.62	2021-05-01 to 2021-05-07. Annual Meeting Association for Research in Vision and Ophthalmology		Exclude	Outcomes
Zhou, Y. J. G., G. L.; Xiao, A. P.	Adjuvant effect of flavored Siwu granules for phlegm and blood stasis mutual junction retinal vein occlusion. [Chinese]	International Eye Science	2016	16(7)	1319-1321	https://dx.doi.org/10.3980/j.issn.1672-5123.2016.7.29	Exclude	Only RVO
Narayanan, R. P., B.; Stewart, M. W.; Das, T.; Chhablani, J.; Jalali, S.; Ali, M. H.	Grid laser with modified pro re nata injection of bevacizumab and ranibizumab in macular edema due to branch retinal vein occlusion: MARVEL report no 2	Clinical Ophthalmology	2016	10	1023-1029	https://dx.doi.org/10.2147/OPTH.S104459	exclude	Outcomes

Zhang, C. N., T. T.	Effect of Ranibizumab with macular grid pattern photocoagulation for macular edema caused by branch retinal vein occlusion. [Chinese]	International Eye Science	2016	16(4)	702-705	https://dx.doi.org/10.3980/j.issn.1672-5123.2016.4.28	Exclude	Duplicate
Hayashi, K. H., H.	Intravitreal versus retrobulbar injections of triamcinolone for macular edema associated with branch retinal vein occlusion	American Journal of Ophthalmology	2005	139(6)	972-982.e2	https://dx.doi.org/10.1016/j.ajo.2004.12.087	Exclude	Outcomes
Higashiyama, T. S., O.; Kakinoki, M.; Sawada, T.; Kawamura, H.; Ohji, M.	Prospective comparisons of intravitreal injections of triamcinolone acetonide and bevacizumab for macular oedema due to branch retinal vein occlusion	Acta Ophthalmologica	2013	91(4)	318-324	https://dx.doi.org/10.1111/j.1755-3768.2011.02298.x	Exclude	Intervention/comparator
Hong, S. W. J., D.	Effect of the Honan intraocular pressure reducer to prevent vitreous reflux after intravitreal bevacizumab injection	European Journal of Ophthalmology	2012	22(4)	615-619	https://dx.doi.org/10.5301/ejo.5000081	Exclude	Outcomes
Zhai, G. X. J., T.; Zhao, S. Y.; Wang, W. Y.; Wang, Y. X.	Efficacy and safety of intravitreal injection of Ranibizumab in the treatment of macular edema secondary to central retinal vein occlusion. [Chinese]	International Eye Science	2015	15(10)	1778-1781	https://dx.doi.org/10.3980/j.issn.1672-5123.2015.10.28	Exclude	Duplicate

Figueroa, M. S.	New perspectives in the approach to central retinal vein occlusion. [Spanish]	Archivos de la Sociedad Espanola de Oftalmologia	2015	90(Supplement 1)	15-23	https://dx.doi.org/10.1016/S0365-6691%2815%2930005-8	Exclude	Study design
Graber, M. G.-B., A.; Fardeau, C.; Massamba, N.; Atassi, M.; Rostaqui, O.; Coscas, F.; Le Hoang, P.; Souied, E. H.	Comparison of early management of central retinal vein occlusion with ranibizumab versus hemodilution. [French]	Journal francais d'ophtalmologie	2015	38(9)	815-821	https://dx.doi.org/10.1016/j.jfo.2015.03.016	Exclude	Population
Liu, B. Y., Y. X.; Liu, X.; Li, W. L.; Mo, Z. Z.	Clinical therapeutic effects of intravitreal Ranibizumab injection combined laser photocoagulation for macular edema in BRVO. [Chinese]	International Eye Science	2014	14(11)	2006-2008	https://dx.doi.org/10.3980/j.issn.1672-5123.2014.11.24	Exclude	Duplicate
Ip, M. S. O., N. L.; Scott, I. U.; VanVeldhuisen, P. C.; Blodi, B. A.; Figueroa, M.; Antoszyk, A.; Elman, M.	SCORE Study Report 3. Study Design and Baseline Characteristics	Ophthalmology	2009	116(9)	1770-1777.e1	https://dx.doi.org/10.1016/j.ophtha.2009.03.022	exclude	Outcomes
Campochiaro, P. A. W., C. C.; Shapiro, H.; Rubio, R. G.; Ehrlich, J. S.	Neutralization of vascular endothelial growth factor slows progression of retinal nonperfusion in	Ophthalmology	2014	121(9)	1783-1789	https://dx.doi.org/10.1016/j.ophtha.2014.03.021	Exclude	Population

	patients with diabetic macular edema							
Karadzic, J. K., I.; Ljikar, J.; Grgic, Z.; Devecerski, G.	Pharmacological Intravitreal Treatment for Macular Edema in Branch Retinal Vein Occlusion - Three-Month Results	Medicinski pregled	2015	68(9-10)	295-300	http://dx.doi.org/10.2298/MPNS1510295K	Exclude	Intervention/comparator
Karimi, S. M., S. A.; Jadidi, K.; Nikkhah, H.; Kheiri, B.	Which quadrant is less painful for intravitreal injection? A prospective study	Eye	2019	33	304-312	https://dx.doi.org/10.1038/s41433-018-0208-y	Exclude	Outcomes
Kuppermann, B. D. H., J. A.; Bandello, F.; Loewenstein, A.; Jiao, J.; Li, X. Y.; Whitcup, S. M.	Onset and duration of visual acuity improvement after dexamethasone intravitreal implant in eyes with macular edema due to retinal vein occlusion	Retina	2014	34(9)	1743-1749	https://dx.doi.org/10.1097/IAE.0000000000000167	Exclude	Study design
Karimi, S. P., F.; Arabi, A.; Shahraki, T.; Safi, S.	Oral Vitamin D Supplementation and Clinical Outcomes of Intravitreal Bevacizumab Injection for Macular Edema Secondary to Retinal Vein Occlusions	Journal of ophthalmic & vision research	2022	Vol.17	376-383p	https://doi.org/10.18502/jovr.v17i3.11575	Exclude	Intervention/comparator

Zhang, C. X., H.; Xu, L.	Intravitreal injection with Ranibizumab combined with laser therapy for macular edema caused by branch retinal vein occlusion. [Chinese]	International Eye Science	2014	14(8)	1399-1402	https://dx.doi.org/10.3980/j.issn.1672-5123.2014.08.08	Exclude	Duplicate
Li, F. S., M.; Guo, J.; Ma, A.; Zhao, B.	Comparison of Conbercept with Ranibizumab for the Treatment of Macular Edema Secondary to Branch Retinal Vein Occlusion	Current Eye Research	2017	42(8)	1174-1178	https://dx.doi.org/10.1080/02713683.2017.1285943	Exclude	Intervention/comparator
Li, Q. Z., S. W.; Zhang, D. N.	Intravitreal injection of Conbercept combined with 532-laser retinal photocoagulation for retinal vein occlusion	International eye science	2017	Vol.17	284-287p	https://doi.org/10.3980/j.issn.1672-5123.2017.2.23	Exclude	Non-english
Campochiaro, P. A. B., R. B.; Shapiro, H.; Rubio, R. G.	Vascular endothelial growth factor promotes progressive retinal nonperfusion in patients with retinal vein occlusion	Ophthalmology	2013	120(4)	795-802	https://dx.doi.org/10.1016/j.ophtha.2012.09.032	Exclude	Study design
Suner, I. J. B., N. M.; Varma, R.; Lee, P.; Dolan, C. M.; Ward, J.; Colman, S.; Rubio, R. G.	Reading speed improvements in retinal vein occlusion after ranibizumab treatment	JAMA Ophthalmology	2013	131(7)	851-856	https://dx.doi.org/10.1001/jamaophthalmol.2013.114	Exclude	Study design

Li, T. T. N., T. T.; Wang, H. L.	Intravitreal injection with ranibizumab combined with triamcinolone acetonide sub-Tenon injection for macular edema due to CRVO. [Chinese]	International Eye Science	2015	15(1)	98-100	https://dx.doi.org/10.3980/j.issn.1672-5123.2015.1.28	Exclude	Non-english
Li, T. T. N., T. T.; Wang, H. L.	Intravitreal injection with ranibizumab combined with triamcinolone acetonide sub-Tenon injection for macular edema due to CRVO	International eye science	2015	Vol.15	98-100p	https://doi.org/10.3980/j.issn.1672-5123.2015.1.28	Exclude	Non-english
Liu, B. Y., Y. X.; Liu, X.; Li, W. L.; Mo, Z. Z.	Clinical therapeutic effects of intravitreal Ranibizumab injection combined laser photocoagulation for macular edema in BRVO	International eye science	2014	Vol.14	2006-2008p	https://doi.org/10.3980/j.issn.1672-5123.2014.11.24	Exclude	Non-english
Liu, L. J. Y., H.	Curative effect of Triamcinolone acetonide combined with macular grid photocoagulation in the treatment of macular edema secondary to BRVO	International eye science	2021	Vol.21	1440-1444p	https://doi.org/10.3980/j.issn.1672-5123.2021.8.25	Exclude	Non-english
Yu, Q. S. L., L. X.; Niu, Y.; He, J. H.; Fan, Y.; Qi, Y. C.	Curative effect of 532nm laser combined with compound anisodine in treatment of branch retinal vein occlusion. [Chinese]	International Eye Science	2012	12(12)	2411-2412	https://dx.doi.org/10.3980/j.issn.1672-5123.2012.12.56	Exclude	Population

Lu, B. W., X.	Effect of Lingqi Huangban granule plus intravitreal ranibizumab on macular edema induced by retinal vein occlusion: a randomized controlled clinical trial	Journal of Traditional Chinese Medicine	2020	40(2)	305-310		Exclude	Intervention/comparator
Martin, A. A., J. R.; Wykoff, C. C.; Lunasco, L.; Arepalli, S.; Srivastava, S. K.; Mugnaini, C. J.; Hu, M.; Reese, J.; Brown, D. M.; Ehlers, J. P.	Correlation of intraocular cytokine expression with quantitative ultra-widefield fluorescein angiographic features in the imagine retinal vein occlusion study	Investigative ophthalmology & visual science		Vol.62	2021-05-01 to 2021-05-07. Annual Meeting Association for Research in Vision and Ophthalmology		Exclude	Outcomes
Peng, Z. H. J., X. Q.; Wu, L.; Song, Y. P.	Comparison of efficacy of laser photocoagulation for the treatment of branch retinal vein occlusion at the early and late stage. [Chinese]	International Eye Science	2012	12(2)	341-342	https://dx.doi.org/10.3969/j.issn.1672-5123.2012.02.48	Exclude	Population
Mishra, S. K. G., A.; Patyal, S.; Kumar, S.; Raji, K.; Singh, A.; Sharma, V.	Intravitreal dexamethasone implant versus triamcinolone acetonide for macular oedema of central retinal vein occlusion:	International Journal of Retina and Vitreous	2018	4(1) (no pagination)		https://dx.doi.org/10.1186/s40942-018-0114-2	Exclude	Intervention/comparator

	Quantifying efficacy and safety							
Moon, J. K., M.; Sagong, M.	Combination therapy of intravitreal bevacizumab with single simultaneous posterior subtenon triamcinolone acetonide for macular edema due to branch retinal vein occlusion	Eye (Basingstoke)	2016	30(8)	1084-1090	https://dx.doi.org/10.1038/eye.2016.96	Exclude	Intervention/comparator
Motarjemizadeh, G. R., M.; Aidenloo, N. S.; Valizadeh, R.	Comparison of treatment response to intravitreal injection of triamcinolone, bevacizumab and combined form in patients with central retinal vein occlusion: A randomized clinical trial	Electronic Physician [Electronic Resource]	2017	9	5068-5074	https://dx.doi.org/10.19082/5068	Exclude	Intervention/comparator

Murata, T. K., M.; Inoue, M.; Nakao, S.; Osaka, R.; Shiragami, C.; Sogawa, K.; Mochizuki, A.; Shiraga, R.; Ohashi, Y.; Kaneko, T.; Chandrasekhar, C.; Tsujikawa, A.; Kamei, M.	Erratum: author Correction: the randomized ZIPANGU trial of ranibizumab and adjunct laser for macular edema following branch retinal vein occlusion in treatment‐naïve patients (Scientific reports (2021) 11 1 (551))	Scientific reports	2021	Vol.11	14400-p	https://doi.org/10.1038/s41598-021-93187-8	Exclude	Study design
Nawar, A. E.	Modified Microneedle for Suprachoroidal Injection of Triamcinolone Acetonide Combined with Intravitreal Injection of Ranibizumab in Branch Retinal Vein Occlusion Patients	Clinical ophthalmology	1139	16	1139-1151	https://doi.org/10.2147/OPTH.S361636	Exclude	Intervention/comparator
Prager, F. M., S.; Kriechbaum, K.; Georgopoulos, M.; Funk, M.; Geitzenauer, W.; Polak, K.; Schmidt-Erfurth, U.	Intravitreal bevacizumab (Avastin) for macular oedema secondary to retinal vein occlusion: 12-month results of a prospective clinical trial	British Journal of Ophthalmology	2009	93(4)	452-456	https://dx.doi.org/10.1136/bjo.2008.141085	Exclude	Study design
Ou, Y. L. Z., X. P.; Xie, L. L.; Tian, T.; Liu, R.; Peng, J. L.; Kuang, G. P.	Anti-VEGF combined with retinal laser in treatment of retinal vein occlusion with macular edema	International Eye Science	2019	19(7)	1162-1165	https://dx.doi.org/10.3980/j.issn.1672-5123.2019.7.18	Exclude	Intervention/comparator

Parodi, M. B. I., P.; Ravalico, G.	Intravitreal triamcinolone acetonide combined with subthreshold grid laser treatment for macular oedema in branch retinal vein occlusion: a pilot study	British Journal of Ophthalmology	2008	92	1046-50	https://dx.doi.org/10.1136/bjo.2007.128025	Exclude	Intervention/comparator
Pece, A. A., D.; Montesano, G.; Dimastrogiovanni, A.	Effect of prophylactic timolol 0.1% gel on intraocular pressure after an intravitreal injection of ranibizumab: a randomized study	Clinical ophthalmology	1131	10	1131-1138	https://doi.org/10.2147/OPTH.S106096	Exclude	Population
Wolf, S. A., O.; Bertram, B.; Schulte, K.; Kaufhold, F.; Teping, C.; Reim, M.	[Hemodilution in patients with central retinal vein thrombosis. A placebo-controlled randomized study]	Fortschritte der Ophthalmologie	1991	88	35-43		Exclude	Population
Pieramici, D. J. R., M.; Castellarin, A. A.; Nasir, M.; See, R.; Norton, T.; Sanchez, A.; Risard, S.; Avery, R. L.	Ranibizumab for the Treatment of Macular Edema Associated with Perfused Central Retinal Vein Occlusions	Ophthalmology	2008	115(10)	e47-e54	https://dx.doi.org/10.1016/j.ophtha.2008.06.021	Exclude	Study design
Qiao, G. Z., X. J.; Zou, Q. X.; He, C. M.; Cao, K.; Dong, W. J.; Liao, W. Y.; Chen, D. B.	Clinical study of macular edema secondary to ischemic branch retinal vein occlusion treated by dual laser and single intravitreal injection with Conbercept	International eye science	2020	Vol.20	311-314p	https://doi.org/10.3980/j.issn.1672-5123.2020.2.27	Exclude	Non-english

Hillier, R. J. A., A.; Thind, G.; Clark, D. I.	Oral transmucosal fentanyl citrate: a novel analgesic agent for use in retinal photocoagulation	Retina	2009	29	1506-12	https://dx.doi.org/10.1097/IAE.0b013e3181ae70d4	Exclude	Population
Scott, I. U. V., P. C.; Oden, N. L.; Ip, M. S.; Blodi, B. A.; Hartnett, M. E.; Cohen, G.	Baseline predictors of visual acuity and retinal thickness outcomes in patients with retinal vein occlusion: Standard Care Versus COrticosteroid for REtinal Vein Occlusion Study report 10	Ophthalmology	2011	118	345-52	https://dx.doi.org/10.1016/j.ophtha.2010.06.034	Exclude	Outcomes
Ramezani, A. E., H.; Entezari, M.; Moradian, S.; Soheilian, M.; Dehsarvi, B.; Yaseri, M.	Three intravitreal bevacizumab versus two intravitreal triamcinolone injections in recent-onset branch retinal vein occlusion	Graefe's Archive for Clinical and Experimental Ophthalmology	2012	250(8)	1149-1160	https://dx.doi.org/10.1007/s00417-012-1941-8	Exclude	Intervention/comparator
Bhisitkul, R. B. C., P. A.; Shapiro, H.; Rubio, R. G.	Predictive value in retinal vein occlusions of early versus late or incomplete ranibizumab response defined by optical coherence tomography	Ophthalmology	2013	120	1057-63	https://dx.doi.org/10.1016/j.ophtha.2012.11.011	Exclude	Outcomes
Rebeiz, A. G. M., Z.; Abdul Fattah, M.; Saad, A.; Safar, A.; Bashshur, Z. F.	Change in cardiac troponin T level after intravitreal anti-vascular endothelial growth factor treatment: Prospective pilot study	European Journal of Ophthalmology	2020	30	563-569	https://dx.doi.org/10.1177/1120672119832171	Exclude	Outcomes

Graber, M. G.-B., A.; Fardeau, C.; Massamba, N.; Atassi, M.; Rostaqui, O.; Coscas, F.; Le Hoang, P.; Souied, E. H.	[Comparison of early management of central retinal vein occlusion with ranibizumab versus hemodilution]	Journal Francais d Opthalmologie	2015	38	815-21	https://dx.doi.org/10.1016/j.jfo.2015.03.016	Exclude	Population
Figueroa, M. S.	[New perspectives in the approach to central retinal vein occlusion]	Archivos de la Sociedad Espanola de Oftalmologia	2015	90 Suppl 1	15-23	https://dx.doi.org/10.1016/S0365-6691(15)30005-8	Exclude	Duplicate
Kreutzer, T. C. W., A.; Dirisamer, M.; Strauss, R. W.; Foerster, P.; Feltgen, N.; Pielen, A.; Hattenbach, L. O.; Kampik, A.; Priglinger, S. G.	Intravitreal ranibizumab versus isovolemic hemodilution in the treatment of macular edema secondary to central retinal vein occlusion: twelve-month results of a prospective, randomized, multicenter trial	Ophthalmologica	2015	233	Aug-17	https://dx.doi.org/10.1159/000369566	Exclude	Duplicate
Tadayoni, R. W., S. M.; Boscia, F.; Gerding, H.; Pearce, I.; Priglinger, S.; Wenzel, A.; Barnes, E.; Gekkieva, M.; Pilz, S.; Mones, J.	Individualized Stabilization Criteria-Driven Ranibizumab versus Laser in Branch Retinal Vein Occlusion: Six-Month Results of BRIGHTER	Ophthalmology	2016	123	1332-44	https://dx.doi.org/10.1016/j.ophtha.2016.02.030	Exclude	Duplicate

Sophie, R. W., P. W.; Channa, R.; Quezada-Ruiz, C.; Clark, A.; Campochiaro, P. A.	Different Factors Associated with 2-Year Outcomes in Patients with Branch versus Central Retinal Vein Occlusion Treated with Ranibizumab	Ophthalmology	2019	126	1695-1702	https://dx.doi.org/10.1016/j.ophtha.2019.07.018	Exclude	Outcomes
Scott, I. U. I., M. S.; VanVeldhuisen, P. C.; Oden, N. L.; Blodi, B. A.; Fisher, M.; Chan, C. K.; Gonzalez, V. H.; Singerman, L. J.; Tolentino, M.	A randomized trial comparing the efficacy and safety of intravitreal triamcinolone with standard care to treat vision loss associated with macular edema secondary to branch retinal vein occlusion: The standard care vs corticosteroid for retinal vein occlusion (SCORE) study report 6	Archives of Ophthalmology	2009	127(9)	1115-1128	https://dx.doi.org/10.1001/archophthalmol.2009.233	Exclude	Intervention/comparator
Etheridge, T. D., E. T. A.; Wiedenmann, M.; Papudesu, C.; Scott, I. U.; Ip, M. S.; Eliceiri, K. W.; Blodi, B. A.; Domalpally, A.	A semi-automated machine-learning based workflow for ellipsoid zone analysis in eyes with macular edema: SCORE2 pilot study	PLoS ONE [Electronic Resource]	2020	15	e0232494	https://dx.doi.org/10.1371/journal.pone.0232494	Exclude	Outcomes
Frederiksen, K. H. V., J. P.; Pedersen, F. N.; Vergmann, A. S.; oslash;rensen, T. L.; Laugesen, C. S.; Kawasaki, R.; Peto, T.; Grauslund, J.	Navigated laser and aflibercept versus aflibercept monotherapy in treatment-naïve branch retinal vein occlusion: a 12-month randomized trial	Acta ophthalmologica	2022	Vol.100	e1503-e1509p	https://doi.org/10.1111/aos.15182	Exclude	Duplicate

Chaudhary, V. G., K.; Mak, M.; Barbosa, J.; Mohammad Mohaghegh, P. S.; Popovic, M.	Waiting room educational media effect on preinjection anxiety for initial intravitreal injections	Canadian journal of ophthalmology	2016	Journal canadien d'ophtalmologie. Vol.51	71-75p	https://doi.org/10.1016/j.jcjo.2015.11.003	Exclude	Intervention/comparator
Scott, I. U. V., P. C.; Oden, N. L.; Ip, M. S.; Domalpally, A.; Doft, B. H.; Elman, M. J.; Blodi, B. A.	Baseline characteristics and response to treatment of participants with hemiretinal compared with branch retinal or central retinal vein occlusion in the Standard Care vs COrticosteroid for REtinal Vein Occlusion (SCORE) study: SCORE study report 14	Archives of Ophthalmology	2012	130(12)	1517-1524	https://dx.doi.org/10.1001/archophthalmol.2012.2728	Exclude	Intervention/comparator
Wei, L. Z., X. M.; Li, Y. L.; Dong, F. F.	Effect of Conbercept combined with laser photocoagulation on macular edema secondary to branch retinal vein occlusion	International eye science	2022	Vol.22	1543-1545p	https://doi.org/10.3980/j.issn.1672-5123.2022.9.24	Exclude	Duplicate
Scott, I. U. V., P. C.; Oden, N. L.; Ip, M. S.; Blodi, B. A.	Month 60 Outcomes After Treatment Initiation With Anti–Vascular Endothelial Growth Factor Therapy for Macular Edema Due to Central Retinal or Hemiretinal Vein Occlusion	American journal of ophthalmology	2022	240	330-341	https://doi.org/10.1016/j.ajo.2022.04.001	Exclude	Duplicate

Sohn, H. J. H., D. H.; Lee, D. Y.; Nam, D. H.	Changes in aqueous cytokines after intravitreal triamcinolone versus bevacizumab for macular oedema in branch retinal vein occlusion	Acta Ophthalmologica	2014	92(3)	e217-e224	https://dx.doi.org/10.1111/aos.12219	Exclude	Intervention/comparator
Wang, L. B. Z., X.; Wu, S. M.; Wang, Y.	Efficacy and safety of ranibizumab combined with laser treatment in patients with BRVO and macular edema	International eye science	2017	Vol.17	1112-1115p	https://doi.org/10.3980/j.issn.1672-5123.2017.6.26	Exclude	Duplicate
Bai, S.	Efficacy of intravitreal ranibizumab or Conbercept combined with laser photocoagulation for macular edema secondary to branch retinal vein occlusion	International eye science	2017	Vol.17	648-651p	https://doi.org/10.3980/j.issn.1672-5123.2017.4.14	Exclude	Duplicate
Georgopoulos, M. S., S.; Vecsei, P. V.; Michels, S.; Kiss, C.; Scholda, C.; Schmidt-Erfurth, U.	Therapy of macular edema with an intravitreal dexamethasone implant	Spektrum der augenheilkunde	2006	Vol.20	231-233p		Exclude	Duplicate
Xiang, Z. Y. L., X. X.; Wang, H. Q.; Yang, M.	Efficacy of anti-VEGF therapy combined with iontophoresis of Xueshuantong injection on retinal vein obstruction with macular edema	International eye science	2021	Vol.21	2150-2155p	https://doi.org/10.3980/j.issn.1672-5123.2021.12.25	Exclude	Intervention/comparator

Gao, H. L., H. L.; Pang, R.	Clinical efficacy of compound anisodine injection combined with anti-VEGF in the treatment of macular edema due to branch retinal vein occlusion	International eye science	2019	Vol.19	323-325p	https://doi.org/10.3980/j.issn.1672-5123.2019.2.33	Exclude	Duplicate
Vinkovic, M. B., D.; Tedeschi Reiner, E.; De Salvo, G.; Matic, S.	Combined treatment with bevacizumab and triamcinolone acetonide for macular edema due to retinal vein occlusion	Acta Clinica Croatica	2020	59(4)	569-575	https://dx.doi.org/10.20471/acc.2020.59.04.01	Exclude	Intervention/comparator
Wang, G. P. S., Y. H.; Han, L. F.; Ding, H.; Wang, X. H.; Jin, H. L.; Liu, J.; Ji, F.	Intravitreal injection of Ranibizumab combined with laser photocoagulation for macular edema secondary to BRVO	International eye science	2018	Vol.18	563-567p	https://doi.org/10.3980/j.issn.1672-5123.2018.3.39	Exclude	Non-english
Wang, L. B. Z., X.; Wu, S. M.; Wang, Y.	Efficacy and safety of ranibizumab combined with laser treatment in patients with BRVO and macular edema. [Chinese]	International Eye Science	2017	17(6)	1112-1115	https://dx.doi.org/10.3980/j.issn.1672-5123.2017.6.26	Exclude	Non-english

Warren, K. B., A. B.; Ip, M. S.; Scott, I. U.; Oden, N.; VanVeldhuisen, P.; Standard Care vs Corticosteroid for Retinal Vein Occlusion Study, Group	Clinic vs. Reading Center Evaluation of Dense Retinal Hemorrhage at Baseline in the SCORE Branch Retinal Vein Occlusion (BRVO) Study	Iovs	3087	48			Exclude	Conference abstract before 2019
Chhablani, J. N., R.; Mathai, A.; Tyagi, M.	Combination of peripheral laser photocoagulation with intravitreal bevacizumab in naïve eyes with macular edema secondary to CRVO: prospective randomized study	Eye (London, England)	2016	Vol.30	1025-1027p	https://doi.org/10.1038/eye.2016.51	Exclude	Review/Editorial
Wang, S. N. X., X. N.; Wu, X. Q.; Mao, K. Z.; Wang, Z. W.; Yu, M. Z.	Clinical curative effect of argon chloride laser in treating retinal branch vein occlusion. [Chinese]	International Eye Science	2013	13(4)	796-798	https://dx.doi.org/10.3980/j.issn.1672-5123.2013.04.52	Exclude	Non-english
Wang, X. B. W., G. J.; Liu, C.	Efficacy of Dexamethasone intravitreal implant combined with anti-VEGF drug in the treatment of retinal vein occlusion	International eye science	2022	Vol.22	1717-1721p	https://doi.org/10.3980/j.issn.1672-5123.2022.10.24	Exclude	Non-english

Pichi, F. E., A. M.; Elhamaky, T. R.	Outcome of “treat and monitor” regimen of aflibercept and ranibizumab in macular edema secondary to non-ischemic branch retinal vein occlusion	International ophthalmology	2019	Vol.39	145-153p	https://doi.org/10.1007/s10792-017-0798-6	Exclude	Duplicate
Wang, X. B. W., G. J.; Zhang, X. Y.; Luo, X. D.; Liu, C.	Intravitreous injection with ranibizumab combined laser photocoagulation for the treatment of branch retinal vein occlusion. [Chinese]	International Eye Science	2013	13(12)	2452-2455	https://dx.doi.org/10.3980/j.issn.1672-5123.2013.12.26	Exclude	Non-english
Wang, X. B. W., G. J.; Zhang, X. Y.; Luo, X. D.; Liu, C.	Intravitreous injection with ranibizumab combined laser photocoagulation for the treatment of branch retinal vein occlusion	International eye science	2013	Vol.13	2452-2455p	https://doi.org/10.3980/j.issn.1672-5123.2013.12.26	Exclude	Duplicate
Wei, L. Z., X. M.; Li, Y. L.; Dong, F. F.	Effect of Conbercept combined with laser photocoagulation on macular edema secondary to branch retinal vein occlusion. [Chinese]	International Eye Science	2022	22(9)	1543-1545	https://dx.doi.org/10.3980/j.issn.1672-5123.2022.9.24	Exclude	Non-english
Willoughby, A. S. V., V. S.; Cunefare, D.; Farsiu, S.; Noronha, G.; Danis, R. P.; Yiu, G.	Choroidal Changes After Suprachoroidal Injection of Triamcinolone Acetonide in Eyes With Macular Edema Secondary to Retinal Vein Occlusion	American Journal of Ophthalmology	2018	186	144-151	https://dx.doi.org/10.1016/j.ajo.2017.11.020	Exclude	Intervention/comparator

Ip, M. S. V. V., P. C.; Scott, I. U.; Blodi, B. A.; Ghuman, T.; Baker, C. W.; Oden, N. L.	SCORE2 month 6 to month 12 results: 12 month outcomes of treatment change among poor responders at month 6	Investigative ophthalmology & visual science	2018	59			Exclude	Conference abstract before 2019
Wang, L. L. L., L. J.; Zheng, B.; Jin, L. Y.; Zhang, W.; Huo, M.; He, B.	Clinical observation of Becacizumab combined with grid photocoagulation for the treatment of cystoid macular edema associated with central retinal vein occlusion. [Chinese]	International Journal of Ophthalmology	2011	11(10)	1769-1771	https://dx.doi.org/10.3969/j.issn.1672-5123.2011.10.028	Exclude	Non-english
Scott, I. U. V., P. C.; Ip, M. S.; Blodi, B. A.; Oden, N. L.; Figueroa, M.; Dugel, P. U.	SCORE2 Report 2. Study Design and Baseline Characteristics	Ophthalmology.	2016	15		https://doi.org/10.1016/j.ophtha.2016.09.038	Exclude	Outcomes
Wroblewski, J. J. H., A. Y.	Topical squalamine 0.2% and intravitreal ranibizumab 0.5 mg as combination therapy for macular edema due to branch and central retinal vein occlusion: An open-label, randomized study	Ophthalmic Surgery Lasers and Imaging Retina	2016	47(10)	914-923	https://dx.doi.org/10.3928/23258160-20161004-04	Exclude	Intervention/comparator

Yang, L. X. L., S. B.; Wei, B.	Treatment of macular edema secondary to branch retinal vein occlusion with Yiqihuoxuehuayu decoction combined with triamcinolone acetonide and 532nm argon laser	International eye science	2019	Vol.19	1741-1745p	https://doi.org/10.3980/j.issn.1672-5123.2019.10.24	Exclude	Non-english
Yeh, W. S. H., J. A.; Lanzetta, P.; Kuppermann, B. D.; Wong, T. Y.; Mitchell, P.; Whitcup, S. M.; Kowalski, J. W.	Effect of the duration of macular edema on clinical outcomes in retinal vein occlusion treated with dexamethasone intravitreal implant	Ophthalmology	2012	119(6)	1190-1198	https://dx.doi.org/10.1016/j.ophtha.2011.12.028	Exclude	Outcomes
Yu, L. T., K.; Rong, Y.; Li, Z.; Song, X.; Chen, X.; Song, L.	Clinical Application Analysis of Calcium Dobesilate Combined with Ranibizumab in Patients with Macular Edema Secondary to Branch Retinal Vein Occlusion	Indian Journal of Pharmaceutical Sciences	2022	84	25-28	https://dx.doi.org/10.36468/pharmaceutical-sciences.spl.449	Exclude	Intervention/comparator
Zhai, G. X. J., T.; Zhao, S. Y.; Wang, W. Y.; Wang, Y. X.	Efficacy and safety of intravitreal injection of Ranibizumab in the treatment of macular edema secondary to central retinal vein occlusion	International eye science	2015	Vol.15	1778-1781p	https://doi.org/10.3980/j.issn.1672-5123.2015.10.28	Exclude	Non-english

Li, X. W., N.; Liang, X.; Xu, G.; Li, X. Y.; Jiao, J.; Lou, J.; Hashad, Y.	Safety and efficacy of dexamethasone intravitreal implant for treatment of macular edema secondary to retinal vein occlusion in Chinese patients: randomized, sham-controlled, multicenter study	Graefe's archive for clinical and experimental ophthalmology	2017			https://doi.org/10.1007/s00417-017-3831-6	Exclude	Duplicate
Zhang, C. N., T. T.	Effect of Ranibizumab with macular grid pattern photocoagulation for macular edema caused by branch retinal vein occlusion	International eye science	2016	Vol.16	702-705p	https://doi.org/10.3980/j.issn.1672-5123.2016.4.28	Exclude	Non-english
Zhang, C. X., H.; Xu, L.	Intravitreal injection with Ranibizumab combined with laser therapy for macular edema caused by branch retinal vein occlusion	International eye science	2014	Vol.14	1399-1402p	https://doi.org/10.3980/j.issn.1672-5123.2014.08.08	Exclude	Non-english
Wang, L. L. L., L. J.; Zheng, B.; Jin, L. Y.; Zhang, W.; Huo, M.; He, B.	Clinical observation of Becacizumab combined with grid photocoagulation for the treatment of cystoid macular edema associated with central retinal vein occlusion	International journal of ophthalmology	2011	Vol.11	1769-1771p	https://doi.org/10.3969/j.issn.1672-5123.2011.10.028	Exclude	Duplicate

Feng, J. W.	Intravitreal injection of triamcinolone acetonide combined with retinal photocoagulation for cystoid macular edema associated with nonischemic central retinal vein occlusion	International journal of ophthalmology	2010	Vol.10	1365-1367p	https://doi.org/10.3969/j.issn.1672-5123.2010.07.044	Exclude	Duplicate

Clinical effectiveness evidence

A 7. Appendix L provides details of a real-world data study. Please explain how this study contributed to the submission.

The study in question was used as qualitative substantiation. This was a retrospective, observational, real-world cohort study using anonymised, electronic health records (EHR) data from participating National Health Service (NHS) ophthalmology sites in the UK with patients matched to the study baseline characteristics. Within the appendices and the CS, we concluded whilst the assumptions and design of BALATON and COMINO were conservative, this study showed a greater proportion of patients extending out to Q12W and Q16W. The data from the real-world study provides additional context, suggesting cost savings incurred by the introduction of faricimab is likely to be greater than the analyses submitted based on trial results alone.

A 8. Appendix M lists the questions used during a clinical expert elicitation exercise.

a) Please explain the format for eliciting responses (e.g., individually or in a group; online or in person).

b) Please elaborate on the degree of independence between the clinical experts and the company.

a) Format for eliciting responses - clinician placed under contract with Roche for discussions. Meeting format was virtual, one 1.5-2 hour individual meeting per clinical expert to discuss the questions attached. Attendees for the meeting were clinical expert, health economist, medical affairs partner and medical writer

b) Professors Ian Pearce and Sobha Sivaprasad have worked with Roche (as well as many other companies), under paid consultancy for activities, such as National and International Congress Attendance, Advisory Boards, Steering groups, 1:1 Clinical Expertise, etc. Roche have regular engagement with ophthalmology experts and both these experts attended the Roche UK RVO Advisory Board (Friday 10th March 2023). Both are Consultant Ophthalmologists with ~20 years' experience treating RVO patients and have

both consulted with and for NICE for prior reimbursement applications in RVO. Professor Sivaprasad is the Chair of the Royal College of Ophthalmologists RVO guidelines committee and a Trustee of the Macular Society. Both experts work with many pharmaceutical companies, both experts are held in the highest esteem and their opinions and advice are completely independent and not influenced in any way.

Indirect treatment comparison (ITC)

A 9. Priority question. The Network Meta-analysis (NMA) presented in Appendix D contains a section referred to as "*Feasibility Assessment*". However, the only mention of heterogeneity is that it has a *"high likelihood"* and, on this basis, a random effects model was chosen (see Technical Support Document (TSD) 3. There is no mention of consistency (see TSD 4). Therefore, please conduct a full feasibility assessment that systematically examines variation between trials in clinical and methodological characteristics, any potential treatment modifying effect and thus the implications for the network for any methods to mitigate heterogeneity or inconsistency with reference to TSD 3 and TSD 4.

Please refer to attached documents for the full NMA report and feasibility assessment which contains the lists of all included studies, excluded studies (with reasoning for exclusion), the study design, population and endpoint definition as well as a comparison of baseline characteristics for potential effect modifiers. It also includes a risk of bias assessment showing that the risk of bias was mostly low. In the NMA we also split RVO in CRVO and BRVO to address any remaining potential confounding. In terms of NMA analysis and heterogeneity: fixed effects models were run as well as unconstrained random effect models to test the sensitivity. In addition, a node-split model was run to test for inconsistency.

A 10. Priority question: Aside from the BALATON and COMINO RCTs, few details are provided of the trials used to populate the NMA.

a) Please provide a list of all RCTs included in the NMA

b) For each RCT included in the NMA please present the following details: trial design; participant flow; participant inclusion and exclusion criteria;

participant demographic and baseline clinical data; treatment schedule for all arms; statistical hypotheses; methods of statistical analyses; analysis populations; list of all outcomes assessed together with methods of measurement; full details of all results (per arm and between-group differences) used to estimate clinical effectiveness and safety and to inform the cost comparison model; and results for relevant population subgroups.

As per A9 above.

Adverse events

No questions.

: Clarification on cost-effectiveness data

Model structure

A 11. Priority question: On page 88 of the CS it is mentioned that patients cannot switch to another therapy if they discontinue their current treatment. Please explain to what extent this is a realistic assumption and what would happen to the results if patients could switch to another treatment.

In reality, patients are likely to switch therapies if they discontinue their current treatment. Reasons for switching include failure to control the disease, drop in vision, to increase time between treatment intervals etc. Hunt et al (1) reported the rate of switching anti-VEGF therapy to an alternative anti-VEGF molecule in a retrospective audit over 8 years of service. Switching occurred in 30% of cases and the rate of switch differed significantly depending on the type of initial VEGF inhibitor. Another study reported the switch rate of anti-VEGF to laser (6.8%) and to steroid (4.1%) in BRVO patients (2).

If patients were to switch their medication, the differences will be seen in injection frequencies. As stated above, reasons for changes are either lack of efficacy or suboptimal frequency of injections. The impact of which would mean potentially longer intervals between treatments due to the therapy being more efficacious. Whilst there will be a differential cost based on the initiating and subsequent therapies, it can be surmised the increased intervals from the subsequent therapy would provide greater

savings to the NHS (worth noting confidential patient access scheme (PAS) discounts have been agreed with the Department of Health for all three treatments, it is therefore difficult to substantiate the difference between therapies from a comparative cost assumption).

A 12. Please provide a rationale for the cut-off points used in the definition of the health states.

The cut-off points used in the definition of health states were obtained from the guideline review by NICE in nAMD from 2018. The document was used to inform the overall model structure including the definitions of visual acuity health states. Please refer to Appendix J: Health Economics for an overview of model schematic, health states and transition.

Clinical input parameters

A 13. Priority question: Page 93 of the CS states that: "patients whose dosing interval had been previously extended and who experience disease worsening that triggered an interval reduction were not allowed to extend the interval again, with the exception of patients whose dosing intervals were reduced to Q4W; their interval could be extended again but only to an interval that was 4 weeks less than their original maximum extension."

a) **Please explain if this approach has also been implemented in the BALATON and COMINO trials. Please also comment on the validity of this assumption in clinical practice.**

b) **The CS also mentions that: "*clinicians also confirmed the interval reduction performed within the study was overly conservative and would not be replicated in clinical practice*". Please clarify if this clinical feedback refers to the assumption above. In that case, please also explain why this assumption is considered "*conservative*" and discuss any potential implications for the model outcomes.**

c) **If clinicians found this assumption conservative and potentially not reflective of clinical practice, please run alternative scenarios to reflect the uncertainty around this assumption.**

a) Yes this approach has been implemented in BALATON and COMINO trials. This approach in the trial design provides a clearer, simplified model that protects the statistical power of the study and thus the analysis and demonstration of outcomes. This would be clearly more complex if patients, in whom their disease interval had been reduced, were allowed to have their treatment intervals extended again.

In the real world there is no restriction upon treatment interval extension, after reduction, and any decision is on an individual patient to patient basis. In many cases, after reduction, the patient's interval may be stabilised and then extended again up to and beyond the previous interval.

b) Yes, the clinical feedback refers to the assumption above. With the difference between the re-extension restriction in the trial and real world practice mentioned above, the approach in BALATON and COMINO means that the estimation of patients in each dosing interval is conservative (because they are not re-extended by trial design) and therefore possibly underestimated.

c) In order to estimate a less conservative approach, the assumption has been made in the analysis that after the treatment phase (6 months) all patients extend out to Q16W. Therefore the estimated annual number of administrations is as follows:

Table 19: Conservative administration frequency

Phase	BRVO	CRVO
Treatment	6	6
Maintenance	3	3
Rest of life	3	3

These values were validated with clinicians who stated from their experience with faricimab in DMO and nAMD these are the average administration numbers expected.

Table 20: Non-conservative results (faricimab at net price; aflibercept and ranibizumab at list price)

Cost	Faricimab 6mg LP→ T&E		Aflibercept 2mg LP → T&E		Ranibizumab 0.5mg LP → T&E	
	BRVO	CRVO	BRVO	CRVO	BRVO	CRVO
Drug cost	[redacted]	[redacted]	£22,121	£18,353	£14,945	£12,400
Administration cost	[redacted]	[redacted]	£9,574	£8,013	£9,579	£8,018
Additional monitoring cost	£0	£0	£0	£0	£0	£0
AE management cost	£0	£0	£0	£0	£0	£0
Costs of visual impairment	£1,313	£760	£1,313	£760	£1,313	£760
Mean total cost	[redacted]	[redacted]	£33,008	£23,925	£25,836	£17,991
Incremental cost vs faricimab	N/A		[redacted]	[redacted]	[redacted]	[redacted]

As has been highlighted, the PTI algorithm in the faricimab T&E phase of the RVO studies was more conservative than in the pivotal faricimab DMO studies. It did not allow patients to extend again if they had their treatment interval reduced from Q8W to Q4W, even if their disease stabilised at a later point. This was by design to avoid a decline in BCVA over time as shown in historical studies in RVO with anti-VEGFs administered as PRN regimen (3-5). As a result, nearly [redacted] of patients in the BALATON and COMINO studies were on Q4W at the end of the study. In contrast, 10% or less of patients on faricimab were on Q4W at the end of the DMO pivotal studies which did not have such protocol restriction (6).

Roche has conducted an exploratory post hoc analysis of BALATON and COMINO to simulate how many patients who were downgraded from Q8W to Q4W in the faricimab Q4W to faricimab PTI arm could have potentially extended treatment intervals again if they had stable disease, to better reflect T&E as performed in clinical practice. Please see the Kaplan Meier below as an illustration.

Figure 4: Exploratory analysis

The analysis suggest, accounting for censoring, around [redacted] of RVO patients reduced to Q4W from Q8W dosing could have potentially extended beyond Q4W had the RVO PTI algorithm not been so conservative (i.e., had the RVO PTI algorithm not prevented any further extension following an interval reduction). Most of the extensions would have occurred 4 weeks following the first interval reduction - i.e. after a single cycle of Q4W dosing. This analysis suggests that faricimab offers the potential for patients to further extend treatment intervals and reduce injection numbers in clinical practice in RVO. This potentially saves healthcare costs and alleviates health system capacity, and reduces burden on patients requiring frequent treatment.

A 14. Priority question: In section B.4.2.4 of the CS it is mentioned that: "as there was no evidence to suggest that mortality rates would differ across treatments, the annual rate of mortality was assumed to be equivalent for faricimab, aflibercept and ranibizumab." Please explain if this statement implies that disease-specific mortality rate has been included in the model in addition to background mortality and set equal between treatments; or if this statement means that only background mortality has been included in the model. In case

disease-specific mortality rate (or excess risk of death due to the disease) is included in the model please provide details on the value(s) used and comment on the validity exercises that have been conducted for the elevated risk input(s).

The model includes additional mortality rates beyond background mortality linked to visual acuity as established in the guideline review by NICE in nAMD conducted in 2018. Patients who are considered blind (visual acuity is less than 26 letters in both eyes) are assigned a hazard ratio of 1.54 and patients which are considered visually impaired (at least one eye has a visual acuity of less than 55 letters) are assigned a hazard ratio of 1.23. Those assumptions are based on Christ *et al* (7), aligned with the nAMD guideline review. Since the model assumed patients to follow an identical trajectory through visual acuity related health states, these mortality assumptions do not constitute any difference between faricimab, aflibercept and ranibizumab. These assumptions have also been used in previous appraisals such as most recently in TA799 for faricimab in DMO (8).

A 15. Priority question: Table 29 of the CS presents the annual treatment discontinuation probabilities that were estimated for the treatment phase and the maintenance phase based on data from the BALATON and COMINO trials. According to the text of the CS, these annual probabilities were implemented for all treatments in the model and for the rest of life phase the respective probability was set equal to the probability estimated for the maintenance phase. However, the company also assumed that 55% would have discontinued after 5 years.

a) Please provide a detailed explanation on how the probabilities of Table 29 were implemented in the electronic model. Were the annual probabilities used for patients in years 2-5 only or also for patients following 5 years of treatment?

b) Please explain how the percentage still on treatment (45%, Scott 2022) and the annual discontinuation relate to each other in the model.

c) The Scott paper showed that 55% of patients was not present at the 60-month visit. Please explain how a distinction can be made between "*patients who stopped coming due to treatment success*", "*patients no*

***longer wanting to receive treatment*" and "*patients no longer wanting to participate in the extension of the RCT*", and which of these patients the discontinuation probabilities try to capture in the model.**

a) Implementation of discontinuation probabilities:

	Patients discontinuing BALATON and COMINO	Excluding deaths as this is accounted for separately in the model	N	Annualisation	Annualised discontinuation probability
Treatment phase (until week 24)	26+12	3+1	729+553	52/24	5.7%
Maintenance phase (week 24 - week 72)	52+48	4+3	729+553	52/48	7.9%

These annual probabilities were transformed to match the model cycle length of 4 weeks using standard methodology ($p = 1 - e^{-rt}$) (9) and assigned by treatment phase (treatment, maintenance, Rest of life) with "Rest of life" (patients on treatment for longer than 5 years) being set to be similar to the maintenance phase in the absence of longer term data. Please see the "Treatment discontinuation" sheet in the model.

b) and c):

The model captures all cause discontinuation regardless of the underlying reasoning for both, the estimates based on BALATON and COMINO as well as Scott *et al.* (10) as the unique objective is to model whether patients are on or off treatment. This allows capturing the most relevant and potentially differentiating cost factors. Using the estimates from BALATON and COMINO approximately 60% of eyes are still on treatment, which is in line with the finding from Scott 2022, considering that patients in that trial were about 5 years older at baseline. UK clinical experts consulted by Roche suggested that in the majority of cases RVO could be well controlled with treatment, and patients would no longer receive anti-VEGF injections after 5 years of treatment. As a conservative assumption, and to reflect the findings in Scott 2022 meaning that a subset of patients may warrant long term treatment, out of those patients still on

treatment after 5 years, about 55% are modelled to discontinue while 45% remain on treatment.

A 16. On page 93 of the CS, the algorithm used for PTI dosing is mentioned. In Figure 4, it can be seen that for improving CST (-10% to –20%) and a BCVA worsening between 0 and –10, the interval is maintained (yellow) whereas for the same BCVA range and a worse CST (-10% to +10%) the interval is extended by 4 weeks (green). Could you please provide the rationale for this?

The RVO PTI algorithm is based on the algorithm used in the Phase 3 diabetic macular oedema trials, and was designed to adjust a patient's treatment interval based on changes in OCT central subfield thickness (CST) and best corrected visual acuity (BCVA) relative to a reference value.

The CST reference is defined as a macula (central 1mm) that has achieved a thickness value of <325 µm (Spectralis). When the CST is within 10% of the reference value, the protocol considers the retinal anatomy stable; this is within the repeatability limits of OCT devices, as well as being the definition of retinal stability used by the TREX-DME study. Treatment interval extension is only permitted if the CST within 10% of its reference, and a BCVA decline is less than 10 letters relative to its reference. These ranges are based on the variability of CST and BCVA measurements, to ensure that treatment extension is not permitted in cases of real and significant worsening of disease.

If a patient is showing an improvement in CST at a specific visit (defined as >10% change in CST compared to the reference value), then the treatment interval is maintained. This is to ensure that an interval extension only occurs when the patient is stable; i.e. has no room for further improvement on the current treatment interval. From a clinical perspective, if a patient is showing a worsening of BCVA in the presence of an improving CST, this would indicate that the BCVA change is not related to the underlying macular oedema, and is more likely related to other factors such as media opacities or under corrected refraction.

However, if a patient shows a significant worsening of CST in the presence of a worsening BCVA, then this would indicate a 'true' worsening of macular edema, and as such would warrant a treatment interval reduction.

A 17. The dosing schedule of faricimab (and the comparators) is based on a T&E regimen as according to clinical feedback is most likely to be used in clinical practice. However, the CS reported that the risk of eye deterioration between intervals in RVO is smaller compared to nAMD and DMO and may require an PRN dosing (as needed regimens based on response to disease activity) and this is the reason the company included this option as a scenario analysis. Please also include the PRN option in the model as currently in the drop-down option defining treatment regimen only the T&E is included (on the Cost inputs sheet).

An option for PRN was not created for faricimab as the data informing faricimab administration was from BALATON and COMINO. Unlike the other studies for ranibizumab and aflibercept, there were no PRN cases within BALATON and COMINO as this was not allowed in the study protocol. Negating the inclusion of PRN within the model. From discussion with clinicians it is unlikely the PRN regimen will be used in clinical practice. Worth noting is the results of BALATON and COMINO showed patients on faricimab were well controlled and maintained visual acuity during the T & E phase.

PRN dosing regime is a “treat as need” regime where patients with a dry macula are monitored every 4-6 weeks without the “planning” for an intravitreal injection. This is not only challenging for the patient, where the disease reactivates and maybe more challenging/aggressive to treat, but also for the service, where the planning of capacity is almost impossible. Development of the treat and extend regime (T&E) as a proactive regimen is the gold standard. The proactive regimen is what most medical retina clinics have adopted or aspire to adopt. The proactivity to detect, control and manage the disease for all retina conditions before recurrence not only improves the outcome for patients but also allows correct service support for the medical retina clinics.

A 18. The sheet ‘Model inputs’ of the electronic model includes inputs on the proportion of patients across health states and 2nd eye involvement. However, the % used for the baseline distribution of the first eye at baseline and second eye with and without disease at baseline are not described in the CS document. Please provide a detailed description of the inputs, how they have been used in the model and how have they been validated.

The model structure is designed to describe the natural course of the disease and the development of RVO and follows the structure of health state definitions used for the guideline review in neovascular age-related macular degeneration (nAMD) conducted by NICE in 2018 (11).

It consists of a two-eye model where both eyes disease progression is independent from each other. The first eye is always assumed to have RVO and being treated for it at the start of the model. No bilateral cases were observed in BALATON and COMINO. The first eye distribution is therefore informed by BALATON and COMINO. For the distribution of the second eye, these were informed by prevalence and incidence rates based on previous submissions. 6.05% at baseline and 12.3% incidence in bilateral cases over 5 years based on the NICE committee papers for aflibercept in BRVO (TA409 (12), p. 9). In CRVO bilateral cases are extremely rare. The ERG report for aflibercept in CRVO (TA305 (13), p. 24) assumed 4%. This was confirmed by clinicians as a reasonable assumption.

A 19. On page 89 of the company submission, the company states that the main data sources used in the model are the pooled data covering the patient populations of BALATON and COMINO, and the populations of studies included in the network meta-analysis. Please explain how the data were pooled, i.e., were data treated as if from one study, or was a form of meta-analysis applied? In addition, please provide an overview of all model inputs based on pooled RCT data versus input based on the indication-specific RCT.

- For BCVA: Transitions between visual acuity related health states (assuming the same rates for all treatments) were estimated using a Markov multi-state model (using the msm package in R) based on the pooled study population from BALATON and COMINO. Differences between the studies were captured using a study covariate.
- Demographic and ocular baseline characteristics were summarised by study
- Injection frequency for faricimab was summarised by study.

Cost inputs

A 20. Priority question: The cost of an injection was estimated as the difference in costs between an injection administration visit and a monitoring visit based on the calculations performed by the evidence review group (ERG) in the appraisal of aflibercept for DMO (TA346). As the TA346 guidance was published in 2015, please explain if these costs are still considered relevant to be used in the current setting, if and how they were validated, and if (and how) they were adjusted for inflation or if they were updated using more recent available sources (NHS costing manual or any other source).

In the absence of a robust estimate for the cost of an injection administration, the cost of an injection administration was sourced from the ERG report in the appraisal of aflibercept for DMO (TA346) (14). The cost was estimated as the difference between the cost of an administration injection visit and a monitoring visit. This was validated as reasonable by clinicians as there was no alternative and was recently used as the assumption in Faricimab for treating diabetic macular oedema (TA799) (8).

Company results

A 21. Priority question: Please confirm if the proportionate interval dosing presented in Table 33 has only been included in the scenario analyses. Please explain how the values in Table 33 have been used to derive the values (for the injection frequencies in the treatment, maintenance and rest of life phases) presented in Table 41 and Table 42 for the proportionate interval dosing scenario analyses. Please give a detailed explanation of the computations.

Yes, this has only been included in the scenario analysis. To derive the injection frequencies, for faricimab the BALATON and COMINO trials were used to inform the percentage of patients on the specified dosing regimen at week 68. Please note, these are patients who were capped at this frequency, for instance if they had been on a longer duration and had to be reduced, they were captured at the reduced frequency. For aflibercept and ranibizumab, the values were informed by the proportions of patients on dosing between Q4W to Q16W based on the CENTERA study (15) and Casselholm De Salles (16) respectively. The frequencies and how they translate into the respective administrations per weekly cycle for each cohort (Q4W - Q16W) were

modelled explicitly (please see sheets "Administration frequency" columns BM and following). These results were averaged to match the 4-weekly model cycle in the respective model phase ("treatment", "maintenance" and "rest of life").

A 22. Priority question: The total costs presented in the CS seem to be accounting for informal care costs and travel costs which does not match to the company's description of the cost items included in the base case results. In Table 37 for instance, the mean total costs are not equal to the sum of the drug acquisition and administration costs, and the costs of visual impairment. Based on the model, it seems that the mean total costs presented throughout the submission consider travel and informal care costs. If this is an error, please update all results accordingly.

Table 21: Updated base case results (faricimab at net price; aflibercept and ranibizumab at list price)

Cost	Faricimab 6mg LP→ T&E		Aflibercept 2mg LP → T&E		Ranibizumab 0.5mg LP → T&E	
	BRVO	CRVO	BRVO	CRVO	BRVO	CRVO
Drug cost	[redacted]	[redacted]	£35,856	£34,551	£24,228	£23,350
Administration cost	[redacted]	[redacted]	£15,543	£15,096	£15,553	£15,108
Additional monitoring cost	£0	£0	£0	£0	£0	£0
AE management cost	£0	£0	£0	£0	£0	£0
Costs of visual impairment	£1,313	£760	£1,313	£760	£1,313	£760
Mean total cost	[redacted]	[redacted]	£52,712	£47,490	£41,094	£36,333
Incremental cost vs faricimab	N/A		[redacted]	[redacted]	[redacted]	[redacted]

Table 22: Updated threshold analysis: incremental cost of faricimab compared with aflibercept and ranibizumab at varying list price discount levels

Discount	Aflibercept			Ranibizumab		
	Discounted aflibercept price	Incremental cost vs faricimab		Discounted ranibizumab price	Incremental cost vs faricimab	
		BRVO	CRVO		BRVO	CRVO
0%	£816.00	[redacted]	[redacted]	£551.00	[redacted]	[redacted]
10%	£734.40	[redacted]	[redacted]	£495.90	[redacted]	[redacted]

20%	£652.80	[redacted]	[redacted]	£440.80	[redacted]	[redacted]
30%	£571.20	[redacted]	[redacted]	£385.70	[redacted]	[redacted]
40%	£489.60	[redacted]	[redacted]	£330.60	[redacted]	[redacted]
50%	£408.00	[redacted]	[redacted]	£275.50	[redacted]	[redacted]
55%	£367.20	[redacted]	[redacted]	£248.00	[redacted]	[redacted]
60%	£326.40	[redacted]	[redacted]	£220.40	[redacted]	[redacted]
65%	£285.60	[redacted]	[redacted]	£192.90	[redacted]	[redacted]

Table 23: Updated scenario analyses results (with faricimab at net prices; aflibercept and ranibizumab at list price) [BRVO]

Scenario	Base-case	Scenario	Incremental cost vs aflibercept	% change from base case incremental cost	Incremental cost vs ranibizumab	% change from base case incremental cost
Base-case	-	-	[redacted]	N/A	[redacted]	N/A
Model starting age	66 years	50 years	[redacted]	[redacted]	[redacted]	[redacted]
		75 years	[redacted]	[redacted]	[redacted]	[redacted]
Discount rate	3.5%	1.5%	[redacted]	[redacted]	[redacted]	[redacted]
Aflibercept dosing regimen	LP → T&E	LP → Q4W/Q8W/Q12W/Q16W) [T&E]	[redacted]	[redacted]	N/A	N/A
		LP → PRN (TD)	[redacted]	[redacted]	N/A	N/A
		LP → T&E (TD)	[redacted]	[redacted]	N/A	N/A
Ranibizumab dosing regimen	LP → T&E	LP → Q4W/Q8W/Q12W/Q16W) [T&E]	N/A	N/A	[redacted]	[redacted]
		LP → PRN (TD)	N/A	N/A	[redacted]	[redacted]
		LP → T&E (TD)	N/A	N/A	[redacted]	[redacted]

LP, loading phase; T&E, treat and extend; QXW, one injection every X weeks; TD, Trial-based dosing

Table 24: Updated scenario analyses results (with faricimab at net prices; aflibercept and ranibizumab at list price) [CRVO]

Scenario	Base-case	Scenario	Incremental cost vs aflibercept	% change from base case incremental cost	Incremental cost vs ranibizumab	% change from base case incremental cost
Base-case	-	-	[redacted]	N/A	[redacted]	N/A
Model starting age	64 years	50 years	[redacted]	[redacted]	[redacted]	[redacted]
		75 years	[redacted]	[redacted]	[redacted]	[redacted]
Discount rate	3.5%	1.5%	[redacted]	[redacted]	[redacted]	[redacted]

Aflibercept dosing regimen	LP → T&E	LP → Q4W/Q8W/Q12W/Q16W) [T&E]	[redacted]	[redacted]	N/A	N/A
		LP → PRN (ITD)	[redacted]	[redacted]	N/A	N/A
		LP → T&E (ITD)	[redacted]	[redacted]	N/A	N/A
Ranibizumab dosing regimen	LP → T&E	LP → Q4W/Q8W/Q12W/Q16W) [T&E]	N/A	N/A	[redacted]	[redacted]
		LP → PRN (ITD)	N/A	N/A	[redacted]	[redacted]
		LP → T&E (ITD)			[redacted]	[redacted]

LP, loading phase; T&E, treat and extend; QXW, one injection every X weeks, TD, Trial-based dosing

Inclusion of travel and informal care costs was in error. Base case results and scenario analyses excluding those have been run and can be seen above. Changes to the results are negligible with minimal changes in results.

A 23. Priority question: Please include all the scenario analyses presented in the CS in the macro in the Excel models that automates the running of scenarios.

In order to change settings within the model for the different scenarios, for regimen changes the drop down menu lists the different regimens further explained in the CS. For discount rate and starting age, the changes need to be made in the Model inputs sheet with the required numbers. Please see Table 25 below for cells to be amended to run the scenarios.

Table 25: Scenario changes

Scenario	Changes
Dosing regimen	Cells E27-E29
Model starting age	Cell F29
Discount rate	Cell F17

: Textual clarification and additional points

A 24. On page 94 of the CS it is mentioned that: “In order to obtain the annual probability, total patient numbers in both trials divides patients discontinuing within the trials less the number of deaths.” It seems like this sentence is incomplete. Please edit accordingly.

The statement is correct, to illustrate the meaning of the statement, using the table referenced for treatment phase (until week 24) the statement implies (patients

discontinuing trials - number of deaths) all divided by total number of patients and annualised to establish the probability i.e. [(38-4)/1282]*100=5.7%

Table 26: Treatment discontinuation probabilities

	Patients discontinuing BALATON and COMINO	Excluding deaths as this is accounted for separately in the model	N	Annualisation	Annualised discontinuation probability
Treatment phase (until week 24)	26+12	3+1	729+553	52/24	5.7%
Maintenance phase (week 24 - week 72)	52+48	4+3	729+553	52/48	7.9%

A 25. Several documents are missing from the submission reference pack. These include the following as referenced in Document B:

- Refs #3, #4 and #8
- Ref #19 (Draft SmPC for faricimab) – this appears to be the same as #70 but please provide both if they are different
- Refs #20, #32, #40, #48, #49
- Refs #57, #58, #59, #60 (clinical study reports for the BALATON and COMINO RCTs)
- Refs #70 (see above) and #71
- In the reference lists for Document B and the Appendices document, details for some references indicate that they should be available online (i.e., an access date is shown) but do not include a link. Examples include #1, #2 and #4 of Document B but the list also includes others. It is helpful that the company has now provided full details in the updated RIS file but please could an updated reference list with full access details also be provided.

Fifteen references have been requested - as two of these (Vabysmo proposed SmPC and Vabysmo proposed USPI) are duplicates, thirteen documents have been provided. Please note that the SmPC provided is a draft as it is not currently approved by the MHRA.

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NICE National Institute for Health and Care Excellence

Cost Comparison Appraisal

Faricimab for treating macular oedema caused by retinal vein occlusion [ID6197]

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 15,000 members who we communicate with on a regular basis, an e-newsletter that is sent monthly to 100,000 people, 370,000 website visitors a year and our Helpline responds to over 16,000 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	AbbVie – Oct 23 - £160 (advisory board support) Bayer - £0 Biogen – Mar 23 - £1,183 (engagement at UK cycle meeting and patient find fee), Jun 23 - £26,802 (grant to support helpline) Genus Pharmaceuticals - £0 Novartis – July 23 - £745 (advisory board support), Aug 23 - £649 (volunteering advisory support) Teva UK - £0

the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	NO
5. How did you gather information about the experiences of patients and carers to include in your submission?	**Wet AMD survey** A survey was conducted by the Macular Society in early 2020 to understand the burden that frequent anti-VEGF injections and ophthalmology appointments has on wet AMD patients and their carers or family. A total of 449 responses were received from across the UK. A full report was published August 2020. **Service users** Users of the 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.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Retinal vein occlusion can significantly reduce vision-related quality of life, particularly in more severe cases. A study which examined the vision-related quality of life (VRQoL) in different subgroups of RVO patients showed overall, RVO patients had a significantly lower total National Eye Institute Visual Functioning Questionnaire-25 (NEI-VFQ-25) score compared to healthy individuals, except in the subscale analysis of specific factors such as ocular pain, colour vision, and driving, where no statistically significant difference was observed. A statistically significant difference was found in the comparison of subgroups, indicating lower VRQoL in central retinal vein occlusion (CRVO) patients. Furthermore, a significant correlation was observed between lower VRQoL and decreased vision as well as longer disease duration. Loss of central vision through RVO can be very frustrating and can greatly affect everyday life as well as financially impact due to changes in employment and ability to drive. RVO can occur in young patients with an estimated global prevalence of 0.26% in people age 30–39 years and 0.44% in people age 40–49 years. The need for intravitreal anti-VEGF is less in young patients with CRVO. However, at least 20% of patients develop poor visual outcome with severe neovascular complications. Some people with RVO experience visual hallucinations called Charles Bonnet syndrome which adds another level of impact on health and mental well-being. **Family and carers** There is a significant burden on family and carers supporting a patient with RVO. A patient with RVO 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.

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 Macular Society Helpline overwhelmingly report how wonderful the NHS is. Many agree their treatment maintains their sight and can be anxious when treatment intervals are extended or stopped. However, personal experiences of cancelled appointments, frustration over communication with clinics, many hours spent waiting around in clinic, are all common themes. Injections are not available in local health care settings, meaning many patients travel a good distance to attend injection clinics and need a driver to accompany them.
8. Is there an unmet need for patients with this condition?	There is no current cure for the condition and treatments can only manage and stabilise the sight loss. There is a need for longer acting treatments to reduce the time between treatment and injections.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	Each appointment where there may be an intravitreal injection can cause anxiety. In our survey of patients with wet AMD, 31% of patients reported always feeling anxious about injection appointments and 24% reported that they were sometimes anxious. When asked to say which of 4 statements on appointments was most important to them, 39% said that 'Keeping the same level of vision with fewer injections' was most important. Some people also experience pain and discomfort following eye injections and a very small minority can suffer serious complications, such as an infection. Monthly eye clinic appointments can disrupt to day to day life, particularly where patients need to be accompanied to appointments by family or friends, who may need to take time off work. There will also be the cost to the patient of attending the eye clinic, such as taxi or bus fares and parking fees. In our survey 62% of patients said that they are driven to hospital by family or friends and 28% take public transport. Patients will also welcome that faricimab is a new innovation in treatment as it is dual action targeting both angiopoietin (Ang-2) and vascular endothelial growth factor (VEGF). This offers additional hope to currently available treatments.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	The main disadvantage is that it will be an intravitreal injection which may need to be given every 4 weeks for up to 6 months. 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. Intravitreal injections carry a very small but serious risk of sight loss due to complications, such as endophthalmitis. Some patients can also experience significant pain for a short time afterwards due to corneal abrasion or drying of the cornea, which can be alleviated with lubricating gel.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	No

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.	• RVO has the potential to significantly affect the quality of life of those affected through loss of central vision • Working age people as well as older people can be affected, potentially impacting on employment. • Loss of central vision can significantly impact family and friends who provide support to patients to manage day to day tasks and access treatment. • Faricimab will be a useful addition to the drugs currently available to treat RVO

Thank you for your time.

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

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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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in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

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

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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:

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

Abbreviations

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

3.1 Systematic literature review methods

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

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

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

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

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

3.2 Identified randomised controlled trials

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

3.3 Observational studies

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

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

Table 3.2: Treatment intervals from real-world study

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

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

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

3.4 Summary and critique of network meta-analysis

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

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

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

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

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

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

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

Based on Section 4.4 of NMA report[8]

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

4. EAG critique of cost comparison evidence submitted

4.1 Decision problem for cost comparison

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

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

4.2 Cost-effectiveness searches

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

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

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

4.3 Company cost comparison model

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

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

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

4.4 Model parameters

4.4.1 Treatment effect

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

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

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

4.4.2 Treatment discontinuation

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

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

Table 4.1: Treatment discontinuation probabilities

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

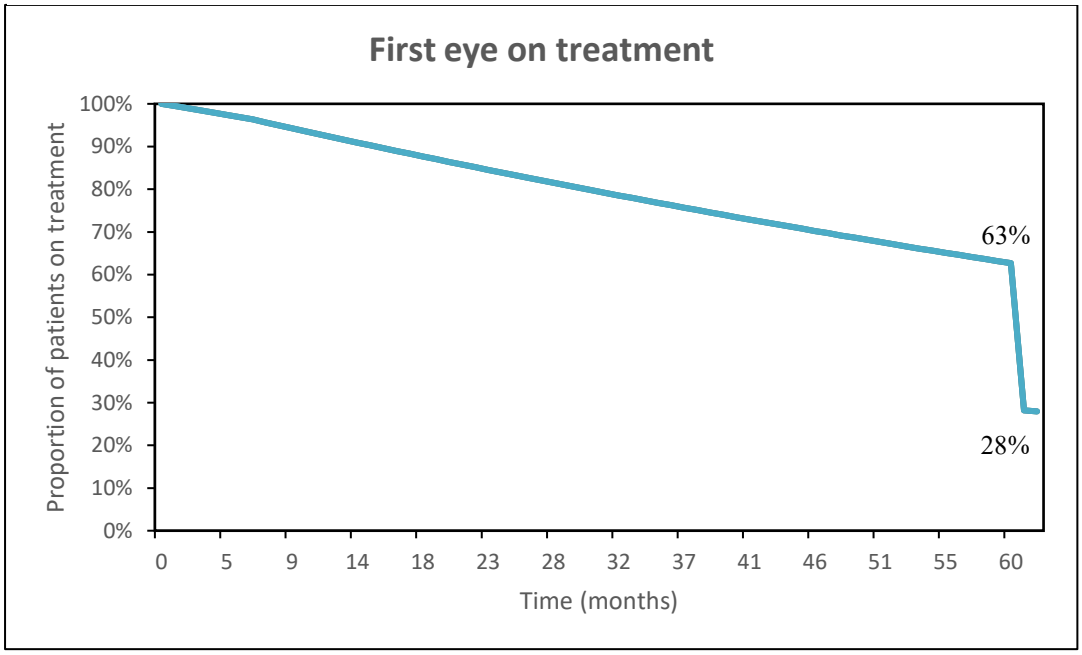
Based on Table 29 of the CS and the company's electronic model[3]
* Excluded as these are accounted for separately in the model

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

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

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

Figure 4.1 Proportion of first eyes on treatment over time



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

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

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

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

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

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

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

4.4.3 Mortality

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

4.4.4 Costs

- *Acquisition costs*

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

- *Treatment frequency*

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

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

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

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

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

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

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

- *Administration costs*

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

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

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

- *Monitoring visits*

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

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

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

- *Adverse events*

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

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

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

4.5 EAG model check

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

Main observations:

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

4.6 Company's model results

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

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

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

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

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

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

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

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

4.7 EAG exploratory analysis

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

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

Table 4.3: EAG scenarios BRVO

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

Table 4.4: EAG scenarios CRVO

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

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

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

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

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

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

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

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

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

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Cost Comparison Appraisal

Faricimab for treating macular oedema caused by retinal vein occlusion [ID6197]

EAG report – factual accuracy check and confidential information check

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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 Thursday 16 May 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 Exclusion of dexamethasone implant as a comparator

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Roche would like to address the EAG view that dexamethasone implant should have been considered a comparator and the stated rationale for exclusion of dexamethasone intravitreal implant: “The clinical experts enlisted by the company suggested that dexamethasone implants would not be used in clinical practice due to inferior efficacy compared to anti-VEGFs and a less favourable safety profile, and may only be used in patients who do not respond to anti-VEGF products”.	Exclusion of dexamethasone implant as a comparator is reasonable based on its reduced use in the clinical practice due to greater benefits seen in anti-VEGF treatments and based on EAG clinical expert opinion it is used in patients who cannot commit to monthly treatment and to patients contra-indicated anti-VEGF treatment, which faricimab has shown would extend out to more than a month. It was also shown to be dominated by ranibizumab as stated in TA305.	Included in our rationale was that similar to TA305, dexamethasone was not considered an appropriate comparator to aflibercept because ranibizumab dominated dexamethasone for treating visual impairment caused by MO-RVO. This gives more nuance to the exclusion of dexamethasone. Firstly, as already stated clinical experts interviewed by Roche stated they no longer use it as anti-VEGF treatment has shown greater benefit. In addition, the clinical expert consulted by the EAG stated “20% to 30% of anti-VEGF starters offered dexamethasone as an alternative treatment during the treatment course because of difficulty in committing to monthly anti-VEGF injections (dexamethasone implants have longer durability) and possible contraindication to anti-VEGF treatment because of a recent cardiovascular event”. The argument for faricimab is its ability for greater durability above 4 weeks	Not a factual inaccuracy. As agreed by the company, the EAG clinical expert stated that it is used in clinical practice and the company has not stated that those who currently receive it would not be eligible for faricimab. It is also not reasonable to exclude it as a comparator based on a previous appraisal that showed it was dominated by a comparator included in the scope i.e. ranibizumab. This is because, despite any shortcomings that it might have, it continues to be used in clinical practice and therefore any positive recommendation by NICE for faricimab might lead to switching from dexamethasone implant to faricimab

		based on DMO and AMD, as such the arguments for patients who cannot commit to monthly injections and have contra-indications to anti-VEGF do not make this population those being assessed. This in addition to the argument presented by the EAG based on their clinical expert statement “I would say with a high degree of confidence that ranibizumab is becoming an obsolete drug due to being replaced by better and more durable alternatives” that it stands true if dexamethasone is dominated by a soon to be obsolete drug and is used by patients who have contraindications to anti- VEGF or unable to commit to 4 weekly injections (for which we have shown at least 8 weekly injections for faricimab) it is not an appropriate comparator for this analysis. Furthermore, whilst UK guidance from RCOphth allows for 1st line use of both anti- VEGF drugs and dexamethasone, it advises that the overall benefit / risk should be explained to the patient. London local guidelines and Greater Manchester Medicines	without an evaluation of the whether that is cost effective. Indeed, the company go on to cite a UK-based source that there are subgroups for whom dexamethasone implant might be currently preferable i.e. “…in patient with recent cardiovascular events, in patient who does not favour monthly injections or in patient with vitrectomized eye”. However, no evidence has been presented in this appraisal for this subgroup and so it is uncertain if faricimab would be more effective or less costly in these patients that appear to be part of the wider population in the decision problem.

		Management Group for example provide greater detail on what this might look like(1,2):- CRVO & BRVO: “Anti-VEGF is preferred in eyes with a previous history of glaucoma and younger patients who are phakic. There is no standard definition for ‘young patient’, but in theory it is not preferable for cataract formation in patients with none pre-existing or in working patient.” “Steroid may be a better choice in patient with recent cardiovascular events, in patient who does not favour monthly injections or in patient with vitrectomized eye.” Since faricimab following the loading dose would be expected to have a treatment interval of 8-weekly or more in 77% of BRVO patients and 65% of CRVO patients, this further strengthens the argument against 1st line steroid use in eligible eyes.	

Issue 2 Company decision problem

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Roche will like to address the EAG comment "the EAG would therefore suggest that a recommendation be made only for this subgroup, i.e., omitting children, those without a visual impairment or anyone with anti-VEGF treatment experience".	The EAG would therefore suggest that a recommendation be made only for this subgroup, i.e., omitting children, those without a visual impairment	The data from part 2 of COMINO / BALATON indicate that eyes previously treated with aflibercept and switched to faricimab maintain good clinical outcomes. Based on the evidence submitted, in Part 2 of the COMINO and BALATON studies, patients who started in the aflibercept 2mg arm of the study (n=244 in BALATON, n=315 in COMINO) were switched to treatment with faricimab 6mg, according to a protocol-driven treat-and-extend regimen. For both studies, regardless of whether eyes received aflibercept or faricimab as their initial treatment, BCVA gains at week 24 (the primary endpoint) were maintained through week 72. Similarly, the important secondary outcome of CST reduction at week 24 was maintained through week 72 regardless of initial treatment assignment	Not a factual inaccuracy. No comparative evidence was presented for the VEGF treatment experience population. It might be that outcomes were maintained after switching from aflibercept to faricimab, but there is no evidence as to what might have happened if a switch not occurred.

		These data support the treatment of both treatment-naive eyes, as well as those having received prior treatment with a different anti-VEGF agent. Also included in the CS, emerging data from the real world in nAMD and DMO patients, who have switched from prior anti-VEGF therapy to faricimab, is starting to report improvements in vision, CST, fluid resolution and treatment intervals, further validating the decision to switch all RVO patents to Faricimab in weeks 24-72 in BALATON and COMINO (3), supporting the improvement in outcomes for patients who switch from another anti-VEGF to faricimab. Both points provide rationale not to exclude previously treated patients.	

Issue 3 Treatment Discontinuation

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Roche will like to address the EAG comment on treatment discontinuation. The EAG assumes treatment discontinuation should be applied from Year 1.		The description of the treatment discontinuation is incorrect. In the model this number is also not affecting discontinuation prior to month 60 but afterwards.	From the company's description of the problem it appears that the EAG did not succeed in clearly conveying the issue brought up in section 4.4.2 of the EAG report. Thus, we have added extra text plus a figure showing the proportion on first eyes still on treatment over time in that section to better explain the issue we observed regarding the way discontinuation was implemented in the model. The 55% of patients that had discontinued in the SCORE2 study was estimated as those patients not being

			present for the 60 month follow up visit out of those patients that had been treated for one year and entered into the long term follow up study. This 55% is applied by the company to the 63% of patients still on treatment after 60 months, leading to only 28% of patients receiving treatment from 61 months onwards (with then again a small 4 week discontinuation rate being applied). In the company submission nor in the expert responses did we find a justification for the 28% of patients continuing from 61 months and further. Obviously, as the same rates are used for all treatments, the impact of the EAG derived

			alternative scenarios on the incremental costs is fairly limited.

Issue 4 Appendix

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Within the submission, Roche did not state the rationale for exclusion of dexamethasone was due to it being less effective than the other treatments as was referenced to the clinical expert by the EAG. For clarity, the reasons behind the exclusion were as follows: - Safety concerns: o Dexamethasone is associated with serious side effects including increased intraocular pressure and cataract formation (4). This was supported by the	As this was a clinical expert interview, an amendment cannot be made to the questions already asked. Consideration should be taken that the information provided was based on an interpretation of the submission exclusion rational which was factually inaccurate.		This is not a factual inaccuracy. Indeed, the EAG cite lack of efficacy in Section 2 of the EAG report, which the company have not identified as a factual inaccuracy. This is notwithstanding any safety concerns, which the EAG clinical expert mentioned. As the EAG clinical expert stated, it might be that dexamethasone is suitable for only a subgroup of patients. However, this subgroup has not been excluded

EAG's clinical expert who quote in the report "the safety profile is slightly less favourable than anti-VEGF, with risk of cataract following successive implants and risk of transient rise of intraocular pressure (due to the drug being a steroid). These make clinicians and patients generally more inclined to start on the anti-VEGF route". - Different population to the scope: o Based on TA305, the ERG at the time highlighted that dexamethasone may be used in patients who do not respond to anti-VEGF drugs,			from the scope, and so it is a comparator in the scope. Nor has it been excluded from the decision problem by the company. Therefore, it cannot be excluded as a comparator.

in effect stating it is a second line treatment. ○ The clinical expert interviewed by the EAG for this submission also stated dexamethasone is usually considered when patients cannot commit to monthly injections. This is in contradiction to the population in question for this submission as the entire premise was on the extension and durability of treatment with patients moving to Q8W - Q16W. Furthermore, if they cannot commit to anti-VEGF treatment it would make their use inappropriate in this			

cohort and by effect not a comparator. - Market share o The above points come together to explain the rationale for why dexamethasone is not used in this population and this can be visualised by [redacted] For the reasons above, Roche concluded that dexmethasone is not representative of the UK standard of care for patients in this population.			

References

1. Moorfields Eye Hospital Guidelines: https://www.ncl-mon.nhs.uk/wp-content/uploads/Guidelines/11_BRVO_pathway.pdf

2. Greater Manchester Medicines Management Group NHS Guideline: https://gmmmg.nhs.uk/wp-content/uploads/2021/08/GMMMG-Macular-Drugs-Pathways-v-1-2-FINAL.pdf

3. Penha FM, Masud M, Khanani ZA, Thomas M, Fong RD, Smith K, et al. Review of real-world evidence of dual inhibition of VEGF-A and ANG-2 with faricimab in NAMD and DME. International Journal of Retina and Vitreous. 2024;10(1):5.