NICE National Institute for Health and Care Excellence

Fast Track Appraisal

Brolucizumab for treating diabetic macular oedema [ID3902]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

FAST TRACK APPRAISAL

Brolucizumab for treating diabetic macular oedema [ID3902]

Contents:

The following documents are made available to consultees and commentators:

The **final scope** and **final stakeholder list** are available on the NICE website.

1. **Technical Briefing**

2. **Company submission** from **Novartis Pharmaceuticals UK Ltd**

3. **Clarification questions and company responses**

4. **Patient group, professional group and NHS organisation submission** from:
   a. Diabetes UK
   b. Macular Society
   c. Royal College of Ophthalmologists, endorsed by the Royal College of Physicians

5. **Expert personal perspectives** from:
   a. Mr Winfried Amoaku, Associate Professor, Reader in Ophthalmology and Honorary Consultant Ophthalmologist – clinical expert, nominated by Novartis Pharmaceuticals UK Ltd
   b. Mr Stephen Scowcroft – patient expert, nominated by the Macular Society (see item 4b.)
   c. Mrs Bernadette Warren – patient expert, nominated by the Macular Society

      Mr Luke Nicholson, Consultant Ophthalmologist – clinical expert, nominated by the Royal College of Ophthalmologists (see item 4c.)

6. **Evidence Review Group report** prepared by **BMJ Technology Assessment Group**

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

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

NICE National Institute for Health and Care Excellence

Brolucizumab for treating diabetic macular oedema

Cost comparison

Technical briefing

EAG: BMJ TAG

Technical team: Luke Cowie, Louise Crathorne, Ross Dent

Company: Novartis

Brolucizumab

Marketing authorisation	Brolucizumab is authorised for the treatment of visual impairment due to diabetic macular oedema (DMO).
Mechanism of action	Brolucizumab is a humanised monoclonal single-chain variable fragment (scFV) which binds with high affinity to VEGF-A isoforms. This prevents binding of VEGF-A to its receptors VEGFR-1 and VEGFR 2, reducing signalling. Increased levels of signalling through the VEGF-A pathway are associated with pathological ocular angiogenesis and retinal oedema (build-up of fluid in the retina) which are characteristics of DMO.
Administration	IVT injection
SmPC	The recommended dose is 6 mg brolucizumab (0.05 ml solution) every 6 weeks for the first 5 doses. Thereafter, the physician may individualise treatment intervals based on disease activity as assessed by visual acuity and/or anatomical parameters. In patients without disease activity, treatment every 12 weeks (3 months) should be considered. In patients with disease activity, treatment every 8 weeks (2 months) should be considered.
Price	List - £816 per 120 mg/mL injection PAS - XXX per 120 mg/mL injection

FTA: cost-comparison

A cost-comparison FTA can be used if the drug provides similar/greater benefits at a similar/lower overall cost than a NICE-recommended comparator

Company submitted a cost-comparison against aflibercept (TA346) and ranibizumab (TA274):

- Positively recommended by NICE.
- Company is positioning brolucizumab in the same subgroup (people with vision impairment due to diabetic macular oedema (DMO) and the eye has a central retinal thickness of 400 µm or more at the start of treatment).

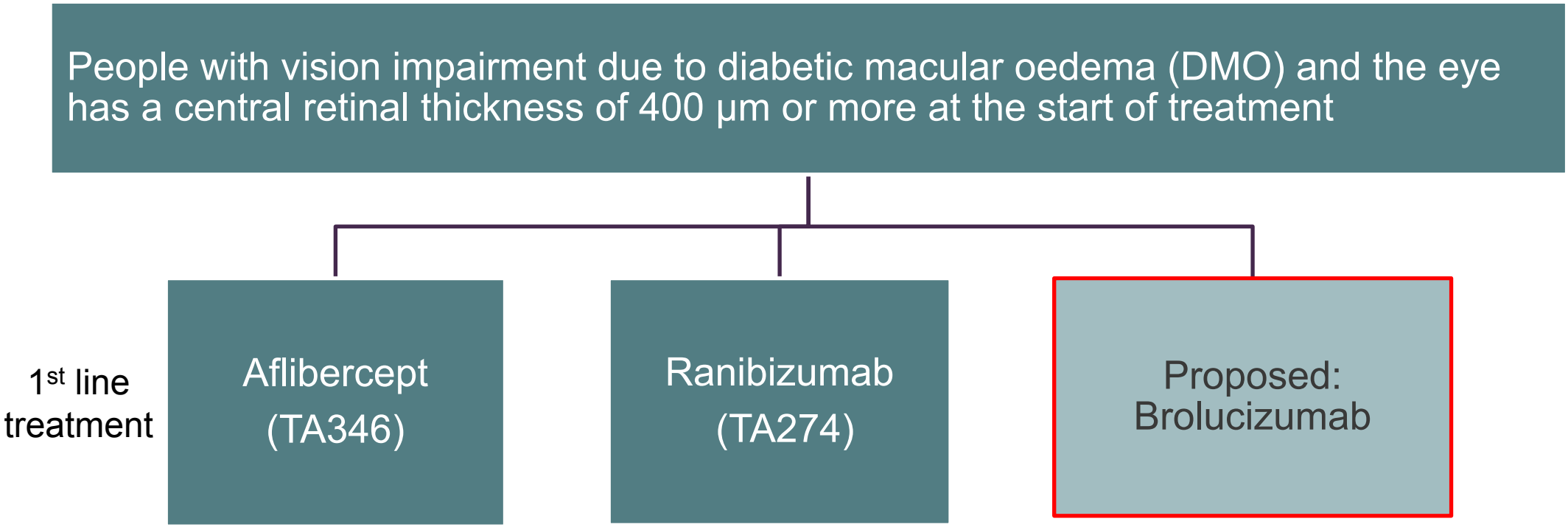
Mechanism of action:

- Brolucizumab is an anti-VEGF treatment, the same as both aflibercept and ranibizumab.

Views from clinical and patient experts at scoping:

- Additional anti-VEGF treatment option, which may work better than the existing drugs for some patients. However it is not a step change in the management of the condition.
- Primary benefit of brolucizumab lies in a longer interval between injections or a decreased injection burden to the patient

Treatment pathway



Clinical trial evidence

Clinical trials: KITE & KESTREL, both comparing brolucizumab with aflibercept.

Primary outcome: mean change from baseline to 1 year in best-corrected visual acuity (BCVA). BCVA is the primary endpoint used in RCTs investigating aflibercept and ranibizumab in DMO.

Clinical effectiveness

- Both KITE and KESTREL met their primary endpoints, demonstrating non-inferiority of brolucizumab 6 mg vs. aflibercept 2 mg with respect to the mean change from baseline in BCVA at Week 52. The mean (LSM) difference was 1.2 letters (95% CI: –0.6, 3.1) in KITE, and –1.3 letters (95% CI: –2.9, 0.3) in KESTREL, ($p<0.001$ for non-inferiority).
- Non-inferior results were also seen in other secondary outcomes.
- Adverse events are likely to be similar between brolucizumab and aflibercept

CRT ≥400 µm subgroup analyses:

- In this post-hoc subgroup analysis, [redacted]

Summary of EAG Assessment Report

- Considers there to be sufficient evidence of equivalent efficacy to support the cost-comparison of brolucizumab and aflibercept. However, EAG did not consider there to be sufficient justification for the brolucizumab versus ranibizumab cost-comparison (NMA not robust).
- Considers the narrower population of DMO patients with visual impairment and a CRT ≥400 µm to be reasonable given the company's decision to submit a cost-comparison versus aflibercept and ranibizumab. However, the EAG notes that the focus of the clinical data from KESTREL and KITE, and from the company NMAs relate to a broader DMO population.
- EAG's clinical experts reported potential safety concerns in terms of intraocular inflammation with brolucizumab. Also that brolucizumab may be used as a second-line treatment with preference for aflibercept or ranibizumab as first-line therapy although the company reports there are no clinical data for second-line use of brolucizumab in DMO.

Company's assumptions: admin and monitoring costs

- EAG considered the company's approach to estimating unit costs to be generally appropriate except for treatment monitoring, for which the EAG's clinical experts identified several monitoring tests which were not costed in the company base case.

- Additionally, a number of concerns were identified with regards to the injection and monitoring frequency estimates used in the company base case.
- EAG provided scenario analyses for its preferred assumptions
  - This includes the cost of 1 additional monitoring visit applied to year 1 for brolucizumab - 6 monitoring visits in the first 6 months of brolucizumab treatment assumed (5 coincide with injection visits)

- EAG was satisfied with the company's injection and monitoring frequency assumptions from year 3 onwards as these were consistent with TA346 and no preferred assumptions were identified.

Company cost-comparison base case

Results include PAS prices for brolucizumab and ranibizumab (known to company), and cPAS/CMU prices for aflibercept

Interventions	Total Costs (£)	Incremental costs (£)
Brolucizumab	XXXX	-
Aflibercept (CMU price)	XXXX	XXXX
Aflibercept (PAS price)	XXXX	XXXX
Ranibizumab	XXXX	XXXX

Note: negative incremental costs indicate brolucizumab is cost saving.
*Caution is advised when interpreting brolucizumab versus ranibizumab results as the EAG did not consider there to be sufficient justification for the brolucizumab versus ranibizumab cost-comparison.

EAG cost-comparison base case

Results include PAS prices for brolucizumab and ranibizumab (known to company), and cPAS/CMU prices for aflibercept

Interventions	Total Costs (£)	Incremental costs (£)
Brolucizumab	XXXX	-
Aflibercept (CMU price)	XXXX	XXXX
Aflibercept (PAS price)	XXXX	XXXX
Ranibizumab	XXXX	XXXX

Note: negative incremental costs indicate brolucizumab is cost saving.
*Caution is advised when interpreting brolucizumab versus ranibizumab results as the EAG did not consider there to be sufficient justification for the brolucizumab versus ranibizumab cost-comparison.

EAG scenario analyses

EAG Scenario	Treatment arm	Total costs	Incremental costs
0	**Company base case**		
	Brolucizumab	XXXX	-
	Aflibercept (CMU price)	XXXX	XXXX
	Aflibercept (PAS price)	XXXX	XXXX
	Ranibizumab	XXXX	XXXX
3	**Unpooled KESTREL trial injection frequencies applied for brolucizumab and aflibercept, with ranibizumab assumed equal to aflibercept injection frequencies**		
	Brolucizumab	XXXX	-
	Aflibercept (CMU price)	XXXX	XXXX
	Aflibercept (PAS price)	XXXX	XXXX
	Ranibizumab	XXXX	XXXX
4	**Cost of one additional monitoring visit applied to year one of brolucizumab arm - 6 monitoring visits in the first 6 months of brolucizumab treatment assumed (5 coincide with injection visits)**		
	Brolucizumab	XXXX	-
	Aflibercept (CMU price)	XXXX	XXXX
	Aflibercept (PAS price)	XXXX	XXXX
	Ranibizumab	XXXX	XXXX

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Single technology appraisal: cost-comparison

Brolucizumab for treating diabetic macular oedema [ID3902]

Document B

Company evidence submission

March 2022

File name	Version	Contains confidential information	Date
ID3902 Document B Fully redacted	**1.0**	**Yes**	**11/03/22**

Contents

Tables and Figures

Abbreviations

AE	Adverse event
AESI	Adverse event of special interest
BCVA	Best-corrected visual acuity
BRB	Blood retinal barrier
CI	Confidence interval
CrI	Credible interval
CRT	Central retinal thickness
CSFT	Central subfield thickness
DAA	Disease activity assessment
DIC	Deviance information criterion
DMO	Diabetic macular oedema
DRSS	Diabetic Retinopathy Severity Scale
DSA	Disease stability assessment
EOS	All enrolled set
EPAR	European public assessment report
ETDRS	Early Treatment Diabetic Retinopathy Scale
EU	European Union
EURETINA	The European Society of Retinal Specialists
FAS	Full analysis set
FFA	Fundus fluorescein angiography
HbA_{1c}	Glycated haemoglobin
HRQoL	Health-related quality-of-life
ILM	Internal limiting membrane
IRF	Intra-retinal fluid
IVT	Intravitreal treatment
KM	Kaplan-Meier
LOCF	Last observation carried forward
LSM	Least squares mean
NEI VFQ-25	National Eye Institute Visual Functioning Questionnaire-25
NHS	National Health Service
NICE	The National Institute for Health and Care Excellence
NMA	Network meta-analysis
OCT	Optical coherence tomography
ONS	Office for National Statistics
PAS	Patient access scheme
PPS	Per protocol set
PRN	Pro re nata
qXw	Every X weeks
RAN	Randomised set
RCT	Randomised controlled trial
RWE	Real-world evidence
SAE	Serious adverse event
SAF	Safety set
SD-OCT	Spectral domain optical coherence tomography
SE	Standard error
SLR	Systematic literature reivew
SoC	Standard of care
SPC	Summary of product characteristics
SRF	Subretinal fluid
SS-OCT	Swept-source optical coherence tomography
SUCRA	Surface under the cumulative ranking curve
TREX	Treat-and-extend
US	United States
VEGF	Vascular endothelial growth factor
wAMD	Wet age-related macular degeneration

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

B.1.1 Decision problem

This submission is for patients with visual impairment caused by diabetic macular oedema (DMO) and a central retinal thickness (CRT) of ≥400 µm. The clinical evidence in this submission is from trials that cover the technology's full anticipated marketing authorisation for this indication. Subgroup analyses aligned to the National Institute for Health and Care Excellence (NICE) recommended comparator population of ≥400 µm are also presented for the primary endpoint.

The comparators considered within the cost comparison analysis are aflibercept and ranibizumab. Both have received marketing authorisation for DMO (1, 2) and are recommended by NICE as cost-effective first-line therapies for use in patients with CRT ≥400 µm in the National Health Service (NHS) (3, 4). Aflibercept and ranibizumab are current standard of care in DMO (5-7).

The decision problem addressed in this submission is provided in Table 1, outlining any differences between the decision problem addressed within the submission and the NICE final scope.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with visual impairment due to DMO	People with visual impairment due to DMO and a CRT of ≥400 µm	This is the optimised population recommended by NICE for both aflibercept (3) and ranibizumab (4) and is addressed in line with the NICE methods guide for cost-comparison (8)
Intervention	Brolucizumab	As per scope	N/A
Comparator(s)	• Laser photocoagulation alone The following technologies alone or in combination with laser photocoagulation: • Aflibercept • Bevacizumab (does not currently have a marketing authorisation in the UK for this indication) • Dexamethasone intravitreal implant • Faricimab (subject to NICE appraisal) • Fluocinolone acetonide intravitreal implant • Ranibizumab	• Aflibercept • Ranibizumab	The following comparators are not considered, for the reasons provided below. **Bevacizumab** • Bevacizumab is not currently licensed for this indication and has not been appraised by NICE. It was listed in the final NICE scope for brolucizumab for the treatment of wAMD, but the appraisal committee agreed that because it has not been appraised by NICE, it could not be considered a comparator in the FTA process (9). **Laser photocoagulation** • UK consensus guidelines on DMO recommend laser photocoagulation (if appropriate) for eyes not meeting NICE criteria (CRT ≥400 µm) (6). Laser photocoagulation is only recommended for use in non-centre involving DMO, thus it occupies a different position in the pathway of care to the anticipated position of brolucizumab. • Use of laser photocoagulation in clinical practice is low. In TA346, clinical experts advised that in recent years, the use of laser photocoagulation has declined due to retinal scarring associated with the procedure and the uptake of new treatments (anti-VEGF therapies and corticosteroids) (10). **Dexamethasone intravitreal implant and fluocinolone acetonide intravitreal implant** • The corticosteroids fluocinolone and dexamethasone are recommended by NICE in different positions in the clinical pathway of care to the anticipated position of brolucizumab (Figure 1) (11, 12).

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			• Clinical experts in TA346 confirmed that these are only given as second-line therapies for patients whose disease has not adequately responded to first-line anti-VEGF treatment (10). **<u>Faricimab (subject to NICE appraisal)</u>** • Faricimab is currently undergoing appraisal by NICE for the treatment of DMO, however NICE guidance will not be published before this submission (publication of faricimab guidance is not expected until the 22nd of June 2022). Therefore, faricimab cannot be considered part of established NHS practice in England and is not a relevant comparator based on Section 6.2.2. of the new NICE methods guide (8). • In TA672 for brolucizumab for the treatment of wAMD, the committee slides confirmed that a cost-comparison only requires comparison against one NICE-recommended comparator (13), therefore a comparison versus faricimab should not be considered necessary.
Outcomes	• BCVA (the affected eye) • BCVA (both eyes) • central foveal subfield thickness • central retinal thickness • contrast sensitivity • disease severity • intraretinal and subretinal fluid • mortality • need for cataract surgery • adverse effects of treatment • health-related quality of life	As per scope, except for: • BCVA (both eyes), contrast sensitivity, need for cataract surgery	The outcomes not addressed in this submission were not captured in the clinical trial programme (the Phase 3 studies KITE and KESTREL).
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	A cost comparison analysis of brolucizumab versus aflibercept and ranibizumab will be presented.	A cost comparison analysis will be presented, as brolucizumab is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication (14). There are two phase 3 head-to-head trials (KITE and KESTREL) comparing brolucizumab with aflibercept in adult patients with visual

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost-comparison may be carried out. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability of any managed access arrangement for the intervention will be taken into account. Cost effectiveness analysis should include consideration of the benefit in the best and worst seeing eye.		impairment due to DMO (Section B.3). In both studies, non-inferiority of brolucizumab 6 mg was demonstrated versus aflibercept 2 mg with respect to the mean CFB in BCVA at Week 52, despite fewer intravitreal treatment injections in the brolucizumab arm, as a result of an extended dosing schedule for patients treated with brolucizumab (15-18) (Section B.3.7.1). Post-hoc subgroup analysis (Section B.3.8) demonstrated that the relative efficacy of brolucizumab versus aflibercept for patients with DMO and CRT ≥400 µm was consistent between the subgroup and the full KITE and KESTREL study populations. Data aligned to the expected brolucizumab marketing authorisation (and KITE and KESTREL full study populations) are used in the cost-comparison since they provide more robust head-to-head evidence whereas the CRT ≥400 µm subgroup data are more limited and uncertain. In the absence of head-to-head data vs. ranibizumab, an NMA was performed (Section B.3.9). The primary analysis covered the wider population of patients with DMO due to data limitations for patients with CRT ≥400 µm. An exploratory (frequentist) analysis in the subgroup is presented in Appendix D. In the primary analysis of all enrolled patients included in the studies, brolucizumab is ranked amongst the best treatments for several outcomes including change in BCVA, improvement in DRSS and decrease in retinal thickness while maintaining a comparable adverse event profile. The comparative benefit of brolucizumab versus aflibercept and ranibizumab in the exploratory analysis (Appendix D) were comparable with the results of the more robust wider network. Therefore, the wider network and FAS population results from the KITE and KESTREL studies can be used as proxies for NICE decision making.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Subgroups to be considered	If the evidence allows the following subgroups will be considered. These include: • type of DMO (focal or diffuse, central involvement, ischaemic or non-ischaemic maculopathy) • duration of DMO • baseline visual acuity • baseline central retinal thickness • previous treatment history (including people who have received no prior treatment, and those who have received and/or whose disease is refractory to laser photocoagulation, ranibizumab or bevacizumab) • prior cataract surgery	Post-hoc subgroup analysis of patients with CRT ≥400 µm, in line with the aflibercept and ranibizumab NICE recommendations	Novartis do not propose to include the subgroups described in the draft scope in the model as brolucizumab is expected to be cost-saving in the optimised population being targeted, aligned to the comparator NICE recommendations. For type of DMO (central involvement, ischaemic or non-ischaemic maculopathy), previous treatment history, and prior cataract surgery, subgroup analyses cannot be performed as data are not available. Clinical subgroup analyses for type of DMO (focal or diffuse), duration of DMO, baseline BCVA, baseline central subfield thickness (considered to be equivalent to central retinal thickness (19)), baseline HbA_{1c}, age, sex and diabetes type all showed [redacted] (15, 16).

Abbreviations: BCVA, best-corrected visual acuity; CFB, change from baseline; DMO, diabetic macular oedema; FTA, fast track appraisal; N/A; not applicable; NHS, National Health Service; NICE, the National Institute for Health and Care Excellence; NMA, network meta-analysis; UK, United Kingdom; VEGF, vascular endothelial growth factor; wAMD, wet age-related macular degeneration.

B.1.2 Description of the technology being appraised

In appendix C include the summary of product characteristics or information for use, and the European public assessment report, scientific discussion or drafts.

The technology being appraised is described in Table 2. The summary of product characteristics (SPC) and European public assessment report (EPAR) are provided in Appendix C.

Table 2: Technology being appraised

UK approved name and brand name	Brolucizumab (BEOVU®)
Mechanism of action	VEGF is a signalling protein that promotes angiogenesis (the formation of new blood vessels). VEGF-A has emerged as the most important regulator of angiogenesis (20), and increased levels of signalling through the VEGF-A pathway are associated with pathological ocular angiogenesis and retinal oedema (build-up of fluid in the retina) (21), which are characteristics of DMO. Brolucizumab is a humanised monoclonal single-chain variable fragment (scFV) which binds with high affinity to VEGF-A isoforms. This prevents binding of VEGF-A to its receptors VEGFR-1 and VEGFR-2, reducing signalling. By inhibiting VEGF-A binding, brolucizumab suppresses endothelial cell proliferation, thereby reducing pathological neovascularisation and decreasing vascular permeability (22). Brolucizumab allows the delivery of a higher dose via Intravitreal treatment (IVT) injection, resulting in the maintenance of pharmacologically relevant drug concentrations for a longer period of time, prolonging its mechanism of action (23). As such, brolucizumab has the potential for lasting disease control with reduced IVT frequency compared to currently available anti-VEGF therapies (Section B.3.11.1).
Marketing authorisation/CE mark status	Brolucizumab does not yet have marketing authorisation for the indication in the submission. A regulatory submission was made to the EMA in [redacted]. CHMP positive opinion was received in February 2022 (24), with marketing authorisation expected to be granted by the European Commission in [redacted]. MHRA approval is expected in [redacted]
Indications and any restriction(s) as described in the summary of product characteristics (SPC)	Brolucizumab is indicated in adults for the treatment of neovascular (wet) age-related macular degeneration. [redacted] Contraindications: • Hypersensitivity to the active substance or to any of the excipients: sodium citrate, sucrose, polysorbate 80, water for injections • Patients with active or suspected intraocular or periocular infections • Patients with active intraocular inflammation (22).
Method of administration and dosage	[redacted]

	[redacted]
Additional tests or investigations	N/A – no additional tests or investigations are required during treatment with brolucizumab.
List price and average cost of a course of treatment	The list price is £816 per 120 mg/mL solution for injection in pre-filled syringe (25). The average cost of a course of treatment is £12,012 (as calculated from the cost-comparison model).
Patient access scheme/commercial arrangement (if applicable)	Brolucizumab is available at a cost of [redacted] per 120 mg/mL solution for injection in pre-filled syringe, via a confidential simple discount patient access scheme.

Abbreviations: CHMP, Committee for Medicinal Products for Human Use; EMA, European Medicines Agency; IVT, intravitreal treatment; N/A, not applicable; MHRA, Medicines and Healthcare products Regulatory Agency; VEFGF-A, vascular endothelial growth factor A; VEGFR-1, vascular endothelia growth factor receptor-1; VEGFR-2, vascular endothelial growth factor receptor-2.

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

Disease overview

- Diabetic macular oedema (DMO) is a common complication of diabetes (estimated prevalence of 5.2% among patients with diabetes in England) (26)
- Diabetic macular oedema is characterised by the accumulation of fluid in the macula (27), leading to progressive retinal dysfunction, and if left untreated, results in permanent vision loss (28-30)

Humanistic burden

- Visual impairment due to DMO has a significant negative impact on health-related quality of life (HRQoL), with patients reporting limitations in performing daily activities (31, 32) and treatment-related anxiety (33), with worsening visual acuity also affecting patients' mental health (34)
- Both patient and carer productivity and work life are affected by frequency of hospital visits for treatment of their DMO (33), in addition to an already high number of hospital visits due to the high comorbidity burden (35-38)

Economic burden

- Diabetic macular oedema is associated with a high economic burden due to high resource use (as a result of frequent clinic visits (39)) and direct and indirect medical costs

Clinical management

- Both UK consensus guidelines and the National Institute for Health and Care Excellence (NICE) recommend the anti-vascular endothelial growth factor (VEGF) therapies aflibercept

and ranibizumab as first-line therapy for patients with visual impairment due to DMO with central retinal thickness ≥400 µm (3, 4, 6)

Unmet need

- There remains an unmet need for anti-VEGF therapies that offer better anatomical outcomes, such as greater fluid resolution. In clinical trials, patients receiving ranibizumab or aflibercept had incomplete fluid resolution (40, 41), which has been associated with poor visual outcomes (42)
- Adherence to current therapies is poor due to high injection frequency in addition to an already high volume of medical appointments for diabetes and comorbidities (38). Poor adherence is associated with worse visual outcomes (43). In addition, mounting pressures on ophthalmology units have been compounded by the COVID-19 pandemic (44). The potential for a reduced injection frequency with brolucizumab may help to tackle the backlog of patients caused by the pandemic

B.1.3.1 Disease overview

Diabetic macular oedema is a common sequela of diabetic retinopathy, which is the most common complication of diabetes mellitus (45) and a leading cause of vision loss (46). Its presence is associated with duration of diabetes (47), poor blood glucose control (hyperglycaemia) (48), and the cardiovascular consequences of hypertension (49), hyperlipidaemia (50), and renal disease (51). Vision loss from DMO can occur at any stage of diabetic retinopathy, regardless of the presence or absence of abnormal blood vessel growth in the retina (52, 53). The VIVID and VISTA trials (investigating aflibercept in DMO) reported that 12.7% of patients with DMO have bilateral disease (54).

Within the retinal vascular system, the blood-retinal barrier (BRB) regulates fluid flow from retinal blood vessels, preventing leakage of excess fluid into retinal tissue (27). Breakdown of the BRB in DMO results in the accumulation of fluid in the intracellular and extracellular space of the macula area (part of the retina responsible for central vision, and most colour vision (55)). Secondary to this, retinal thickening occurs from the formation of hard exudates (composed of lipid and proteinaceous material that leak from the damaged blood vessels and settle in the retina) (27, 56). The increased retinal fluid in DMO leads to progressive retinal dysfunction, and if left untreated, results in permanent vision loss (28-30).

Hyperglycaemia-induced oxidative stress (where high glucose levels increase the levels of reactive oxygen species) leads to overproduction of vascular endothelial growth factor (VEGF)-A, disrupting the BRB and causing capillaries in the retina to leak fluid (57, 58). Fluid build-up is associated with worse visual outcomes, with patients with higher fluid levels having worse visual acuity than patients with lower fluid levels (42).

Hallmark features of DMO include blurred vision, dark spots, impaired colour vision, metamorphopsia (linear objects appear curved or rounded), washed-out vision in bright light, and poor dark-light adaptation (59, 60). It can also lead to irreversible vision loss and blindness (28-30).

B.1.3.1.1 *Epidemiology*

In 2019, the prevalence of diabetes was 3,919,505 in the UK, and 3,319,266 in England (61). A UK database analysis estimated that the prevalence of DMO among patients with diabetes was 7.1% in England (2010), with 2.7% experiencing clinically significant DMO with visual impairment (62).

In a meta-analysis of 35 population-based observational studies in Europe (1996–2016), across seven UK studies identified, the prevalence of clinically significant DMO was estimated to be 5.2% among individuals with diabetes (26).

B.1.3.2 Humanistic burden

With the prevalence of diabetes increasing globally, diabetic eye disease is a rising concern for healthcare bodies. An English study reported that visual impairment affects approximately 37%[1] of patients with DMO and 1.6%[2] of patients with DMO are legally blind (best corrected visual acuity [BCVA] ≤20/200) (62).

Visual impairment due to DMO has a significant effect on patient health-related quality of life (HRQoL), impacting both physical and emotional wellbeing. Globally, 64% of patients with DMO experience limitations in performing daily activities (31), which can be a challenge for independent living. In addition, it has been reported that there is an association between worse visual acuity and patients' mental health (34).

One study found that for the National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25 [note, a lower score indicates worse outcomes]), patients with DMO score lowest for the subscale of general health, and highest for the subscale of dependency (63). In addition, patients with DMO report treatment-related anxiety (33). A total of 75% of patients experience anxiety related to their most recent intravitreal treatment (IVT) injection, with 54% being anxious for ≥2 days prior (33). Patients also report guilt related to asking a carer for assistance, exacerbating their anxiety regarding the appointment (33).

[1]Percentage calculated as number patients with diabetes with visual impairment due to DMO (62,083)/number of patients with diabetes with DMO (166,325)*100 (62)

[2]Percentage calculated as number patients with diabetes who are blind due to DMO (2,642)/number of patients with diabetes with DMO (166,325)*100 (62)

The debilitating effects of worsening visual acuity in DMO can affect both patient and carer productivity and work life. One European study reported that the average patient appointment (including travel time) was 4.5 hours, with 53% of patients needing to take ≥1 day off work (33). In addition, 71% of patients required a carer's assistance around the time of the appointment, totalling an average of 6.3 hours, with the majority (59%) needing to take time off to support the patient.

Improvements in vision have been shown to improve HRQoL in patients with DMO. One study found that patients with BCVA improvements of ≥5 letters had increases of 3–7 points for the NEI VFQ-25 composite score, and the general vision, near activities, dependency, and driving subscales, compared with patients with no change in BCVA ($p < 0.05$) (64).

B.1.3.3 Economic burden

There is a scarcity of data regarding the total costs associated with DMO, however it is associated with a high economic burden, owing to high resource use and direct and indirect medical costs (65). A literature review reported that on average patients with DMO incur 2–3-fold higher costs than patients with diabetic retinopathy only (66). In 2010, the total health and social care costs of DMO in the UK were estimated to be over £116 million, with direct medical costs accounting for 80% of the total cost (62).

Resource use is high in patients with DMO, owing to the high number of clinic, treatment, and optical coherence tomography (OCT) visits (39). Indirect costs of DMO include productivity losses due to the impact on ability to work; patients are typically of working age (67). In addition, carers may also need to take time off work (33).

B.1.3.4 Diagnosis and monitoring

Adults diagnosed with diabetes should immediately be referred to local eye screening services (68). For both the diagnosis, evaluation, and monitoring of DMO, OCT is now in widespread use, with most examinations carried out at eye hospital service visits (6).

Spectral domain (SD-OCT) and swept-source (SS-OCT) are used to assess macular thickness and examine morphological signs of DMO, such as subretinal fluid (SRF), and intra-retinal fluid (IRF) or intra-retinal cysts (5).

Fluorescein angiography is the only technique that can detect vascular leakage; this imaging modality remains the gold standard for assessing DMO prior to considering treatment, and may be used in combination with OCT (6). For the monitoring of an individual's response to anti-VEGF treatment, OCT is considered the most useful imaging technique.

B.1.3.5 Clinical pathway of care and proposed positioning of brolucizumab

In UK NHS practice, the key considerations when determining treatment for DMO are the level of visual acuity, central subfield thickness (CSFT; which is considered equivalent to CRT (19)) on OCT, and patient choice (6). The clinical pathway of care for the treatment of patients with DMO with CRT ≥400 µm is discussed below, based on Europe-wide clinical guidelines from The European Society of Retinal Specialists (EURETINA) (5), the UK consensus working group (6), and evidence-based recommendations for the available treatments from NICE (3, 4, 11, 12). Clinical insight gathering was also performed, to further understand current NHS treatment of patients with visual impairment due to DMO with a CRT of ≥400 µm (Appendix J).

NICE recommends the anti-VEGF therapies aflibercept (TA346) (3) and ranibizumab (TA274) for patients with CRT ≥400 µm (4). In clinical insight gathering (Appendix J), [redacted]

NICE and the UK consensus working group recommend the corticosteroids dexamethasone and fluocinolone acetonide for patients with pseudophakic eyes (i.e. the patient has an artificial lens implanted), and an insufficient response to anti-VEGFs, or where anti-VEGFs are not appropriate (6, 11, 12).

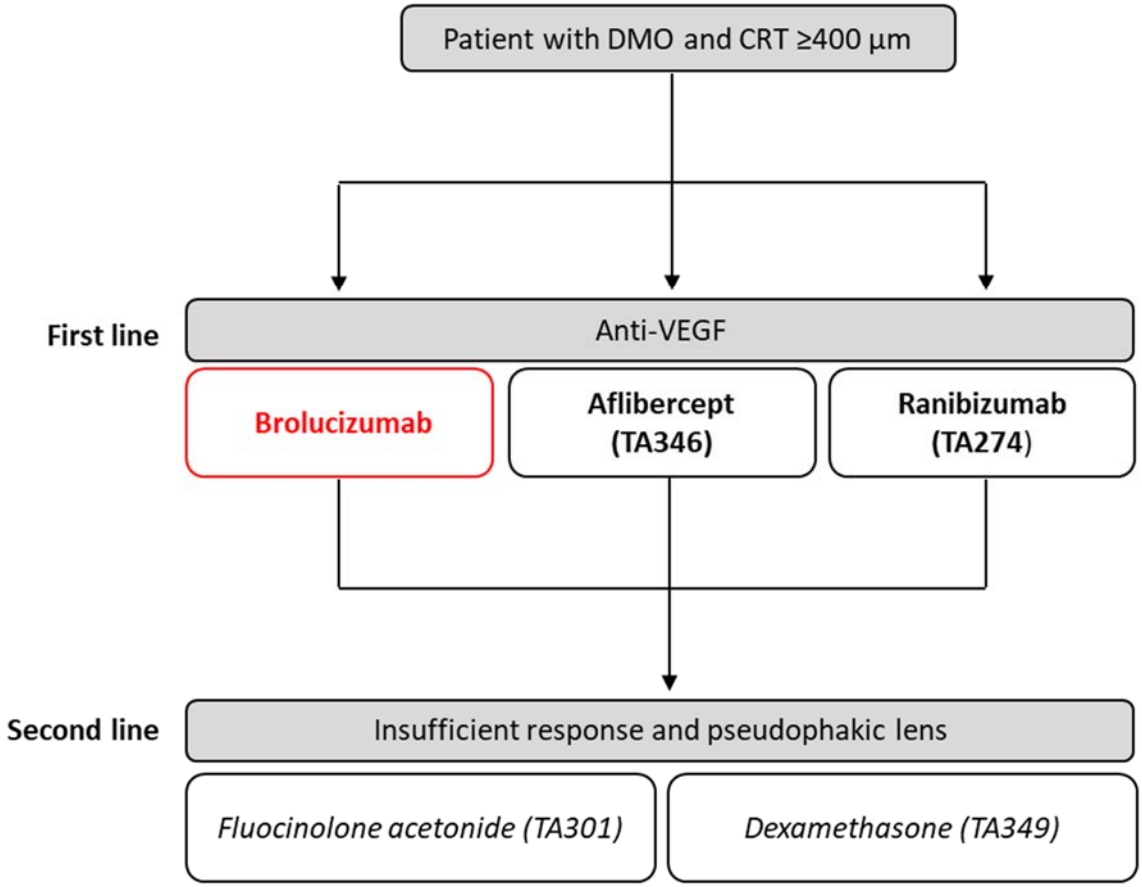
In the clinical insight gathering, [redacted]

Although it was the first available treatment for DMO in 1980 (69), the use of laser photocoagulation has declined since the introduction of anti-VEGF therapies, and is no longer considered standard of care (SoC) (5). Laser may be acceptable in a small subgroup of patients where the leaking microvascular changes are far from the fovea (>500 µm) with a large volume of associated fluid/exudate (6) (5), or if anti-VEGFs are contraindicated, or if the patient has severe injection anxiety (70). The clinical insight gathering (Appendix J) [redacted]

Switching between anti-VEGF therapies, and from anti-VEGF to corticosteroids, occurs in clinical practice in the UK, however, the rationale for switching therapies is not uniformly agreed upon and there is no formal definition of treatment failure (6). [redacted]

Brolucizumab is anticipated to be used in clinical practice for the treatment of patients with visual impairment due to DMO and CRT ≥400 µm, a subgroup of the licensed indication. The relevant comparators in this position, and in the context of this appraisal, are aflibercept and ranibizumab. The current clinical pathway of care, along with the proposed positioning of brolucizumab, is presented in Figure 1.

Figure 1: The clinical pathway of care comprising current NICE recommended therapies and the proposed positioning of brolucizumab



Interventions that are italicised are not considered as comparators in this submission (Section B.1.1).
Abbreviations: CRT, central retinal thickness; DMO, diabetic macular oedema; MA, marketing authorisation; VEGF, vascular endothelial growth factor.

Figure 2 outlines the pharmacological management of patients with DMO using currently available anti-VEGF therapies, and the anticipated licensed posology of brolucizumab, based on each interventions' SPC (1, 2) (Appendix C).

Figure 2: Pharmacological management of patients with DMO using anti-VEGF (including anticipated posology of brolucizumab)

†Based on visual and/or anatomical outcomes.
Abbreviations: DA, disease activity; DMO, diabetic macular oedema; q4w, every 4 weeks; q6w, every 6 weeks; q8, every 8 weeks; q12w, every 12 weeks; q16w, every 16 weeks; TREX, treat and extend; VA, visual acuity.

B.1.4 Unmet need

Despite the treatment success of existing anti-VEGF therapies, there is a need for an anti-VEGF that offers better anatomical outcomes, such as greater fluid resolution. In their respective clinical trials, a high proportion of patients receiving aflibercept or ranibizumab had residual fluid present at Week 52 (indicated by the mean CRT remaining >300 µm) (40, 41). The incomplete fluid resolution is associated with poor visual outcomes; higher IRF and SRF are associated with lower visual acuity (42).

There are also distinct challenges related to the frequency of IVT injections and the need for regular monitoring of disease activity. In the real world, adherence to treatment is poor, with 44%

of patients being non-adherent after the first year (43). This may be explained by the burden that frequent IVT injections with current anti-VEGFs places on patients and healthcare systems. Poor adherence is associated with worse visual outcomes; non-adherence is linked to a 10-fold higher rate of significant vision loss than that in patients who are adherent to treatment (43). In addition, clinical capacity can be an issue, as IVT injections are typically performed in operating theatres or dedicated sterile rooms (71, 72). Furthermore, the COVID-19 pandemic has compounded the already mounting pressures on ophthalmology units (44). Flexible regimens are common for the treatment of DMO; these reduce the treatment burden associated with IVT injections, and are adopted usually once DMO resolves or there is no further improvement in visual acuity (73). Regimens include pro re nata (PRN) and treat-and-extend (TREX). However, in the UK, many ophthalmology clinics run at full capacity, so some clinics cannot maintain recommended follow-up and re-treatment intervals (74). Clinical insight gathering [redacted]

Patients have expressed a need for a lower treatment burden; in a survey the most desired improvements were a lower injection frequency without compromising outcomes (42%), fewer appointments (22%), and reductions in waiting times (14%) (33).

There remains a significant unmet need for treatment options that improve adherence and/or reduce resource use and injection frequency, while maintaining visual acuity at the same level as more frequent treatment regimens. In addition, early identification of patients who are likely to be able to maintain a longer treatment interval will assist with planning clinic capacity, helping to reduce the risk of undertreatment. Reduced injection frequency may also potentially help ease some of the pressure on ophthalmology units resulting from a backlog of patients following the COVID-19 pandemic.

B.1.5 The value of brolucizumab

Brolucizumab allows the delivery of a higher dose via IVT injection compared with aflibercept and ranibizumab, resulting in the maintenance of pharmacologically relevant drug concentrations for a longer period of time, prolonging its mechanism of action (23). Brolucizumab is already recommended by NICE for the treatment of patients with wet-age related macular degeneration (wAMD) (75), [redacted]

The potential for brolucizumab to provide lasting disease control with reduced IVT frequency could reduce the treatment burden on patients, carers, and healthcare resources.

B.1.6 Equality considerations

No equality issues are anticipated.

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

- Two previous NICE technology appraisals have been published for treatments in diabetic macular oedema (TA274 **(76)** and TA346 **(77)**).
- The key clinical outcome in both TA247 and TA346 was the probability of gaining or losing 10 Early Treatment Diabetic Retinopathy Study (ETDRS) letters and is considered in the NMA for the current appraisal. The probability of gaining or losing 15 ETDRS letters was also evaluated in TA346.
- Cost types considered in both TA274 and TA346 were drug acquisition and administration, monitoring, adverse events, and the cost of blindness.
- No concerns were raised by the committees on the type of costs considered in the appraisals.

B.2.1 Clinical outcomes and measures

The relevant comparators for brolucizumab in DMO in this appraisal are:

- Ranibizumab, evaluated in NICE TA274, published in February 2013 (4)
- Aflibercept, evaluated in NICE TA346, published in July 2015 (3).

Further detail on the comparators included in this submission is available in Section B.1.1.

In these appraisals, the key clinical outcomes used in the cost-effectiveness analyses were:

- Probability of gaining or losing 10 Early Treatment Diabetic Retinopathy Study (ETDRS) letters
- Probability of gaining or losing 15 ETDRS letters (TA346 only).

In TA274, the committee heard from the clinical specialists that “a clinically significant gain in visual acuity is 10-15 letters”. No concerns were raised by the appraisal committees on the suitability of the selected clinical outcome measure(s).

The network meta-analysis (NMA) conducted for the current appraisal includes the probability of gaining or losing 10 or 15 ETDRS letters as an outcome (Section B.3.9).

B.2.2 Resource use assumptions

The resource use and associated costs considered in the technology appraisals for aflibercept and ranibizumab were (Table 3):

- Drug acquisition costs (including injection frequency)
- Drug administration costs
- Monitoring costs (including monitoring frequency)

- Costs associated with blindness
- Adverse event (AE) costs.

All cost types, except for costs associated with blindness, were included in the current cost-comparison analysis for brolucizumab in DMO. Costs associated with blindness were not considered relevant, given that the considered technologies are associated with similar efficacy

Table 3: Resources and associated costs appraised in published NICE guidance for the comparators

Appraisal	Cost category	Item	Unit cost (£)	Manufacturer's assumptions	Committee's preferred assumptions
TA346 (3)	Drug acquisition costs	Cost per vial of aflibercept Cost per vial of ranibizumab	£816.00 £742.17	Derived from the BNF	No comment was made by the Committee.
	Drug administration costs	Cost of laser administration	£139	Cost based on the result of an online survey of 34 ophthalmologists.	The ERG suggested the cost of laser administration was better informed using the NHS reference costs (£194) and assumed the cost of a laser administration and intravitreal injection are equivalent, to which the Committee agreed.
		Cost per injection visit	£194	The manufacturer assumed an injection visit includes both an injection and a standard monitoring visit.	-
	Injection frequency	**Aflibercept** Year 1: 8.00 Year 2: 5.45 **Ranibizumab** Year 1: 7.77 Year 2: 5.45	–	Injection frequency was informed by the VISTA and VIVID trials; year 2 aflibercept injection frequency was assumed identical to ranibizumab. An online survey supported the assumption of a similar number of injections for ranibizumab and aflibercept in year 1 and 2.	The ERG believed the number of injections of aflibercept should be increased to 8.55 year 1, as the SPC for aflibercept implied 4-weekly dosing and decreased to 4.00 in year 2 to align with the mean number of injections for aflibercept in VISTA and VIVID. The Committee aligned with the ERG; modelling of aflibercept treatment should be based on trial data for aflibercept. Equivalent frequencies for aflibercept and ranibizumab were suggested to be explored through sensitivity analysis.
	Monitoring costs	Cost per monitoring visit	£139.22	The manufacturer assumed all treatment visits would double as monitoring visits; therefore, this cost is encompassed in the cost per injection visit. The cost of a monitoring visit was derived from the NHS reference costs of one non-admitted consultant visit plus one ultrasound scan	No comment was made by the Committee.

Appraisal	Cost category	Item	Unit cost (£)	Manufacturer's assumptions	Committee's preferred assumptions
	Monitoring frequency	**Aflibercept** Year 1: 8.00 Year 2: 6.00 Year 3: 4.00 Year 5: 2.00 **Ranibizumab** Year 1: 12.00 Year 2: 6.30 Year 3: 4.00 Year 4: 4.00 Year 5: 2.00 **Laser** Year 1: 4.00 Year 2: 4.00 Year 3: 2.60 Year 4: 2.20 Year 5: 1.90	–	Monitoring visits for aflibercept and ranibizumab were estimated based on their SPCs in year 1. Monitoring visits for laser treatment were estimated from VISTA and VIVID (year 1) and a physician survey (years 2–5).	The ERG suggested laser monitoring visits should be increased to 12.00 in year 1 to reflect VISTA & VIVID. However, the Committee concluded this increase was not appropriate as monitoring in trials reflects the need to collect data at regular intervals and aligned with the manufacturer. Professional guidance also suggested no more than 4 monitoring visits per year.
	Adverse event costs	Cataract Endophthalmitis Retinal detachment Vitreous haemorrhage Ocular hypertension Glaucoma	£1,146.87 £1,541.74 £1,843.16 £1,666.58 £3.57 £1,151.00	Adverse event costs for cataract, endophthalmitis, retinal detachment, vitreous haemorrhage were derived from the NHS reference costs. The cost of ocular hypertension was informed from aflibercept CRVO NICE submission and TA301 ERG fluocinolone NICE submission for glaucoma.	No comment was made by the Committee.
	Cost of blindness		£6448	The manufacturer obtained this from literature and updated for inflation.	No comment was made by the Committee.

Appraisal	Cost category	Item	Unit cost (£)	Manufacturer's assumptions	Committee's preferred assumptions
TA274 (4)	Drug acquisition costs	Cost of ranibizumab per injection	£761.20	–	No comment was made by the Committee.
	Drug administration	Ranibizumab and laser photocoagulation Ranibizumab alone Laser photocoagulation alone	£184 £150 £150	For combination therapy, it was assumed ranibizumab injections and laser photocoagulation would occur in the same visit. It was assumed treatment with both ranibizumab and laser photocoagulation occurs on an outpatient basis costing £150 per visit.	No comment was made by the Committee.
	Injection frequency	**Ranibizumab monotherapy** Year 1: 7 Year 2: 3 **Ranibizumab combination therapy** Year 1: 7 Year 2: 2 **Laser photocoagulation alone** Year 1: 2 Year 2: 1 **Laser photocoagulation combination therapy** Year 1: 2 Year 2: 1	–	The manufacturer included a stopping rule such that those with VA of ≥76 letters in the treated eye would not receive active treatment and therefore, not incur treatment costs. Treatment with ranibizumab or laser photocoagulation was assumed to not take place after the second year as in clinical practice these would be the same frequency in both arms and therefore cancel out in the model.	The Committee noted it was unlikely those receiving 3 injections in year 3 would receive no injections in year 4. The Committee also raised uncertainty regarding whether people would require ranibizumab beyond 4 years and what the associated costs of ongoing treatment would be.
	Monitoring costs	Cost per monitoring visit	£126	The full cost of laser photocoagulation was assumed to be included within the NHS reference cost for a clinic visit.	No comment was made by the Committee.

Appraisal	Cost category	Item	Unit cost (£)	Manufacturer's assumptions	Committee's preferred assumptions
	Monitoring frequency	**Ranibizumab monotherapy** Year 1: 12 Year 2: 10 Year 3+: 4 **Combination therapy** Year 1: 12 Year 2: 8 Year 3+: 4 **Laser photocoagulation alone:** All years: 4	–	It was assumed a treatment visit for people treated with ranibizumab and laser photocoagulation doubles as a monitoring visit.	The Committee preferred this assumption in comparison to the assumption in the Manufacturer's original analysis in TA237, in which a visit for treatment did not double up as a monitoring visit for laser monotherapy (76).
	Adverse events	Cataract Endophthalmitis Retinal detachment Vitreous haemorrhage	NR	Adverse events were informed by a pooled analysis of RESTORE and DRCR.net. Costs were taken from the NHS reference costs.	No comment was made by the Committee
	Cost of blindness		Year 1: £6067 Year 2: £5936	Cost of blindness accounted for items including low-vision aids, rehabilitation, residential care, district nursing, community care and falls. This cost was largely derived from Meads and Hyde, 2003, a UK study in age-related macular degeneration (78).	No comment was made by the Committee.

Abbreviations: BNF, British National Formulary; ERG, evidence review group; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; NR, not reported; SPC, summary of product characteristics; UK, United Kingdom; VA, visual acuity.

B.3 Clinical effectiveness

The evidence base for brolucizumab comprises two Phase 3 randomised controlled head-to-head trials versus aflibercept, KITE and KESTREL

[redacted]

Both trials met their primary endpoint, demonstrating noninferiority of brolucizumab 6 mg vs. aflibercept 2 mg with respect to the mean change from baseline in best-corrected visual acuity (BCVA) at Week 52

- The least squares mean (LSM) difference was 1.2 letters (95% confidence interval [CI]: –0.6, 3.1) and –1.3 letters (95% CI: –2.9, 0.3) in KITE and KESTREL, respectively ($p<0.001$ for both comparisons, non-inferiority margin of ≤4 letters)
- [redacted]Over the first 52 Weeks, the mean number of intravitreal treatment (IVT) injections received was 7.0 and 6.8 in the brolucizumab 6 mg arms of KITE and KESTREL, respectively, and 8.5 in the aflibercept 2 mg arm of both studies. More than half of the patients in the brolucizumab 6 mg arms (in both studies) remained on a once every 12 week (q12w) treatment regimen immediately after the loading dose up to Week 52. [redacted]
- [redacted] despite less frequent IVT injections in the brolucizumab arms
- Of the patients in the brolucizumab 6 mg arms who qualified for treatment every 12 weeks at Week 36 (based on their Week 32 and 36 disease activity assessments [DAAs]), a high proportion remained on a 12-week dosing schedule at Week 52 (95.1% in KITE; 87.6% in KESTREL) [redacted]

[redacted]

Overall, brolucizumab 6 mg had a favourable benefit/risk profile with no new safety signals in patients with DMO

- Ocular adverse events were reported with similar frequency across treatment arms in both studies, [redacted]

Comparative effectiveness

- In the absence of head-to-head data versus ranibizumab, a network meta-analysis (NMA) was performed to assess the relative efficacy and safety of brolucizumab compared with relevant comparators. The primary analysis considered the wider population of patients with DMO, while an exploratory (frequentist) analysis was performed in the subgroup of patients with central subfield thickness (CSFT ≥400 µm)
- In the primary analysis of all enrolled patients included in the studies, brolucizumab is ranked amongst the best treatments for several outcomes including change in BCVA, improvement in DRSS and decrease in retinal thickness while maintaining a comparable adverse event profile.
- The comparative benefit of brolucizumab versus aflibercept and ranibizumab in the exploratory analysis (Appendix D) were comparable with the results of the more robust wider network. Therefore, the wider network and FAS population results from the KITE and KESTREL studies can be used as proxies for NICE decision making.

B.3.1 Identification and selection of relevant studies

A systematic literature review (SLR) was conducted to identify all relevant clinical evidence on the efficacy and safety of brolucizumab and relevant comparators for the treatment of patients with DMO. In total, the SLR identified 140 records reporting on 44 unique studies. See Appendix D for full details of the process and methods used to identify and select the clinical evidence relevant to the technology being appraised.

B.3.2 List of relevant clinical effectiveness evidence

The primary sources of clinical effectiveness evidence for brolucizumab in DMO are the Phase 3 randomised controlled trials (RCTs) KITE (EudraCT no. 2017-003960-11) (15, 17, 18, 79) and KESTREL (EudraCT no. 2017-004742-23) (16-18, 79) (Table 4).

Table 4: Clinical effectiveness evidence – KITE and KESTREL

Study	KITE (15, 17, 18, 79, 80) (EudraCT no. 2017-003960-11)	KESTREL (16-18, 79) (EudraCT no. 2017-004742-23)(80)
Study design	Two-year, Phase 3, randomised (1:1), double-masked, multicentre, active controlled, two-arm study	Two-year, Phase 3, randomised (1:1:1), double-masked, multicentre, active controlled, three-arm study
Population	Adult patients (≥18 years) with visual impairment in the study eye due to DMO, with: • Type 1 or Type 2 diabetes mellitus • HbA_{1c} ≤10% • BCVA score 78–23 letters at 4 meters • CSRT ≥320 µm on SD-OCT at screening	
Intervention(s)	Brolucizumab 6 mg/0.05 mL, 5 loading doses (once every 6 weeks), with subsequent doses per protocol-specified maintenance schedule (once every 12 or 8 weeks); with an option to extend treatment interval at week 72 (by 4 weeks)	Brolucizumab 3 mg/0.05 mL or 6 mg/0.05 mL, 5 loading doses (once every 6 weeks), with subsequent doses per protocol-specified maintenance schedule (once every 12 or 8 weeks)
Comparator(s)	Aflibercept 2 mg/0.05 mL, 5 loading doses (once every 4 weeks), with subsequent doses every 8 weeks	
Indicate if trial supports application for marketing authorisation (yes/no)	Yes	
Reported outcomes specified in the decision problem	• BCVA (study eye) • Parameters derived from SD-OCT, colour fundus photography and fluorescein angiography (study eye) • DR status (ETDRS DRSS) • Ocular and non-ocular AEs • PRO (VFQ-25) • Macular vascular pathology by OCT angiography • Peripheral retinal pathology by wide-field angiography and wide-field fundus photography	
All other reported outcomes	• Proportion of patients maintained on extended dosing cycles • Treatment status • Vital signs and laboratory values • Genetic factors influencing disease phenotype or treatment response • Proportion of patients reassigned and maintained on extended dosing cycles • Systemic brolucizumab exposure • Immunogenicity (ADA status)	• Proportion of patients maintained on extended dosing cycles • Treatment status • Vital signs and laboratory values • Genetic factors influencing disease phenotype or treatment response •

Abbreviations: AE, adverse event; BCVA, best-corrected visual acuity; CSRT, central subfield retinal thickness; DMO, diabetic macular oedema; DR, diabetic retinopathy; DRSS, Diabetic Retinopathy Severity Scale; ETDRS, Early Treatment Diabetic Retinopathy Study; HbA_{1c}, haemoglobin A_{1c}; PRO, patient reported outcomes; SD-OCT, spectral domain optical coherence tomography; SPC, summary of product characteristics; VFQ-25, Visual Functioning Questionnaire-25.

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

KITE and KESTREL are two-year, randomised, Phase 3, double-masked, multicentre, active controlled trials which assessed the efficacy and safety of brolucizumab compared with aflibercept in patients with visual impairment due to DMO.

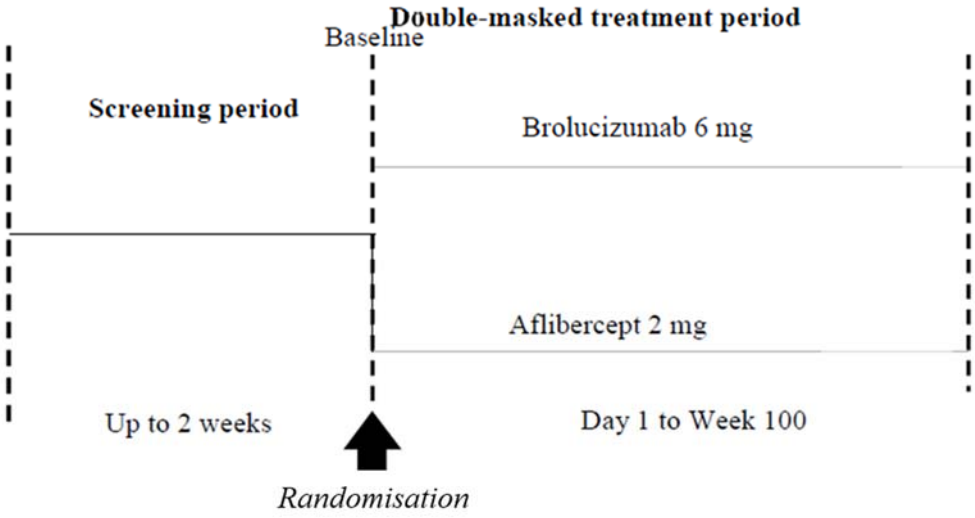
The trial protocols were identical, except KESTREL included an additional brolucizumab treatment arm (3 mg), and KITE had the option for patients to extend their dosing schedule by 4 weeks at Week 72 (Table 4). [redacted] Both the KITE and KESTREL trials shared an identical primary endpoint and similar secondary efficacy endpoints. Given the significant overlap in methodology, a combined summary is presented.

B.3.3.1 Trial design

In KITE, patients were randomised 1:1 to receive brolucizumab 6 mg/0.05 mL or aflibercept 2 mg/0.05 mL. In KESTREL, patients were randomised 1:1:1 to receive brolucizumab 6 mg/0.05 mL, brolucizumab 3 mg/0.05 mL or aflibercept 2 mg/0.05 mL.

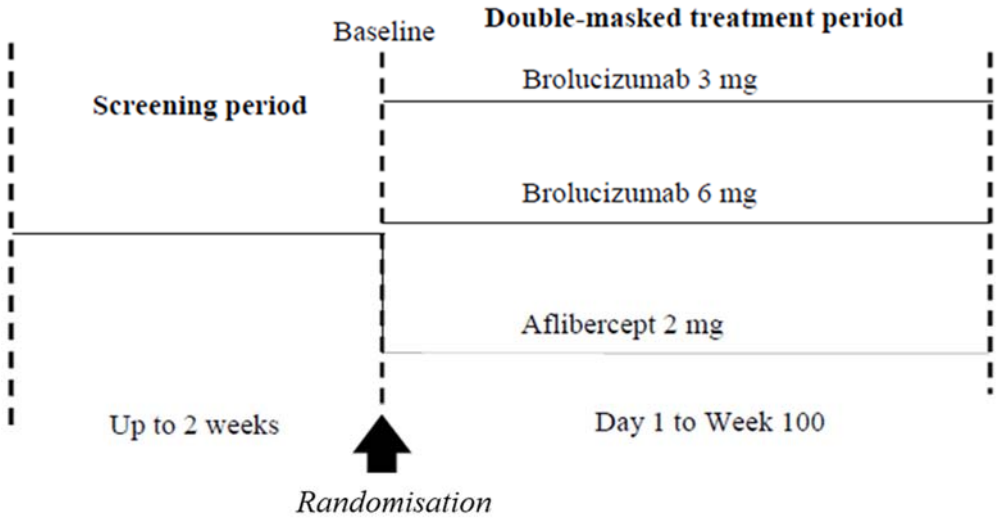
Both studies included a screening period of up to 2 weeks to assess patient eligibility, followed by a double-masked treatment period (Day 1 to Week 96). After the last treatment visit, there was a post-treatment follow-up period of 4 weeks (Week 96 to Week 100). The treatment period included a loading phase (baseline, Weeks 6, 12, 18 and 24) and a maintenance phase (Weeks 24 to 100). The study designs for KITE and KESTREL are illustrated in Figure 3 and Figure 4, respectively.

Figure 3: Study design – KITE



Source: KITE clinical study report (15).

Figure 4: Study design – KESTREL



Source: KESTREL clinical study report (16).

Only one eye was selected as the study eye and treated with study medication. If both eyes were eligible, the eye with the worst visual acuity was selected, however the eye with better visual acuity could be selected based on medical reasons or local ethical requirements.

Data presented in this submission relate to the cut-off date at which the last patient underwent their Week 52 visit (29th June 2020 for KITE and 11th November 2020 for KESTREL; the primary analysis was based on Week 52 data). The submission also presents data collected after patients completed their Week 100 visit or exited early due to study discontinuation.

B.3.3.2 Eligibility criteria

Key inclusion and exclusion criteria for both studies are listed in Table 5.

Table 5: Key Inclusion and exclusion criteria in KITE and KESTREL

Key inclusion criteria	Key exclusion criteria
• Written informed consent obtained before any assessment is performed • Aged ≥18 years at BL • Type 1 or 2 diabetes mellitus and HbA_{1c} of ≤10% at screening • Medication for the management of diabetes had to be stable within 3 months prior to randomisation and is expected to remain stable during the course of the study • Visual impairment due to DMO in the study eye, with: o BCVA score 78–23 letters, inclusive, using ETDRS visual acuity testing charts at a testing distance of 4 meters (approximate	• Active PDR in the study eye as per investigator • Concomitant conditions or ocular disorders in the study eye at screening or BL which could, in the opinion of the investigator, prevent response to study treatment or could confound interpretation of study results, compromise visual acuity or require medical or surgical intervention during the first 12-month study period (e.g., cataract, vitreous haemorrhage, retinal vascular occlusion, retinal detachment, macular hole, or choroidal neovascularisation of any cause) • Any active intraocular or periocular infection or active intraocular inflammation (e.g., infectious conjunctivitis, keratitis, scleritis, endophthalmitis, infectious blepharitis, uveitis) in study eye at screening or BL • Structural damage of the fovea in the study eye at screening likely to preclude improvement in visual acuity following the resolution of macular oedema, including atrophy of the retinal pigment epithelium, subretinal

Key inclusion criteria	Key exclusion criteria
Snellen equivalent of 20/32 to 20/320) at screening and BL o DMO involving the centre of the macula, with CSFT (measured from RPE to ILM inclusively) of ≥320µm on SD-OCT at screening • If both eyes were eligible, the eye with the worse visual acuity was selected for study eye. However, the investigator could have selected the eye with better visual acuity, based on medical reasons or local ethical requirements	fibrosis, laser scar(s), epiretinal membrane involving fovea or organized hard exudate plaques • Uncontrolled glaucoma in the study eye defined as IOP >25 mmHg on medication or according to investigator's judgment at screening or BL • History of idiopathic or autoimmune uveitis in the study eye • Previous treatment with any anti-VEGF drugs or investigational drugs in the study eye • Use of dexamethasone intravitreal implant (Ozurdex) or fluocinolone acetonide intravitreal implant (Iluvien) in study eye at any time. Prior use of other intraocular or periocular corticosteroids in the study eye is not an exclusion provided at least 6-month wash-out prior to BL • Laser photocoagulation (focal/grid or panretinal) in the study eye during the 3-month period prior to BL • Intraocular surgery including YAG laser in the study eye during the 3-month period prior to BL • Systemic anti-VEGF therapy during the 3-month period prior to BL • Stroke or myocardial infarction during the 6 month period prior to baseline • Uncontrolled blood pressure defined as a systolic value ≥160 mmHg or diastolic value ≥100 mmHg at screening or baseline

Abbreviations: BCVA, best-corrected visual acuity; BL, baseline; BL, baseline; CSFT, central subfield thickness; DMO, diabetic macular oedema; ETDRS, Early Treatment Diabetic Retinopathy Study; HbA_{1c}, haemoglobin A_{1c}; ILM, internal limiting membrane; IOP, intraocular pressure; PDR, proliferative diabetic retinopathy; RPE, retinal pigment epithelium; SD-OCT, spectral domain optical coherence tomography; VEGF, vascular endothelial growth factor; YAG; yttrium aluminium garnet.
Source: KITE and KESTREL Week 52 clinical study reports (15, 16).

B.3.3.3 Settings and locations where the data were collected

The total number of study centres and countries included in each trial is presented in Table 6.

There were [redacted] (81, 82).

Table 6: Number of study centres and countries for each trial

Trial	Total no. of centres	Total no. of countries	Countries (number of centres)
KITE (15)	79	23	Belgium (1), Bulgaria (3), Czech Republic (3), Denmark (2), Estonia (2), France (12), Germany (7), Hungary (5), India (5), Republic of Korea (6), Latvia (1), Lebanon (3), Lithuania (2), Malaysia (2), Norway (1), Poland (1), Russia (5), Singapore (2), Slovakia (5), Sweden (1), Switzerland (2), Taiwan (3), Turkey (5)
KESTREL (16)	118	13	Argentina (5), Australia (9), Austria (3), Canada (4), Colombia (3), Israel (8), Italy (6), Japan (18), Netherlands (3), Portugal (7), Spain (6), United Kingdom (5), United States (41)

Source: KITE and KESTREL Week 52 clinical study reports (15, 16).

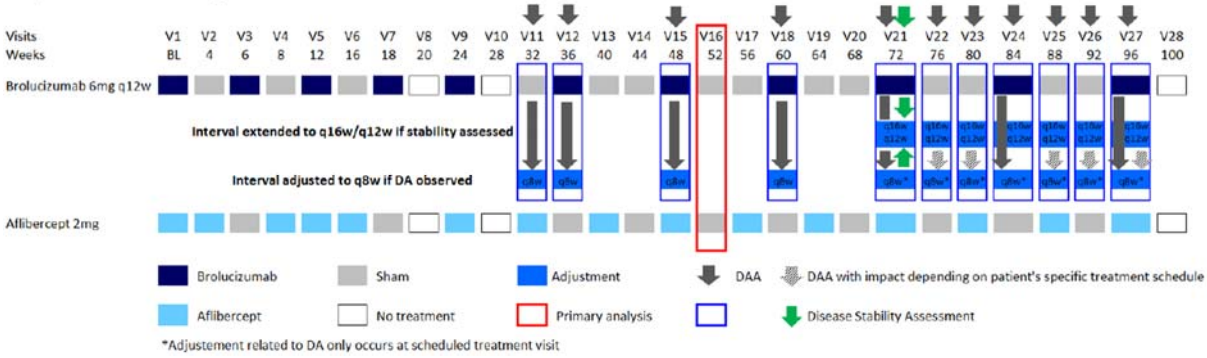
B.3.3.4 Trial drugs and concomitant treatments

B.3.3.4.1 *Brolucizumab*

In both studies, brolucizumab was administered via IVT injections, with 5 loading doses (once every 6 weeks [5xq6w]; baseline, Weeks 6, 12, 18 and 24), then with subsequent doses per the protocol-specified maintenance schedule (once every 12 or 8 weeks [q12w or q8w]). Patients were initially scheduled at q12w; disease activity assessment (DAA) visits were carried out at Weeks 32, 36, 48, 60 and 72 in both trials, then every 4 weeks for KITE and every 12 weeks for KESTREL, until Week 96 (Figure 5 and Figure 6). If disease activity was identified based on anatomical and functional parameters at any DAA visit, patients could be assigned to receive treatment q8w for the remainder of the study.

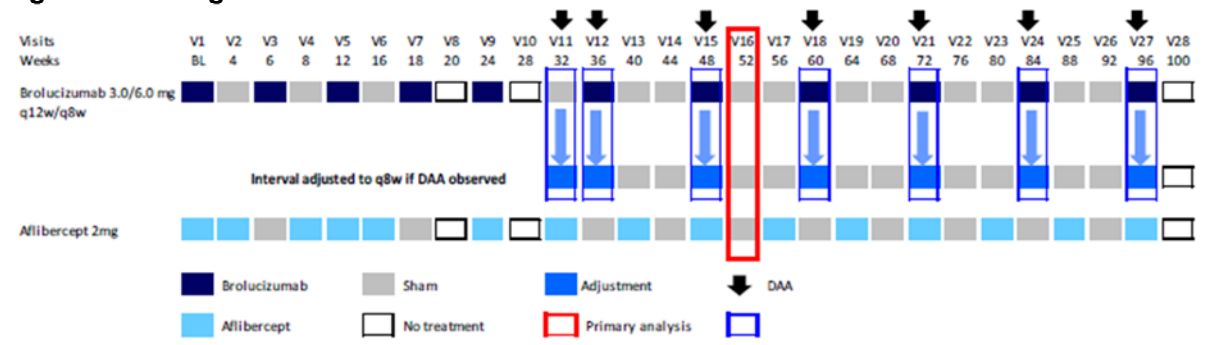
The q8w need was identified based on assessment of disease activity in the study eye by the masked investigator, with reference to the patient's disease status at Week 28 (the end of the brolucizumab loading phase). This was defined as disease activity requiring more frequent anti-VEGF treatment, e.g. ≥5 letter loss in BCVA, which was attributable to DMO disease activity based on anatomical parameters.

Figure 5: Dosing schedule – KITE



Abbreviations: BL, baseline; DA, disease activity; DAA, disease activity assessment; q8w, every 8 weeks; q12w, every 12 weeks; q16w, every 16 weeks; V, visit.
Source: KITE clinical study report (15).

Figure 6: Dosing schedule – KESTREL



Abbreviations: BL, baseline; DAA, disease activity assessment; q8w, every 8 weeks; q12w, every 12 weeks; V, visit.
Source: KESTREL clinical study report (16).

KITE included the option for patients to extend their treatment interval by 4 weeks during the second year (from q8w to q12w or q12w to q16w [every 16 weeks]). Those considered were patients receiving brolucizumab who demonstrated disease stability under their current assigned treatment regimen, based on masked investigator assessment, at a one-time disease stability assessment (DSA) at Week 72 (in both study arms). Disease activity assessments were performed at every visit from Week 72 to Week 96 (every 4 weeks), where patients could have their treatment interval modified accordingly. The dosing and DAA schedules for KITE and KESTREL are presented in Figure 5 and Figure 6, respectively.

B.3.3.4.2 *Aflibercept*

In both trials, aflibercept was administered via IVT injections once every 4 weeks, five times, during the loading phase, then q8w during the maintenance phase (to Week 100). The dosing schedules for both studies are presented in Figure 5 and Figure 6.

Aflibercept 2 mg is an established SoC option for DMO. It was chosen as comparator for this study due to the consistency of the approved label of aflibercept (Eylea®) for DMO across many countries, especially the EU and US. The dosing schedule was chosen as the labels recommend one injection per month (q4w) for five consecutive doses, followed by one injection every 2 months (q8w) for the first year of treatment.

B.3.3.4.3 *Treatment masking*

Due to the different dosing regimens in each arm, patients in all arms received sham or active injections at every visit to establish an identical treatment schedule and ensure masking (with the exception of Weeks 20, 28 and 100 where no treatment was scheduled) (Figure 5 and Figure 6).

B.3.3.4.4 *Dose adjustments and study drug interruptions*

Study treatment dose adjustments and/or interruptions from the assigned schedule were not permitted unless interruptions were warranted by an AE.

B.3.3.4.5 *Rescue medication*

In KITE and KESTREL, study eyes in both treatment arms that were identified as needing q8w at a previous DAA visit could receive rescue treatment with laser photocoagulation, along with study treatment, from Week 36 if DMO worsened (loss of ≥10 letters at two consecutive visits or ≥15 letters at one visit, compared with best previous measurement, with BCVA not better than baseline). Pan-retinal photocoagulation was permitted at any time, based on investigator assessment, with the patient able to continue the study.

B.3.3.4.6 *Concomitant/prohibited medications*

In the fellow (non-study) eye, SoC/other treatments (according to the investigator's practice) were permitted at any time for DMO and other diseases.

In the study eye, use of intra- or peri-ocular corticosteroids was prohibited at any time during the study after screening (except if needed as short-term treatment of an AE). Use of anti-VEGF therapy other than the assigned study medication was also prohibited. Laser photocoagulation (focal/grid) was prohibited prior to Week 36 (after which it was permitted as rescue therapy; see Section B.3.3.4.5).

Systemic anti-VEGF therapy and any systemic investigational drug, biologic, or device were also prohibited at any time during the study, after screening.

Where use of prohibited medications was deemed in the best interest of the patient, study treatment was to be discontinued, except when corticosteroids were used for short-term treatment of an AE; if laser photocoagulation was used prior to Week 36, continuation of study treatment was at the investigator's discretion.

B.3.3.5 Outcomes specified in the scope

B.3.3.5.1 *Primary endpoint*

The primary objective of both studies was to demonstrate that brolucizumab is non-inferior to aflibercept with respect to the change from baseline in BCVA in the study eye at Week 52. Best corrected visual acuity is the primary endpoint used in RCTs investigating aflibercept and ranibizumab in DMO (40, 41), and BCVA is vital for patient HRQoL (64). Best corrected visual acuity measurements were taken from a sitting position using ETDRS-like visual acuity testing charts at an initial testing distance of 4 meters.

B.3.3.5.2 *Secondary endpoints*

The secondary objectives relevant to the scope were identical in both studies, except for objectives in KITE related to extending treatment intervals for brolucizumab patients during the second year of treatment. Table 7 and Table 8 present shared and KITE-specific pre-specified secondary endpoints (and their objectives) related to the outcomes specified in the scope, respectively.

Table 7: Secondary outcomes – KITE and KESTREL

Objective	KITE endpoint(s)	KESTREL endpoint(s)
Secondary objectives		
To demonstrate that brolucizumab is non-inferior to aflibercept with respect to visual outcome during the last 3 months of the first year of treatment	Change from baseline in BCVA, Weeks 40–52	

Objective	KITE endpoint(s)	KESTREL endpoint(s)
To estimate the proportion of patients treated at q12w frequency with brolucizumab	Proportion of patients maintained at q12w up to Weeks 52 and 100	
To estimate the predictive value of the first q12w cycle for maintenance of q12w treatment with brolucizumab	Proportion of patients maintained at q12w up to Week 52, within those patients that qualified for q12w at Week 36 Proportion of patients maintained at q12w up to Week 100, within those patients that qualified for q12w at Week 36	
To evaluate the functional and anatomical outcomes with brolucizumab relative to aflibercept	Change from baseline by visit, up to Week 100 in BCVA and in parameters derived from SD-OCT, colour fundus photography and fluorescein angiography	
To evaluate the effect of brolucizumab relative to aflibercept on DR status	Change in ETDRS DRSS score up to Week 100	
To assess the safety of brolucizumab relative to aflibercept	Incidence of ocular and non-ocular AEs, vital signs, and laboratory values up to Week 100	
To evaluate the effect of brolucizumab relative to aflibercept on patient-reported outcomes (VFQ-25)	Change in patient reported outcomes (VFQ-25) total and subscale scores from baseline up to Week 100	

Abbreviations: AE, adverse event; BCVA, best-corrected visual acuity; DR, diabetic retinopathy; DRSS, Diabetic Retinopathy Severity scale; ETDRS, Early Treatment Diabetic Retinopathy Study; q8w, every 8 weeks; q12w, every 12 weeks; q16w, every 16 weeks; SD-OCT, spectral domain optical coherence tomography; VFQ-25, Visual Functioning Questionnaire-25.
Source: KITE and KESTREL Week 52 clinical study reports (15, 16).

Table 8: Secondary outcomes specific to KITE

Objective	Secondary endpoint
To estimate the predictive value of the first q12w cycle for maintenance of q12w treatment with brolucizumab	Proportion of patients maintained at q12w/q16w up to Week 100, within those patients that qualified for q12w at Week 36
To assess the potential to extend treatment intervals for brolucizumab patients during the second year of treatment	Proportion of patients maintained on q16w up to Week 100 within the patients on q12w at Week 68 and on q16w at Week 76 Proportion of patients re-assigned and maintained on q12w up to Week 100 within the patients on q8w at Week 68 and on q12w at Week 80 Treatment status at Week 100

Abbreviations: q12w, every 12 weeks; q16w, every 16 weeks.
Source: KITE Week 52 clinical study report (15, 16).

B.3.4 Baseline patient characteristics

Key patient demographics and baseline disease characteristics (diabetes and ocular characteristics of the study eye) are presented for both studies in Table 9.

In KITE, the general demographic characteristics were comparable between patients in the brolucizumab and aflibercept arms. Baseline diabetes characteristics and ocular characteristics for the study eye were also generally comparable. Of note, most patients presented with Type 2 diabetes mellitus (92.8%), however there were slightly more patients with Type 1 diabetes mellitus in the brolucizumab arm (10.6%) compared with the aflibercept arm (3.9%). In addition, the mean baseline BCVA in the study eye was 2.3 letters higher in the brolucizumab arm (66.0±10.77 letters) vs. the aflibercept arm (63.7±11.70 letters), [redacted]

[redacted]

In KESTREL, baseline patient demographics and disease characteristics were also generally comparable between the treatment arms. Of note, there were slightly more patients in the brolucizumab arms with Type 1 diabetes mellitus (6.3% in the 6 mg arm) vs. the aflibercept arm (3.2%). There was also a higher proportion of patients in the brolucizumab 6 mg arm with glycated haemoglobin (HbA_{1c}) levels ≥7.5% at baseline compared with the aflibercept arm (59.6% vs. 42.8%, respectively).

Table 9: Baseline demographic, background, diabetes and ocular characteristics of patients in KITE and KESTREL (FAS)

Participant characteristic	KITE			KESTREL			
	Brolucizumab 6 mg (N=179)	Aflibercept 2 mg (N=181)	Overall (N=360)	Brolucizumab 3 mg (N=190)	Brolucizumab 6 mg (N=189)	Aflibercept 2 mg (N=187)	Overall (N=566)
Demographic and background characteristics							
Age group (years), n (%)							
<65 years	100 (55.9)	102 (56.4)	202 (56.1)	97 (51.1)	104 (55.0)	93 (49.7)	294 (51.9)
≥65 years	79 (44.1)	79 (43.6)	158 (43.9)	93 (48.9)	85 (45.0)	94 (50.3)	272 (48.1)
Age (years)							
Mean	62.3	62.2	62.2	64.4	62.4	63.9	63.6
SD	10.55	9.48	[redacted]	9.76	10.14	10.09	[redacted]
Sex, n (%)							
Male	120 (67.0)	115 (63.5)	235 (65.3)	119 (62.6)	110 (58.2)	126 (67.4)	355 (62.7)
Female	59 (33.0)	66 (36.5)	125 (34.7)	71 (37.4)	79 (41.8)	61 (32.6)	211 (37.3)
Race[†], n (%)							
White	133 (74.3)	132 (72.9)	265 (73.6)	151 (79.5)	158 (83.6)	153 (81.8)	462 (81.6)
Black or African American	3 (1.7)	1 (0.6)	4 (1.1)	13 (6.8)	4 (2.1)	7 (3.7)	24 (4.2)
Asian	43 (24.0)	48 (26.5)	91 (25.3)	25 (13.2)	25 (13.2)	27 (14.4)	77 (13.6)
Native Hawaiian or Other pacific Islander	0	0	0	0	2 (1.1)	0	2 (0.4)
American Indian or Alaska native	0	0	0	1 (0.5)	0	1 (0.5)	2 (0.4)
Diabetes characteristics							
Diabetes type (based on primary diagnosis), m (%)							
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Type 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Type 2	160 (89.4)	174 (96.1)	334 (92.8)	180 (94.7)	177 (93.7)	181 (96.8)	538 (95.1)
HbA_{1c}, %							
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean	7.55	7.46	7.50	7.52	7.69	7.44	7.55
SD	1.174	1.161	[redacted]	1.160	1.067	1.132	[redacted]

Participant characteristic	KITE			KESTREL			
	Brolucizumab 6 mg (N=179)	Aflibercept 2 mg (N=181)	Overall (N=360)	Brolucizumab 3 mg (N=190)	Brolucizumab 6 mg (N=189)	Aflibercept 2 mg (N=187)	Overall (N=566)
Ocular characteristics							
BCVA, letters							
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean	66.0	63.7	64.9	65.7	66.6	65.2	65.8
SD	10.77	11.70	[redacted]	11.09	9.67	12.38	[redacted]
BCVA group, m (%)							
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≤65 letters	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>65 letters	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time since DMO diagnosis (months)							
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean	10.4	9.9	10.2	12.5	9.4	9.6	10.5
SD	16.56	20.73	[redacted]	30.82	19.47	24.17	[redacted]
Time since DMO diagnosis group, m (%)							
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≤3 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>3–<12 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥12 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Macular oedema type, m (%)							
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Focal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diffuse	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Can’t grade	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
N/A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CSFT, µM							
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean	481.1	484.4	482.7	456.0	453.1	475.6	461.5
SD	132.46	134.58	133.35	118.04	123.42	135.84	126.11
CSFT group, m (%)							
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
<450 µm	85 (47.5)	82 (45.6)	167 (46.5)	111 (58.4)	107 (56.6)	96 (51.3)	314 (55.5)
≥450 – < 650 µm	74 (41.3)	79 (43.9)	153 (42.6)	64 (33.7)	70 (37.0)	71 (38.0)	205 (36.2)
≥650 µm	20 (11.2)	19 (10.6)	39 (10.9)	15 (7.9)	12 (6.3)	20 (10.7)	47 (8.3)

Participant characteristic	KITE			KESTREL			
	Brolucizumab 6 mg (N=179)	Aflibercept 2 mg (N=181)	Overall (N=360)	Brolucizumab 3 mg (N=190)	Brolucizumab 6 mg (N=189)	Aflibercept 2 mg (N=187)	Overall (N=566)
Leakage on fluorescein angiography, m (%)							
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Present	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Absent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IRF, m (%)							
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Present	176 (98.3)	179 (98.9)	355 (98.6)	190 (100)	189 (100)	184 (98.4)	563 (99.5)
Absent	3 (1.7)	2 (1.1)	5 (1.4)	0	0	3 (1.6)	3 (0.5)
SRF, m (%)							
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Present	56 (31.3)	67 (37.0)	123 (34.2)	60 (31.6)	62 (32.8)	61 (32.6)	183 (32.3)
Absent	123 (68.7)	114 (63.0)	237 (65.8)	130 (68.4)	127 (67.2)	126 (67.4)	383 (67.7)
DRSS, m (%)							
n	176	177	353	185	186	184	555
1-DR absent	3 (1.7)	1 (0.6)	4 (1.1)	1 (0.5)	0	0	1 (0.2)
2-Microaneurysms only	0	2 (1.1)	2 (0.6)	3 (1.6)	1 (0.5)	3 (1.6)	7 (1.3)
3-Mild NPDR	49 (27.8)	37 (20.9)	86 (24.4)	56 (30.3)	57 (30.6)	52 (28.3)	165 (29.7)
4-Moderate NPDR	55 (31.3)	68 (38.4)	123 (34.8)	51 (27.6)	54 (29.0)	59 (32.1)	164 (29.5)
5-Moderately severe NPDR	30 (17.0)	20 (11.3)	50 (14.2)	25 (13.5)	15 (8.1)	16 (8.7)	56 (10.1)
6-Severe NPDR	26 (14.8)	34 (19.2)	60 (17.0)	39 (21.1)	45 (24.2)	40 (21.7)	124 (22.3)
7-Mild PDR	9 (5.1)	7 (4.0)	16 (4.5)	6 (3.2)	3 (1.6)	7 (3.8)	16 (2.9)
8-Moderate PDR	3 (1.7)	5 (2.8)	8 (2.3)	4 (2.2)	8 (4.3)	5 (2.7)	17 (3.1)
9-High risk PDR	1 (0.6)	2 (1.1)	3 (0.8)	0	3 (1.6)	2 (1.1)	5 (0.9)
10-Very high-risk PDR	0	0	0	0	0	0	0
11-Advanced PDR	0	1 (0.6)	1 (0.3)	0	0	0	0
12-Very advanced PDR	0	0	0	0	0	0	0

[†]A patient can have multiple races.

n=number of patients with an assessment. Percentages are calculated based on n; m=number of patients with an assessment meeting the criterion for the given categorical variable.

Abbreviations: BCVA, best-corrected visual acuity; CSFT, central subfield thickness; DMO, diabetic macular oedema; DR, diabetic retinopathy; DRSS, diabetic retinopathy severity scale; FAS, full analysis set; HbA_{1c}, haemoglobin A_{1c}; IRF, intraretinal fluid; N/A, not applicable; NPDR, non-proliferative diabetic retinopathy; N/R, not reported; OD, oculus dexter; OS, oculus sinister; PDR, proliferative diabetic retinopathy; SD, standard deviation; SRF, subretinal fluid.

Source: Brown 2022 (80); KITE and KESTREL Week 52 clinical study reports (15, 16).

B.3.5 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

B.3.5.1 Analysis sets (KITE and KESTREL)

The following analysis sets were defined in the trials:

All enrolled set (EOS): included all patients who signed informed consent.

Randomised set (RAN): included all randomised patients. Patients were analysed according to the treatment assigned at randomisation.

Full analysis set (FAS): included all randomised patients who received at least one IVT injection of the study treatment. Patients were analysed according to the treatment assigned at randomisation.

Per-protocol set (PPS): subset of the FAS that excluded patients with important protocol deviations and analysis restrictions that were expected to majorly affect the validity of the assessment of efficacy and/or safety at Week 52 (e.g. lack of compliance [including missed treatment and treatment misallocation], missing data, prohibited concomitant medications and deviations from inclusion/exclusion criteria). Confounded data or discontinuation from study treatment due to lack of efficacy and/or safety data did not constitute a reason for exclusion from the PPS.

Safety set (SAF): included all patients who received at least one study drug IVT injection. Patients in the SAF were analysed according to the treatment arm in which they received the majority of treatment up to and including Week 48.

Analysis of the primary and secondary endpoints was based on the FAS (with last observation carried forward [LOCF; see Table 11]). A summary of the number of patients in each analysis set in KITE and KESTREL is presented in Table 10.

Table 10: Analysis sets in KITE and KESTREL (Week 52 analysis)

Population	KITE		KESTREL		
	Brolucizumab 6 mg, n (%)	Aflibercept 2 mg, n (%)	Brolucizumab 3 mg, n (%)	Brolucizumab 6 mg, n (%)	Aflibercept 2 mg, n (%)
EOS	179	181	190	189	187
RAN	179 (100)	181 (100)	190 (100)	189 (100)	187 (100)
FAS	179 (100)	181 (100)	190 (100)	189 (100)	187 (100)
SAF	179 (100)	181 (100)	190 (100)	189 (100)	187 (100)
PPS	143 (79.9)	137 (75.7)	142 (74.7)	152 (80.4)	145 (77.5)

Abbreviations: EOS, all enrolled set; FAS, full analysis set; PPS, per protocol set; RAN, randomised set; SAF, safety set.
Source: Brown 2022 (80).

B.3.5.2 Statistical methods used to compare groups for primary and secondary outcomes

In both studies, the primary efficacy and safety analysis was based on the Week 52 data, i.e. all data up to and including Week 52. This analysis was performed once all patients completed their Week 52 visits or discontinued the study before Week 52. All patients continued to receive masked treatment through the planned study duration of 100 weeks. The statistical methods used to compare groups for the primary and secondary outcomes are presented in Table 11.

Table 11: Statistical methods for analysis of primary and secondary outcomes in the KITE and KESTREL trials

	KITE	KESTREL
Primary and first key efficacy endpoints	• The statistical hypotheses for the primary and first key secondary endpoints were intended to demonstrate the non-inferiority of brolucizumab to aflibercept with respect to the change from baseline in BCVA, considering a margin of 4 ETDRS letters o H1: Average change from baseline in BCVA at Week 52 o H2: Average change from baseline in BCVA averaged over Weeks 40–52	• The statistical hypotheses for the primary and first key secondary endpoints were intended to demonstrate the non-inferiority of brolucizumab to aflibercept with respect to the change from baseline in BCVA, considering a margin of 4 ETDRS letters o H1: Average change from baseline in BCVA at Week 52 (brolucizumab 6 mg vs. aflibercept 2 mg) o H2: Average change from baseline in BCVA averaged over Weeks 40–52 (brolucizumab 6 mg vs. aflibercept 2 mg) o H3: Average change from baseline in BCVA at Week 52 (brolucizumab 3 mg vs. aflibercept 2 mg) o H4: Average change from baseline in BCVA averaged over Weeks 40–52 (brolucizumab 3 mg vs. aflibercept 2 mg)
Additional key secondary endpoints	• No statistical hypotheses were tested for the additional key secondary endpoints: o the proportion of patients maintained at q12w to Week 52, and o the proportion of patients maintained at q12w up to Week 52, within those patients that qualified for q12w at Week 36	
Additional efficacy endpoints	• Additional efficacy hypotheses tested the superiority of brolucizumab vs. aflibercept: o H3: Average change from baseline in CSFT over the period of Week 40–Week 52 in the study eye o H4: Average change from baseline in BCVA over the period of Week 40–Week 52 in the study eye	• Additional efficacy hypotheses tested the superiority of brolucizumab 6 mg vs aflibercept 2 mg (not brolucizumab 3 mg vs aflibercept 2 mg): o H5: Average change from baseline in CSFT over the period of Week 40–Week 52 in the study eye o H6: Absence of fluid in the study eye at Week 52 (no=absence of SRF and IRF)

	KITE	KESTREL
	o H5: Fluid-status 'yes/no' in the study eye at Week 52 (no= absence of SRF and IRF)	o H7: Change from baseline in CSFT at Week 4 in the study eye o H8: Average change from baseline in BCVA over the period of Week 40–Week 52 in the study eye
Statistical analysis	• Primary and first key secondary endpoints: o Non-inferiority was considered established (i.e. the null hypothesis was rejected) if the lower limit of the 95% CI for the corresponding treatment difference (brolucizumab – aflibercept) was >–4 letters • Additional secondary endpoints: o Superiority testing of hypotheses was performed on the condition that proof on non-inferiority related to BCVA was successful for the primary and first key secondary endpoints. All tests were one-sided for the superiority of brolucizumab 6 mg vs. aflibercept 2 mg based on the FAS, with LOCF imputation of missing or censored data. Alternative hypotheses were tested hierarchically; confirmatory testing required rejection of the previous null hypothesis • Additional key secondary endpoints: o The proportion of patients with a positive q12w treatment status was derived using the 'efficacy/safety approach' in the FAS, following the estimand concept. The proportion of patients with a positive q12w at Week 52 was derived from KM time-to-event analyses for the event 'first q8w need'. For the endpoint evaluating the patients maintained at q12w up to Week 52, within those patients that qualified for q12w at Week 36, the proportion of patients was based on the subset of FAS patients with no identified q8w need at Week 32 and Week 36, where a valid Week 36 DAA was required, while a missing Week 32 assessment was considered as no q8w need	
Sample size and power calculation	A sample size of 160 patients per arm was considered to allow the demonstration of the noninferiority of brolucizumab 6 mg vs. aflibercept 2 mg (KITE) or brolucizumab 6 mg or 3 mg (either treatment regimen; KESTREL) vs. aflibercept 2 mg with respect to the change from baseline in BCVA at Week 52 (non-inferiority margin of 4 ETDRS letters), with 90% power at a one-sided alpha level of 0.025, assuming equal means and a common SD of 11 letters. Assuming that averaging over the four time points would not lead to an increase in the SD, a power of ≥90% could also be expected for its corresponding non-inferiority claim. Considering a drop-out rate of 10%, a total of 356 patients were planned to be randomised in KITE, and 534 in KESTREL (178 patients per arm in both studies)	
Data management and patient withdrawals	• For the primary and secondary key efficacy endpoints, missing BCVA values were imputed by LOCF as a primary approach. For patients with no post-baseline BCVA value, the baseline value was carried forward. Data collected after the start of alternative DMO treatment in the study eye (e.g. other anti-VEGF treatment, laser or intraocular corticosteroids) were censored in the primary analysis • For the two additional key secondary endpoints, in the case of missing or confounded data attributable to lack of efficacy and/or safety, a q8w need allocation was applied. The requirements of the sufficient efficacy and safety approach were addressed by considering patients, including those without an explicit 'q8w need = Yes', as having a negative q12w status in case any of the following confounding factors was attributable to lack of efficacy and or safety of the study treatment: early treatment/study discontinuation, missed DAA. The q8w need was imputed as 'Yes' at the DAA visit following early treatment/study discontinuation due to lack of efficacy and/or lack of safety of the study treatment (applies to both missing and non-missing DAAs) • For other secondary endpoints, missing data was imputed by LOCF, with LOCF replacement for censored data (unless otherwise specified)	

Abbreviations: BCVA, best corrected visual acuity; CI, confidence interval; CSFT, central subfield thickness; DAA, disease activity assessment; DMO, diabetic macular oedema; FAS, full analysis set; ETDRS, Early Treatment Diabetic Retinopathy Scale; IRF, intraretinal fluid; LOCF, last observation carried forward; q8w, every 8 weeks; q12w, every 12 weeks; SRF, subretinal fluid; VEGF, vascular endothelial growth factor receptor.
Source: KITE and KESTREL Week 52 clinical study reports (15, 16).

B.3.5.3 Participant flow in KITE and KESTREL

Details of participant flow in KITE and KESTREL are provided in Appendix D.

B.3.6 Quality assessment of the relevant clinical effectiveness evidence

Quality assessment for each trial included in the SLR is presented in Appendix D. Table 12 presents the quality assessment for KESTREL and KITE.

Table 12: Quality assessment results for parallel group RCTs

Trial number (acronym)	KESTREL	KITE
Was randomisation carried out appropriately?	Yes, Interactive Response Technology to generate numbers linked to treatment arms	Yes, Interactive Response Technology to generate numbers linked to treatment arms
Was the concealment of treatment allocation adequate?	Yes, allocation generated by automated system	Yes, allocation generated by automated system
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes, though there was a slightly higher proportion of patients with Type 1 diabetes in the brolucizumab arms compared with the aflibercept arm.	Yes, though there was a higher proportion of patients with Type 1 diabetes in the brolucizumab arm compared with the aflibercept arm. The proportion of patients with BCVA ≤65 letters at baseline was lower in the brolucizumab group (36.3% vs. 50.3%), however, in sensitivity analyses for these subgroups, outcomes were consistent with the overall population.
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes, double-blind design	Yes, double-blind design
Were there any unexpected imbalances in drop-outs between groups?	No, drop-out rates were similar between the groups.	No, although there was a higher rate of drop-outs in the brolucizumab arm compared with the aflibercept arm. However, all drop-outs were accounted for.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No, all outcomes cited in the protocol are reported in CSR.	No, all outcomes cited in the protocol are reported in CSR.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods	Yes, outcomes reported for FAS using LOCF imputation for missing data. Outcomes also reported for PP set.	Yes, outcomes reported for FAS using LOCF imputation for missing data. Outcomes also reported for PP set.

used to account for missing data?		
Adapted from Systematic reviews: CRD's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination)		

Abbreviations: CRD, Centre for Reviews and Dissemination; CSR, clinical study report; FAS, full analysis set; LOCF, last observation carried forward; PP, per protocol.

B.3.7 Clinical effectiveness results of the relevant trials

In the clinical trial programme, outcomes were captured for the study eye only, thus the results in this section refer to the study eye [redacted]

- Both KITE and KESTREL met their primary endpoints, demonstrating non-inferiority of brolucizumab 6 mg vs. aflibercept 2 mg with respect to the mean change from baseline in BCVA at Week 52. The LSM difference was 1.2 letters (95% CI: –0.6, 3.1) in KITE, and –1.3 letters (95% CI: –2.9, 0.3) in KESTREL, ($p<0.001$ for non-inferiority)
- The mean number of injections in KITE was 7.0 in the brolucizumab 6 mg arm vs. 8.5 in the aflibercept arm at Week 52 and [redacted] vs. [redacted] at Week 100. In KESTREL, the mean number of injections was 6.8 in the brolucizumab 6 mg arm vs. 8.5 in the aflibercept 2 mg arm and [redacted] vs. [redacted] at Week 100.
- Across both trials, patients in the [redacted], despite fewer IVT injections with brolucizumab; [redacted]
- [redacted] Of the patients in the brolucizumab arms who qualified for q12w at Week 36, a high proportion remained on a q12w dosing at Week 52 (95.1% in KITE, 87.6% in KESTREL). Up to Week 100, the cumulative probability of these patients remaining on q12w/q16w (KITE) or q12w (KESTREL) was [redacted] and [redacted] respectively.
- [redacted]

A summary of outcomes in the multiple testing strategy in both trials is provided in Table 13.

Table 13: Summary of the multiple testing strategy and outcomes

Hypothesis	Outcome
KITE	
H1: Average change from baseline in BCVA in the brolucizumab – aflibercept arm ≤4 letters, at Week 52	Non-inferiority of brolucizumab demonstrated
H2: Average change from baseline in BCVA in the brolucizumab – aflibercept arm ≤4 letters, averaged over Week 40–Week 52	Non-inferiority of brolucizumab demonstrated
H3: Average change from baseline in CSFT over the period of Week 40–Week 52 in the study eye	Superiority of brolucizumab demonstrated
H4: Average change from baseline in BCVA over the period of Week 40–Week 52 in the study eye	Superiority testing did not reach statistical significance
H5: Fluid-status 'yes/no' in the study eye at Week 52 (no= absence of SRF and IRF)	[redacted]
KESTREL	
H1: Average change from baseline in BCVA in the brolucizumab 6 mg – aflibercept arm ≤4 letters, at Week 52	Non-inferiority of brolucizumab 6 mg demonstrated
H2: Average change from baseline in BCVA in the brolucizumab 6 mg – aflibercept arm ≤4 letters, averaged over Week 40–Week 52	Non-inferiority of brolucizumab 6 mg demonstrated
H3: Average change from baseline in BCVA in the brolucizumab 3 mg – aflibercept arm ≤4 letters, at Week 52	Brolucizumab 3 mg did not achieve non-inferiority
H4: Average change from baseline in BCVA in the brolucizumab 3 mg – aflibercept arm ≤4 letters, averaged over Week 40–Week 52	Non-inferiority not tested
H5†: Average change from baseline in CSFT over the period of Week 40–Week 52 in the study eye	Superiority not tested
H6†: Absence of fluid in the study eye at Week 52 (no=absence of SRF and IRF)	[redacted]
H7†: Change from baseline in CSFT at Week 4 in the study eye	[redacted]
H8†: Average change from baseline in BCVA over the period of Week 40–Week 52 in the study eye	[redacted]

†H5-H8 were planned to test the superiority of brolucizumab 6 mg vs. aflibercept 2 mg only (not brolucizumab 3 mg vs. aflibercept 2 mg).
Abbreviations: BCVA, best-corrected visual acuity; CSFT, central subfield thickness; IRF, intraretinal fluid; SRF, subretinal fluid.
Source: KITE and KESTREL Week 52 clinical study reports (15, 16).

B.3.7.1 Primary endpoint

B.3.7.1.1 *Change in BCVA from baseline to Week 52*

Best corrected visual acuity is a measure of the best vision correction that can be achieved using glasses or contact lenses. This measurement has historically been used as the primary endpoint investigating other anti-VEGFs in DMO (40, 41), and BCVA is vital for patient HRQoL (64).

Both studies confirmed the non-inferiority of brolucizumab 6 mg compared with aflibercept 2 mg for the primary endpoint (Table 14). In KITE, the least squares mean (LSM) estimate for the change from baseline in BCVA at Week 52 was +10.6 letters in the brolucizumab arm, and +9.4 letters in the aflibercept arm; the LSM difference was 1.2 letters (95% confidence interval [CI]: –0.6, 3.1) for brolucizumab ($p<0.001$ for non-inferiority).

In KESTREL, the LSM change from baseline in BCVA at Week 52 was +9.2 letters in the brolucizumab 6 mg arm and +10.5 letters in the aflibercept 2 mg arm (LSM difference: –1.3 letters; 95% confidence interval [CI]: –2.9, 0.3); p<0.001 for non-inferiority).

Table 14: ANOVA results for change from baseline in BCVA (letters read) at Weeks 52 for the study eye (FAS – LOCF)

Trial name	KITE		KESTREL		
FAS population	**Brolucizumab 6 mg (N=179)**	**Aflibercept 2 mg (N=181)**	**Brolucizumab 3 mg (N=190)**	**Brolucizumab 6 mg (N=189)**	**Aflibercept 2 mg (N=187)**
n	179	181	190	189	187
Brolucizumab 3 mg vs. aflibercept 2 mg					
LSM (SE)	–	–	[redacted]	–	[redacted]
95% CI for LSM	–	–	[redacted]	–	[redacted]
Brolucizumab 6 mg vs. aflibercept 2 mg					
LSM (SE)	10.6 [redacted]	9.4 [redacted]	–	9.2 [redacted]	10.5 [redacted]
95% CI for LSM	[redacted]	[redacted]	–	[redacted]	[redacted]
Brolucizumab – aflibercept					
LSM difference (SE)	1.2 [redacted]	–	–3.3 [redacted]	–1.3 [redacted]	–
95% CI for treatment difference	–0.6, 3.1	–	–5.1, –1.4	–2.9, 0.3	–
p-value for non-inferiority (1-sided)	<0.001	–	0.227	<0.001	–

n=estimated number of patients with data used in the model.
Analysed using the ANOVA model with baseline BCVA categories (≤65, >65 letters), age categories (<65, ≥65 years) and treatment as fixed effect factors.
BCVA assessment after the start of alternative DMO treatment in the study eye are censored and replaced by the last value prior to the start of the alternative treatment.
Abbreviations: ANOVA, analysis of variance; BCVA, best-corrected visual acuity; CI, confidence interval; FAS, full analysis set; LOCF, last observation carried forward; LSM, least squares mean; SE, standard error.
Source: KITE and KESTREL Week 52 clinical study reports (15, 16).

B.3.7.2 Key secondary endpoints

B.3.7.2.1 *Average change in BCVA from baseline over the period Week 40–Week 52*

This first key secondary endpoint was intended to evaluate the consistency of the treatment effect over time within the period preceding the primary endpoint evaluation, by accounting for potential fluctuations in BCVA values after the q12w or q8w dosing regimen.

In KITE, the LSM change from baseline in BCVA averaged over Weeks 40–52, was +10.3 letters in the brolucizumab arm and +9.4 letters in the aflibercept arm (LSM difference: 0.9 letters; 95% CI: –0.9, 2.6; p<0.001 for non-inferiority) (Table 14). Superiority testing did not reach statistical significance (p=0.164).

In KESTREL, the LSM change from baseline in BCVA over Weeks 40–52 was +9.0 letters in the brolucizumab 6 mg arm compared with +10.5 letters in the aflibercept 2 mg arm (LSM difference: –1.5 letters; 95% CI: –3.0, 0.0; p<0.001 for non-inferiority) (Table 14). [redacted]

Table 15: ANOVA results for change from baseline in BCVA (letters read) over Weeks 40–52 for the study eye (FAS – LOCF)

Trial name	KITE		KESTREL		
FAS population	**Brolucizumab 6 mg (N=179)**	**Aflibercept 2 mg (N=181)**	**Brolucizumab 3 mg (N=190)**	**Brolucizumab 6 mg (N=189)**	**Aflibercept 2 mg (N=187)**
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Brolucizumab 3 mg vs. aflibercept 2 mg					
LSM (SE)	–	–	7.0 (0.63)	–	10.5 (0.64)
95% CI for LSM	–	–	5.8, 8.3	–	9.2, 11.7
Brolucizumab 6 mg vs. aflibercept 2 mg					
LSM (SE)	10.3 (0.62)	9.4 (0.62)	–	9.0 (0.53)	10.5 (0.53)
95% CI for LSM	9.1, 11.5	8.2, 10.6	–	7.9, 10.0	9.4, 11.5
Brolucizumab – aflibercept					
LSM difference - (SE)	0.9 (0.88)	–	–3.5 (0.90)	–1.5 (0.75)	–
95% CI for treatment difference	–0.9, 2.6	–	–5.2, –1.7	–3.0, –0.0	–
p-value for non-inferiority (1-sided)	<0.001	–	–[†]	<0.001	–
p-value for superiority (1-sided)	0.164	–	–	–[‡]	–

n=estimated number of patients with data used in the model.
Analysed using the ANOVA model with baseline BCVA categories (≤65, >65 letters), age categories (<65, ≥65 years), and treatment as fixed effect factors.
BCVA assessment after the start of alternative DMO treatment in the study eye are censored and replaced by the last value prior to the start of the alternative treatment.
[†]Non-inferiority testing was not performed, as per the approach for multiple testing, as non-inferiority of brolucizumab 3 mg vs. aflibercept 2 mg was not achieved with respect to the primary endpoint;
[‡][redacted]
Abbreviations: ANOVA, analysis of variance; BCVA, best-corrected visual acuity; CI, confidence interval; FAS, full analysis set; LOCF, last observation carried forward; LSM, least squares mean; SE, standard error.
Source: Brown 2022 (80); KITE and KESTREL Week 52 clinical study reports (15, 16).

B.3.7.2.2 *Proportion of patients maintaining q12w treatment status up to Week 52 and q12w/q16w (KITE) or q12w (KESTREL) up to Week 100*

Disease activity assessments were performed to identify q8w treatment need in both arms at Weeks 32, 36, 48, 60 and 72 in both trials, followed by every 4 weeks for KITE and every 12 weeks for KESTREL, until Week 96. The q8w need was defined as disease activity identified by the masked investigator, requiring more frequent anti-VEGF treatment. This was for example,

a ≥5 letter loss in BCVA (compared with Week 28, at the end of the brolucizumab loading phase), which based on anatomical parameters, was attributable to DMO disease activity. The proportion of patients maintained on q12w in the brolucizumab arm was derived based on Kaplan-Meier (KM) estimates. Patients in the aflibercept 2 mg arm were on a q8w dosing schedule as per the protocol.

In both studies, at Week 52, more than half of patients in the brolucizumab 6 mg arm were maintained on a q12w dosing regimen (i.e. a 3-month dosing interval during Year 1) following the loading phase (50.3% in KITE, [redacted] in KESTREL) (Table 16; Figure 7 and Figure 8). At Week 100, [redacted] and [redacted] of patients were maintained on a q12w dosing regimen in KITE and KESTREL, respectively.

In KITE, [redacted] brolucizumab treated patients were identified as having q8w need up to Week 100. The [redacted] ([redacted] patients) and [redacted] ([redacted] patients), with the remainder identified later on (Table 16).

Similarly, in KESTREL, [redacted]. In the brolucizumab 6 mg arm, of the [redacted] patients with q8w need identified up to Week 100, [redacted] and [redacted] (Table 16).

Table 16: Time-to-first q8w treatment need by DAA visit in the brolucizumab arm (FAS – efficacy/safety approach†)

Trial	Time (week)	No. of patients with first q8w need	No. of patients under q8w-need risk¶	No. of patients censored‡	Probability (95% CI) (survival)
KITE	**Brolucizumab 6 mg (N=179)**				
	Probability of maintaining on q12w				
	0	[redacted]	[redacted]	[redacted]	[redacted]
	32	[redacted]	[redacted]	[redacted]	[redacted]
	36	[redacted]	[redacted]	[redacted]	[redacted]
	48	[redacted]	[redacted]	[redacted]	0.503 (0.425, 0.577)
	60	[redacted]	[redacted]	[redacted]	[redacted]
	Probability of maintaining on q12w/q16w				
	72	[redacted]	[redacted]	[redacted]	[redacted]
	76	[redacted]	[redacted]	[redacted]	[redacted]
	80	[redacted]	[redacted]	[redacted]	[redacted]
	84	[redacted]	[redacted]	[redacted]	[redacted]
	88	[redacted]	[redacted]	[redacted]	[redacted]
	92	[redacted]	[redacted]	[redacted]	[redacted]
	96	[redacted]	[redacted]	[redacted]	[redacted]
KESTREL	**Brolucizumab 3 mg (N=190)**				
	Probability of maintaining on q12w				
	0	[redacted]	[redacted]	[redacted]	[redacted]
	32	[redacted]	[redacted]	[redacted]	[redacted]
	36	[redacted]	[redacted]	[redacted]	[redacted]
	48	[redacted]	[redacted]	[redacted]	0.474 (0.393, 0.551)
	60	[redacted]	[redacted]	[redacted]	[redacted]
	72	[redacted]	[redacted]	[redacted]	[redacted]

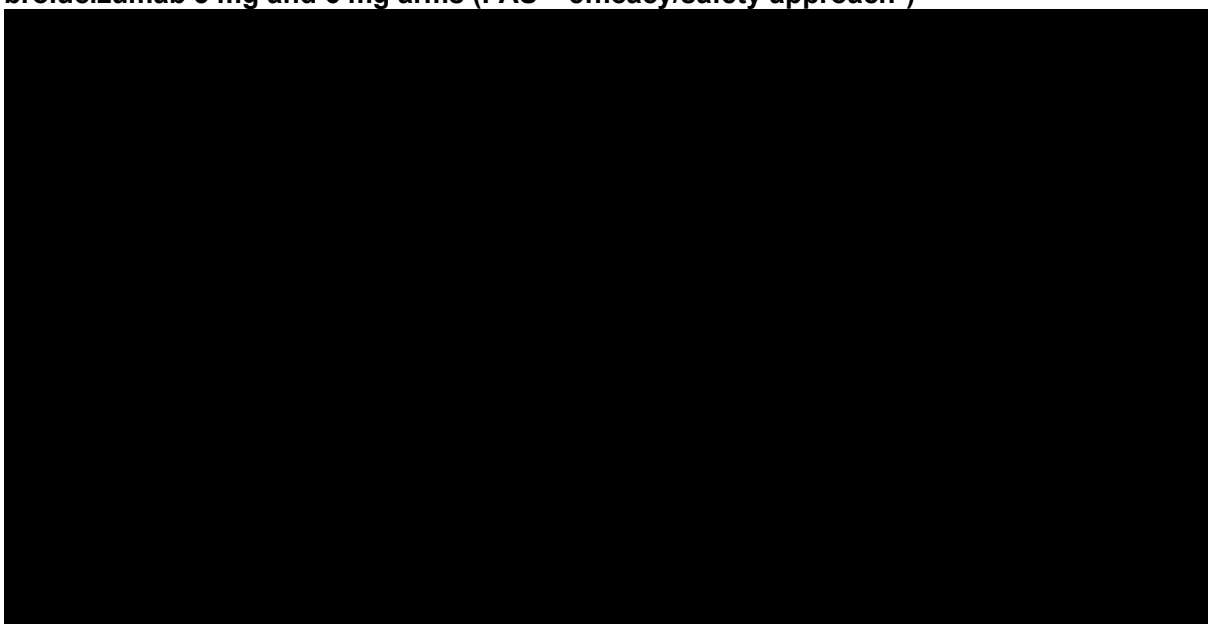
Trial	Time (week)	No. of patients with first q8w need	No. of patients under q8w-need risk¶	No. of patients censored‡	Probability (95% CI) (survival)
	84	[redacted]	[redacted]	[redacted]	[redacted]
	96	[redacted]	[redacted]	[redacted]	[redacted]
	Brolucizumab 6 mg (N=189)				
	Probability of maintaining on q12w				
	0	[redacted]	[redacted]	[redacted]	[redacted]
	32	[redacted]	[redacted]	[redacted]	[redacted]
	36	[redacted]	[redacted]	[redacted]	[redacted]
	48	[redacted]	[redacted]	[redacted]	[redacted]
	60	[redacted]	[redacted]	[redacted]	[redacted]
	72	[redacted]	[redacted]	[redacted]	[redacted]
	84	[redacted]	[redacted]	[redacted]	[redacted]
	96	[redacted]	[redacted]	[redacted]	[redacted]

†Censored data attributable to lack of efficacy and/or safety are imputed with q8w need = Yes at the next DAA visit; ‡Patients are considered to no longer be under risk for q8w need identification at later visits; ¶In KITE, patients extended to q16w after Week 72 are included as no q8w need.
Abbreviations: CI, confidence interval; DAA, disease activity assessment; FAS, full analysis set; NA, not applicable; q8w, every 8 weeks; q12w, every 12 weeks.
Source: Data on file (79).

Figure 7: Time-to-first q8w treatment need by DAA visit (KITE) – KM plot for the brolucizumab arm (FAS – efficacy/safety approach†)

Censored=patients are considered to no longer be under risk for q8w need identification at later visits; †Censored data attributable to lack of efficacy and/or safety are imputed with q8w need=Yes at the next DAA visit; Patients extended to q16w after Week 72 are included as no q8w need.
Abbreviations: DAA, disease activity assessment; FAS, full analysis set; q8w, every 8 weeks; q12w, every 12 weeks.
Source: Data on file (79).

Figure 8: Time-to-first q8w treatment need by DAA visit (KESTREL) – KM plot for the brolucizumab 3 mg and 6 mg arms (FAS – efficacy/safety approach†)



Censored=patients are considered to no longer be under risk for a q8w-need identification at later visits;
†Censored data attributable to lack of efficacy and/or safety are imputed with q8w-need=yes at the next DAA visit.
Abbreviations: DAA, disease activity assessment; FAS, full analysis set; KM, Kaplan-Meier; q8w, every 8 weeks; q12w, every 12 weeks.
Source: Data on file (79).

B.3.7.2.3 *Proportion of patients maintaining q12w treatment status up to Week 52 and q12w/q16w (KITE) or q12w (KESTREL) up to Week 100, within those patients that qualified for q12w at Week 36*

In KITE, during the initial q12w cycle (i.e. at the Week 32 and Week 36 DAA visits), [redacted] patients were identified as having no q8w need. In total, 95.1% remained on a q12w dosing regimen at Week 52 and [redacted] were maintained on a q12w/q16w dosing regimen at Week 100 (note, patients had the option to extend to q16w during the second year at the Week 72 DSA) (Table 17). In KESTREL, of the [redacted] patients receiving brolucizumab 6 mg who had no q8w need identified during the first q12w cycle, 87.6% and [redacted] remained on q12w at Week 52 and Week 100, respectively (Table 17). [redacted]

Table 17: Time-to-first q8w treatment need by DAA visit in the brolucizumab arm, within patients with no q8w need during the initial q12w cycle (FAS – efficacy/safety approach†)

Trial	Week	No. of patients with first q8w need	No. of patients under q8w-need risk¶	No. of patients censored‡	Probability (95% CI) (survival)
KITE	**Brolucizumab 6 mg (N=87)**				
	Probability of maintaining on q12w				
	0	[redacted]	[redacted]	[redacted]	[redacted]
	32	[redacted]	[redacted]	[redacted]	[redacted]
	36	[redacted]	[redacted]	[redacted]	[redacted]
	48	[redacted]	[redacted]	[redacted]	0.951 (0.874, 0.981)
	60	[redacted]	[redacted]	[redacted]	[redacted]

Trial	Week	No. of patients with first q8w need	No. of patients under q8w-need risk¶	No. of patients censored‡	Probability (95% CI) (survival)
	Probability of maintaining on q12w/q16w				
	72	[redacted]	[redacted]	[redacted]	[redacted]
	76				
	80				
	84				
	88				
	92				
	96				
KESTREL	**Brolucizumab 3 mg (N=82)**				
	Probability of maintaining on q12w				
	0	[redacted]	[redacted]	[redacted]	[redacted]
	32				
	36				
	48				0.870 (0.772, 0.928)
	60				[redacted]
	72				
	84				
	96				
	Brolucizumab 6 mg (N=98), probability of maintaining on q12w				
	Probability of maintaining on q12w				
	0	[redacted]	[redacted]	[redacted]	[redacted]
	32				
	36				
	48				0.876 (0.788, 0.930)
	60				[redacted]
	72				
	84				
	96				

†Censored data attributable to lack of efficacy and/or safety are imputed with q8w need=Yes at the next DAA visit; ‡Patients are considered to no longer be under risk for q8w need identification at later visit; ¶In KITE, patients extended to q16w after Week 72 are included as no q8w need.
Abbreviations: CI, confidence interval; DAA, disease activity assessment; FAS, full analysis set; NA, not applicable; q8w, every 8 weeks; q12w, every 12 weeks.
Source: Data on file (79).

B.3.7.3 Other secondary endpoints: Treatment outcomes (KITE only)

Further assessments were performed in KITE to assess the potential to extend treatment intervals for brolucizumab during the second year of treatment. At the Week 72 DSA, KITE included the option for patients to extend their treatment interval by 4 weeks (from q8w to q12w or from q12w to q16w). This was at the investigators discretion, based on a patients disease status (e.g. the patient showed no disease activity during their last two DAAs) (83).

B.3.7.3.1 *Proportion of patients maintained at q16w up to Week 100, within those patients on q12w at Week 68 and on q16w at Week 76*

Of [redacted] patients who were on a q12w dosing regimen at Week 68 and q16w at Week 76, the cumulative probability of maintaining on a q16w dosing regimen at Week 100 was [redacted].

Table 18: Time-to-first q8w treatment need by DAA visit within those patients on q12w at Week 68 and on q16w at Week 76 (FAS – efficacy/safety approach†)

Time (week)	No. of patients with first q8w-need at visit	No. of patients under q8w-need risk at this visit	No. of patients censored‡	Prob. of maintaining on q16w (95% CI) (survival)
76				
80				
84				
88				
92				
96				

†Censored data attributable to lack of efficacy and/or safety are imputed with q8w need=Yes at the next DAA visit; ‡Patients are considered to no longer be under risk for q8w need identification at later visit.
Abbreviations: CI, confidence interval; DAA, disease activity assessment; FAS, full analysis set; NA, not applicable; q8w, every 8 weeks; q12w, every 12 weeks; q16w, every 16 weeks.
Source: Data on file (79).

B.3.7.3.2 *Proportion of patients re-assigned and maintained on q12w up to Week 100, within the patients on q8w at Week 68 and on q12w at Week 80*

Of the [redacted] patients who were on a q8w dosing regimen at Week 68 and q12w at Week 80, the cumulative probability of maintaining on q12w at Week 100 was [redacted].

Table 19: Time-to-q8w treatment need by DAA within those patients on q8w at Week 68 and on q12w at Week 80 (FAS – efficacy/safety approach†)

Time (week)	No. of patients with first q8w-need at visit	No. of patients under q8w-need risk at this visit	No. of patients censored‡	Prob. of maintaining on q12w (95% CI) (survival)
80				
84				
88				
92				
96				

†Censored data attributable to lack of efficacy and/or safety are imputed with q8w need=Yes at the next DAA visit; ‡Patients are considered to no longer be under risk for q8w need identification at later visit.
Abbreviations: CI, confidence interval; DAA, disease activity assessment; FAS, full analysis set; NA, not applicable; q8w, every 8 weeks; q12w, every 12 weeks; q16w, every 16 weeks.
Source: Data on file (79).

B.3.7.3.3 *Treatment status at Week 100*

At Week 100, [redacted] of patients in the brolucizumab arm were on a q8w dosing regimen, [redacted] were on q12w and [redacted] were on q16w.

Table 20: Treatment status at Week 100 (FAS)

Treatment status	Brolucizumab 6 mg (N=179) n/M (%)
q8w	
q12w	
q16w	

n=the number of patients satisfying the condition. M=the number of patients who completed study treatment.
Abbreviations: q8w, every 8 weeks, q12w, every 12 weeks; q16w, every 16 weeks.
Source: Data on file (79).

B.3.7.4 Other secondary endpoints: Functional outcomes

The results of other secondary endpoints related to BCVA are presented in Table 21 and Appendix K for both trials. These include the change from baseline in BCVA to each post-baseline visit up to Week 100 (Appendix K), the proportion of patients who experienced a BCVA gain of ≥5, ≥10 or ≥15 letters or a BCVA of ≥84 letters at Week 52 and Week 100, the proportion of patients with a BCVA loss of ≥5, ≥10 or ≥15 letters at Week 52 and Week 100, and the proportion of patients with an absolute BCVA of ≥73 letters (equivalent to 20/40 on the Snellen scale) at Week 52 and Week 100, corresponding to the threshold for performing daily tasks requiring an adequate level of visual acuity (in the UK this is the minimum requirement for a driving license (84)) (Table 21). The time-to-first achieving a gain of ≥5, ≥10, or ≥15 letters is also presented in Appendix K.

Table 21: Other secondary endpoints related to BCVA (FAS – LOCF)

Trial name		KITE			KESTREL				
Secondary endpoint	**Week**	**Brolucizumab 6 mg (N=179), n/M (%)**	**Aflibercept 2 mg (N=181), n/M (%)**	**Treatment difference, (brolucizumab 6 mg vs. aflibercept†), % (95% CI‡)**	**Brolucizumab 3 mg (N=190), n/M (%)**	**Brolucizumab 6 mg (N=189) n/M (%)**	**Aflibercept 2 mg (N=187), n/M (%)**	**Treatment difference, brolucizumab 3 mg vs. aflibercept†, % (95% CI‡)**	**Treatment difference, brolucizumab 6 mg vs. aflibercept†, % (95% CI‡)**
	Proportion of patients with BCVA gain of ≥5, ≥10 or ≥15 letters								
≥5 letters gain from baseline or BCVA of ≥84 letters	W52	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	W100	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥10 letters gain from baseline or BCVA of ≥84 letters	W52	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	W100	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥15 letters gain from baseline or BCVA of ≥84 letters	W52	[redacted] (46.4)	[redacted] (37.6)	[redacted]	[redacted] (34.2)	[redacted] (37.0)	[redacted] (39.0)	[redacted]	[redacted]
	W100	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Trial name		KITE			KESTREL				
Secondary endpoint	**Week**	**Brolucizumab 6 mg (N=179), n/M (%)**	**Aflibercept 2 mg (N=181), n/M (%)**	**Treatment difference, (brolucizumab 6 mg vs. aflibercept†), % (95% CI‡)**	**Brolucizumab 3 mg (N=190), n/M (%)**	**Brolucizumab 6 mg (N=189) n/M (%)**	**Aflibercept 2 mg (N=187), n/M (%)**	**Treatment difference, brolucizumab 3 mg vs. aflibercept†, % (95% CI‡)**	**Treatment difference, brolucizumab 6 mg vs. aflibercept†, % (95% CI‡)**
	Proportion of patients with BCVA loss of ≥5, ≥10 or ≥15 letters								
≥5 letters loss from baseline	W52	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	W100	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥10 letters loss from baseline	W52	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	W100	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥15 letters loss from baseline	W52	[redacted] (1.1)	[redacted] (1.7)	[redacted]	[redacted] (1.6)	[redacted] (0.0)	[redacted] (0.5)	[redacted]	[redacted]
	W100	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Proportion of patients with absolute BCVA ≥73¶ letters								
BCVA ≥73	W52	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	W100	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

n=number of patients satisfying the criteria of the response variable.
M=number of patients with an assessment of the criterion.
BCVA assessments after start of alternative DMO treatment in the study eye are censored and replaced by the last value prior to start of this alternative treatment.
†Estimate of treatment difference from statistical model using logistic regression adjusting for baseline BCVA categories (≤65, >65 letters), age categories (<65, ≥65 years) and treatment as fixed effect factors; ‡95% CI for the treatment difference estimated using bootstrap method; ¶A BCVA of ≥73 letters (Snellen equivalent of 20/40) is the threshold for performing daily life activities without difficulty.
Abbreviations: BCVA, best-corrected visual acuity; CI, confidence interval; DMO, diabetic macular oedema; FAS, full analysis set; LOCF, last observation carried forward.
Source: Data on file (79).

B.3.7.5 Other secondary endpoints: Anatomical outcomes

B.3.7.5.1 *CSFT related endpoints to Week 100*

Central subfield thickness is a key anatomical parameter of the central macula and is defined as the average thickness of the macula in a 1 mm circular area centred around the fovea, measured from Bruch's membrane to the internal limiting membrane (ILM), inclusive. Central subfield thickness is assessed by SD-OCT. An increase in CSFT in DMO is an important measure of abnormal fluid accumulation and oedema and may result in reduced vision. A reduction in CSFT indicates better control of disease activity (42, 85-87). In addition to the endpoints presented in this section, other CSFT related endpoints are presented in Appendix K.

B.3.7.5.1.1 Change in CSFT from baseline to each post-baseline visit up to Week 100

The LSM change from baseline (±standard error [SE]) in CSFT to each post-baseline visit up to Week 100 is presented in Figure 9 and Figure 10 for KITE and KESTREL, respectively. In both studies, the first treatment administration resulted in an initial rapid reduction in CSFT in all arms (with a numerically higher decrease with brolucizumab 6 mg compared with the aflibercept in KITE). Central subfield thickness continued to decrease up to Week 20, [redacted].

In KITE, at each post-baseline visit, numerically greater reductions were consistently observed for the brolucizumab versus aflibercept arm, except at Week 36, [redacted] At Week 52 and Week 100, the LSM difference in the change from baseline in CSFT between brolucizumab and aflibercept was [redacted] (Table 22). [redacted] (Appendix K).

In KESTREL, in general, there was no difference between the brolucizumab 6 mg and aflibercept 2 mg arms at each post-baseline visit, [redacted]

[redacted] At Week 52 and 100, the LSM difference in the change from baseline in CSFT between brolucizumab 6 mg and aflibercept 2 mg was [redacted] and [redacted], respectively, [redacted] (Table 22). [redacted] (Appendix K).

Figure 9: LSM change from baseline (±SE) in CSFT (µm) by visit (FAS – LOCF) – KITE

[redacted]

LS mean and SE estimates are based on an ANOVA model with baseline CSFT categories (<450, ≥450–650, ≥650 µm), age categories (<65, ≥65 years) and treatment as fixed effect factors.
CSFT assessments after start of alternative DMO treatment in the study eye are censored and replaced by the last value prior to start of this alternative treatment.
Abbreviations: CSFT, central subfield thickness; DMO, diabetic macular oedema; FAS, full analysis set; LOCF, last observation carried forward; LSM, least squares mean; SE, standard error.
Source: Data on file (79).

Figure 10: LSM change from baseline (±SE) in CSFT (µm) by visit (FAS – LOCF) – KESTREL

LS mean and SE estimates are based on an ANOVA model with baseline CSFT categories (<450, ≥450–650, ≥650 µm), age categories (<65, ≥65 years) and treatment as fixed effect factors.
CSFT assessments after start of alternative DMO treatment in the study eye are censored and replaced by the last value prior to start of this alternative treatment.
Abbreviations: CSFT, central subfield thickness; DMO, diabetic macular oedema; FAS, full analysis set; LOCF, last observation carried forward; LSM, least squares mean; SE, standard error.
Source: Data on file (79).

Table 22: ANOVA results for change from baseline in CSFT (µm) at Week 52 and Week 100 for the study eye (FAS – LOCF)

Trial name		KITE		KESTREL		
Time (Week)	**FAS population**	**Brolucizumab 6 mg (N=179)**	**Aflibercept 2 mg (N=181)**	**Brolucizumab 3 mg (N=190)**	**Brolucizumab 6 mg (N=189)**	**Aflibercept 2 mg (N=187)**
	n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 52	**Brolucizumab 3 mg vs. aflibercept 2 mg**					
	LSM (SE)	–	–	[redacted]	–	[redacted]
	95% CI for LSM	–	–	[redacted]	–	[redacted]
	Brolucizumab 6 mg vs. aflibercept 2 mg					
	LSM (SE)	[redacted]	[redacted]	–	[redacted]	[redacted]
	95% CI for LSM	[redacted]	[redacted]	–	[redacted]	[redacted]
	Brolucizumab – aflibercept					
	LSM difference (SE) (brolucizumab – aflibercept)	[redacted]	–	[redacted]	[redacted]	–
	95% CI for treatment difference	[redacted]	–	[redacted]	[redacted]	–
Week 100	**Brolucizumab 3 mg vs. aflibercept 2 mg**					
	LSM (SE)	–	–	[redacted]	–	[redacted]
	95% CI for LSM	–	–	[redacted]	–	[redacted]
	Brolucizumab 6 mg vs. aflibercept 2 mg					
	LSM (SE)	[redacted]	[redacted]	–	[redacted]	[redacted]
	95% CI for LSM	[redacted]	[redacted]	–	[redacted]	[redacted]
	Brolucizumab – aflibercept					
	LSM difference (SE) (brolucizumab – aflibercept)	[redacted]	–	[redacted]	[redacted]	–
	95% CI for treatment difference	[redacted]	–	[redacted]	[redacted]	–

n=number of patients with data used in the model.
Analysed using ANOVA model with baseline CSFT categories (<450, ≥450–<650, ≥650 µm), age categories (<65, ≥65 years) and treatment as fixed effect factors.
CSFT assessments after start of alternative DMO treatment in the study eye are censored and replaced by the last value prior to start of this alternative treatment.
Abbreviations: ANOVA, analysis of variance; CI, confidence interval; CSFT, central subfield thickness; FAS, full analysis set; LOCF, last observation carried forward; LSM least squares mean; SE, standard error.
Source: Data on file (79).

B.3.7.5.1.2 Proportion of patients with CSFT <280 µm

A CSFT of <280 µm, assessed via SD-OCT, is considered to have no centrally involved macular oedema. [redacted]

In KITE, [redacted] a higher proportion of patients treated with brolucizumab had CSFT <280 µm compared with aflibercept, except for at Week 36, in line with the prior treatment regimens. At Week 52 and Week 100, the treatment difference between brolucizumab 6 mg and aflibercept 2 mg was 16.3% (95% CI: 5.7, 25.9) and [redacted], respectively. During the first year of treatment, [redacted]. In KESTREL, [redacted] At Week 52, the treatment difference in the proportion of patients with CSFT <280 µm was 13.4% (95% CI: 4.9, 23.7). At Week 100, the treatment difference was [redacted]

Figure 11: The proportion of patients (%) with CSFT <280 µm in the study eye, at each post-baseline visit up to Week 52 (FAS – LOCF) – KITE

[redacted]

CSFT assessment after the start of alternative DMO treatment in the study eye are censored and replaced by the last value prior to start of this alternative treatment.
Abbreviations: CSFT, central subfield thickness; DMO, diabetic macular oedema; FAS, full analysis set; LOCF, last observation carried forward. Source: Data on file (79).

Figure 12: The proportion of patients (%) with CSFT <280 µm in the study eye, at each post-baseline visit up to Week 52 (FAS – LOCF) – KESTREL

CSFT assessment after the start of alternative DMO treatment in the study eye are censored and replaced by the last value prior to start of this alternative treatment.
Abbreviations: CSFT, central subfield thickness; DMO, diabetic macular oedema; FAS, full analysis set; LOCF, last observation carried forward.
Source: Data on file (79).

B.3.7.5.2 *SRF and IRF related endpoints to Week 100*

The increase in VEGF concentrations seen in DMO causes increased retinal fluid accumulation and oedema, which may cause functional deterioration and lead to vision loss due to disruption of the retinal architecture (28-30). Fluid build-up is associated with worse visual outcomes, with patients with higher fluid levels having worse visual acuity than those with lower fluid levels (42). Therefore, SRF and IRF are important measures of both fluid accumulation and disease activity, with reductions in fluid indicating better control of disease activity.

B.3.7.5.2.1 The proportion of patients with presence of SRF and/or IRF (central subfield) in the study eye at each post-baseline visit up to Week 100

The proportion of patients with the presence of SRF and/or IRF in the study eye (assessed by SD-OCT) at each post-baseline visit up to Week 100 is presented in Figure 13 and Figure 14 for KITE and KESTREL, respectively. Across all arms,

In KITE,

At Week 52, the treatment difference between the brolucizumab and aflibercept arm was –18.4% (95% CI: –28.5, –8.3), in favour or brolucizumab (Appendix K). Following the hierarchical testing strategy

[redacted] During the second year, the proportion of patients with SRF/IRF in the study eye was [redacted]; at Week 100, [redacted]

In KESTREL, during Year 1, [redacted] despite fewer overall IVT injections administered in the brolucizumab arm because of the extended dosing interval. A lower proportion of patients with retinal fluid at Week 52 was observed in the brolucizumab 6 mg arm (60.3%) compared with aflibercept 2 mg (73.3%). The LSM difference was –13.2% (95% CI: –23.2, –3.8), in favour of brolucizumab (Appendix K). [redacted]

During Year 2, [redacted]

Figure 13: Proportion of patients (%) with presence of SRF and/or IRF in the study eye by visit (FAS – LOCF) – KITE

Fluid status (SRF and/or IRF) assessments after start of alternative DMO treatment in the study eye are censored and replaced by the last value prior to start of this alternative treatment.
Abbreviations: DMO, diabetic macular oedema; FAS, full analysis set; IRF, intraretinal fluid; LOCF, last observation carried forward; SRF, subretinal fluid.
Source: Data on file (79).

Figure 14: Proportion of patients (%) with SRF and/or IRF in the study eye, by visit (FAS – LOCF) – KESTREL

Fluid status (SRF and/or IRF) assessments after start of alternative DMO treatment in the study eye are censored and replaced by the last value prior to start of this alternative treatment.
Abbreviations: DMO, diabetic macular oedema; FAS, full analysis set; IRF, intraretinal fluid; LOCF, last observation carried forward; SRF, subretinal fluid.
Source: Data on file (79).

B.3.7.5.2.2 Presence of leakage on fluorescein angiography at Week 52 and Week 100

In KITE and KESTREL, at both Week 52 and Week 100, [redacted] with fewer IVT injections administered in the brolucizumab arms.

Table 23: Proportion of patients (%) with leakage on fluorescein angiography in the study eye (FAS – LOCF)

Visit	Study name	KITE		KESTREL		
	FAS population	Brolucizumab 6 mg (N=179)	Aflibercept 2 mg (N=181)	Brolucizumab 3 mg (N=190)	Brolucizumab 6 mg (N=189)	Aflibercept 2 mg (N=187)
Week 52	n/M (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	95% CI†	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Comparison of brolucizumab 3 mg vs. aflibercept 2 mg‡					
	Proportion estimates, %	–	–	[redacted]	–	[redacted]
	Difference, %	–	–	[redacted]	–	–
	95 % CI¶ for treatment difference	–	–	[redacted]	–	–
	Comparison of brolucizumab 6 mg vs. aflibercept 2 mg‡					
	Proportion estimates, %	[redacted]	[redacted]	–	[redacted]	[redacted]
	Difference, %	[redacted]	–	–	[redacted]	–
	95 % CI¶ for treatment difference	[redacted]	–	–	[redacted]	–
Week 100	n/M (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	95% CI†	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Comparison of brolucizumab 3 mg vs. aflibercept 2 mg‡					
	Proportion estimates, %	–	–	[redacted]	–	[redacted]
	Difference, %	–	–	[redacted]	–	–
	95 % CI¶ for treatment difference	–	–	[redacted]	–	–
	Comparison of brolucizumab 6 mg vs. aflibercept 2 mg‡					
	Proportion estimates, %	[redacted]	[redacted]	–	[redacted]	[redacted]
	Difference, %	[redacted]	–	–	[redacted]	–
	95 % CI¶ for treatment difference	[redacted]	–	–	[redacted]	–

n=number of patients satisfying the criteria of the response variable.
M=number of patients with an assessment of the criterion.
Leakage on fluorescein angiography assessments after start of alternative DMO treatment in the study eye are censored and replaced by the last value prior to start of this alternative treatment.
†95% CI for binomial proportions is based on Clopper-Pearson exact method; ‡Statistical model used logistic regression adjusting for baseline leakage on fluorescein angiography status, age categories (<65, ≥65 years) and treatment as fixed effect factors; ¶95% CI for the treatment difference estimated using bootstrap method.
Abbreviations: CI, confidence interval; FAS, full analysis set; LOCF, last observation carried forward.
Source: KITE and KESTREL Week 52 clinical study reports (15, 16) and data on file (79).

B.3.7.6 Other secondary endpoints: Disease severity outcomes

The proportion of patients with a ≥2 or ≥3-step improvement or worsening in ETDRS diabetic retinopathy severity scale (DRSS) score from baseline to Week 28, 52, 76 and 100 is presented in Appendix K.

B.3.7.7 Other secondary endpoints: Patient reported outcomes

The VFQ-25 is a standard validated instrument used to measure vision-targeted HRQoL in patients with chronic eye conditions. It consists of a base set of 25 vision-targeted questions representing 11 vision-related subscales, plus an additional single-item general health-rating question. The 11 subscales are general vision, ocular pain, near activities, distance activities, social functioning, mental health, role difficulties, dependency, driving, colour vision, and peripheral vision.

The VFQ-25 questionnaire has been used in clinical studies investigating aflibercept and ranibizumab in DMO (40, 41). The overall VFQ-25 score was calculated as the average of the 11 subscales corresponding to categories of questions. Each subscale of the VFQ-25 ranged from 0 to 100. Higher scores represent better functioning, and lower scores represent worse functioning.

B.3.7.7.1 *Change in patient reported outcomes (VFQ-25) total and subscale scores from baseline to Week 100*

The change from baseline in VFQ-25 total score, by visit is presented for each study in Table 24.

[redacted]

In KESTREL, at Week 28, 52, 76 and 100, the improvement in VFQ-25 overall score (composite) from baseline [redacted].

Table 24: ANCOVA results for change from baseline in VFQ-25 overall score by visit (FAS – Observed)

Visit	Study name	KITE		KESTERL		
	FAS population	Brolucizumab 6 mg (N=179)	Aflibercept 2 mg (N=181)	Brolucizumab 3 mg (N=190)	Brolucizumab 6 mg (N=189)	Aflibercept 2 mg (N=187)
Week 28	n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	LSM estimate (brolucizumab 3 mg)	–	–	[redacted]	–	[redacted]
	LSM estimate (brolucizumab 6 mg)	[redacted]	[redacted]	–	[redacted]	[redacted]
	LSM difference (brolucizumab – aflibercept)	[redacted]	–	[redacted]	[redacted]	–
	95% CI for LSM difference	[redacted]	–	[redacted]	[redacted]	–
Week 52	n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	LSM estimate (brolucizumab 3 mg)	[redacted]	[redacted]	[redacted]	–	[redacted]
	LSM estimate (brolucizumab 6 mg)	[redacted]	[redacted]	–	[redacted]	[redacted]
	LSM difference (brolucizumab – aflibercept)	[redacted]	–	[redacted]	[redacted]	–
	95% CI for LSM difference	[redacted]	–	[redacted]	[redacted]	–
Week 76	n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	LSM estimate (brolucizumab 3 mg)	–	–	[redacted]	–	[redacted]
	LSM estimate (brolucizumab 6 mg)	[redacted]	[redacted]	–	[redacted]	[redacted]
	LSM difference (brolucizumab – aflibercept)	[redacted]	–	[redacted]	[redacted]	–
	95% CI for LSM difference	[redacted]		[redacted]	[redacted]	–
Week 100	n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	LSM estimate (brolucizumab 3 mg)	–	–	[redacted]	–	[redacted]
	LSM estimate (brolucizumab 6 mg)	[redacted]	[redacted]	–	[redacted]	[redacted]
	LSM difference (brolucizumab – aflibercept)	[redacted]		[redacted]	[redacted]	–
	95% CI for LSM difference	[redacted]	–	[redacted]	[redacted]	–

n=number of patients with a non-missing value at baseline and the corresponding post-baseline visit.
Analysed using the ANCOVA model with treatment as a fixed effect factor and corresponding baseline value of the endpoint as a covariate.
Data after start of alternative DMO treatment in the study eye are censored and are not included in this analysis.
Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; FAS, full analysis set; LSM; least squares mean; VFQ-25, visual functioning questionnaire-25.
Source: Data on file (79).

B.3.8 Subgroup analysis

B.3.8.1 Patients with CRT ≥400 µm

The population in the subgroup analysis aligns with the population in which aflibercept and ranibizumab are approved by NICE (patients with CRT ≥400 µm) (3, 4). This analysis was performed to demonstrate that the relative health benefit of brolucizumab compared with aflibercept in the subpopulation is similar to that of the FAS population, and therefore the expected licensed DMO population for brolucizumab. This is a post-hoc analysis, therefore p-values are not presented (note, the one-sided p-values testing non-inferiority or superiority presented in Section B.3.7 were pre-defined as part of the multiple testing strategy).

B.3.8.1.1 *Baseline characteristics (patients with CRT ≥400 µm)*

Approximately [redacted] of patients in KITE ([redacted] in the brolucizumab 6 mg arm, [redacted] aflibercept 2 mg arm) and [redacted] of patients in KESTREL ([redacted] in the brolucizumab 6 mg arm, [redacted] aflibercept 2 mg arm) had a CRT of ≥400 µm at baseline. The baseline demographics, ocular and diabetes characteristics of the subgroup of patients with CRT ≥400 µm are presented in Table 25. [redacted]

Table 25: Baseline demographics, background, diabetes, and ocular characteristics of patients with CRT ≥400 µm in KITE and KESTREL

Participant characteristic	KITE			KESTREL			
	Brolucizumab 6 mg (N=119)	Aflibercept 2 mg (N=125)	Overall (N=244)	Brolucizumab 3 mg (N=111)	Brolucizumab 6 mg (N=110)	Aflibercept 2 mg (N=125)	Overall (N=346)
Demographic and background characteristics							
Age group (years), n (%)							
<65 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥65 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age (years)							
Mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sex, n (%)							
Male	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race[†], n (%)							
White	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Black or African American	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Native Hawaiian or Other Pacific Islander	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Participant characteristic	KITE			KESTREL			
	Brolucizumab 6 mg (N=119)	Aflibercept 2 mg (N=125)	Overall (N=244)	Brolucizumab 3 mg (N=111)	Brolucizumab 6 mg (N=110)	Aflibercept 2 mg (N=125)	Overall (N=346)
American Indian or Alaska Native	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diabetes characteristics							
Diabetes type (based on primary diagnosis), m (%)							
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Type 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Type 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HbA_{1c}, %							
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocular characteristics							
BCVA, letters							
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BCVA group, m (%)							
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≤65 letters	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>65 letters	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time since DMO diagnosis (months)							
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time since DMO diagnosis group, m (%)							
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≤3 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>3–<12 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥12 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Participant characteristic	KITE			KESTREL			
	Brolucizumab 6 mg (N=119)	Aflibercept 2 mg (N=125)	Overall (N=244)	Brolucizumab 3 mg (N=111)	Brolucizumab 6 mg (N=110)	Aflibercept 2 mg (N=125)	Overall (N=346)
Macular oedema type, m (%)							
n							
Focal							
Diffuse							
Can't grade							
N/A							
CSFT, µM							
n							
Mean							
SD							
CSFT group, m (%)							
n							
<450 µm							
≥450 – < 650 µm							
≥650 µm							
Leakage on fluorescein angiography, m (%)							
n							
Present							
Absent							
IRF, m (%)							
n							
Present							
Absent							
SRF, m (%)							
n							
Present							
Absent							
DRSS, m (%)							
n							
1-DR absent							
2-Microaneurysms only							
3-Mild NPDR							

Participant characteristic	KITE			KESTREL			
	Brolucizumab 6 mg (N=119)	Aflibercept 2 mg (N=125)	Overall (N=244)	Brolucizumab 3 mg (N=111)	Brolucizumab 6 mg (N=110)	Aflibercept 2 mg (N=125)	Overall (N=346)
4-Moderate NPDR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5-Moderately severe NPDR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6-Severe NPDR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7-Mild PDR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8-Moderate PDR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9-High risk PDR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10-Very high-risk PDR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
11-Advanced PDR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12-Very advanced PDR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[†]A patient can have multiple races.
n=number of patients with an assessment. Percentages are calculated based on n; m=number of patients with an assessment meeting the criterion for the given categorical variable.
Diabetes type is based on primary diagnosis
Abbreviations: BCVA, best-corrected visual acuity; CRT, central retinal thickness; CSFT, central subfield thickness; DMO, diabetic macular oedema; DR, diabetic retinopathy; DRSS, diabetic retinopathy severity scale; $HbA_{1c,}$ haemoglobin A_{1c}; IRF, intraretinal fluid; N/A, not applicable; NPDR, non-proliferative diabetic retinopathy; N/R not reported; OD, oculus dexter; OS, oculus sinister; PDR, proliferative diabetic retinopathy; SD, standard deviation; SRF, subretinal fluid.
Source: Data on file (88).

B.3.8.1.1.1 Primary endpoint

B.3.8.1.1.1.1 *Change in BCVA from baseline to Week 52*

Subgroup analysis of patients with CRT ≥400 µm for the primary endpoint showed that at Week 52, in KITE the LSM change from baseline in BCVA was [redacted] letters [redacted] for patients receiving brolucizumab 6 mg versus [redacted] letters ([redacted] for patients receiving aflibercept 2 mg, with an LSM difference of [redacted] letters ([redacted]) (Table 26). In KESTREL, patients in the brolucizumab 6 mg arm gained [redacted] letters ([redacted]) from baseline versus [redacted]([redacted]) in the aflibercept 2 mg arm; the treatment difference was [redacted] ([redacted]) (Table 26).

Table 26: ANOVA results for change from baseline in BCVA (letters read) at Week 52 for the study eye (baseline CRT ≥400 µm subgroup – LOCF)

Trial name	KITE		KESTREL		
FAS population	**Brolucizumab 6 mg (N=119)**	**Aflibercept 2 mg (N=125)**	**Brolucizumab 3 mg (N=111)**	**Brolucizumab 6 mg (N=110)**	**Aflibercept 2 mg (N=125)**
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Brolucizumab 3 mg vs. aflibercept 2 mg					
LSM (SE)	–	–	[redacted]	–	[redacted]
95% CI for LSM	–	–	[redacted]	–	[redacted]
Brolucizumab 6 mg vs. aflibercept 2 mg					
LSM (SE)	[redacted]	[redacted]	–	[redacted]	[redacted]
95% CI for LSM	[redacted]	[redacted]	–	[redacted]	[redacted]
Brolucizumab – aflibercept					
LSM difference (SE)	[redacted]	–	[redacted]	[redacted]	–
95% CI for treatment difference	[redacted]	–	[redacted]	[redacted]	–

n=the number of patients with data used in the model.
Patients with baseline CRT <400 are excluded from this analysis Analysed using the ANOVA model with baseline BCVA categories (≤65, >65 letters), age categories (<65, ≥65 years) and treatment as fixed effect factors.
BCVA assessment after the start of alternative DMO treatment in the study eye are censored and replaced by the last value prior to the start of the alternative treatment.
Abbreviations: ANOVA, analysis of variance; BCVA, best-corrected visual acuity; CI, confidence interval; CRT, central retinal thickness; LOCF, last observation carried forward; LSM, least squares mean; SE, standard error.
Source: Data on file (88).

The results are further presented in a forest plot in Figure 15. [redacted] results of the subgroup analysis of the primary endpoint are consistent with the FAS results for the change from baseline in BCVA to Week 52.

Figure 15: Forest plot of ANOVA results for change from baseline in BCVA (letters read) at Weeks 52 for the study eye (FAS, baseline CRT <400 µm and baseline CRT ≥400 µm subgroups – LOCF)

n=the number of patients with data used in the model.
Analysed using ANOVA model with baseline BCVA categories (≤65, >65 letters), age categories (<65, ≥65 years) and treatment as fixed effect factors.
BCVA assessments after the start of alternative DMO treatment in the study eye are censored and replaced by the last value prior to start of this alternative treatment.
Abbreviations: AFL, aflibercept; ANOVA, analysis of variance; BCVA, best-corrected visual acuity; BRO, brolucizumab; CRT, central retinal thickness; CSFT, central subfield thickness; DMO, diabetic macular oedema; FAS, full analysis set; LOCF, last observation carried forward; LSM, least squares mean.
Source: Data on file (88).

The studies were not powered to assess non-inferiority using a margin of 4 letters for the post-hoc subgroup. Formal testing as defined in the CSR is limited by sample size and lack of statistical powering.

B.3.9 Meta-analysis

Not applicable.

B.3.10 Indirect and mixed treatment comparisons

B.3.10.1 Summary of analyses performed

Two analyses were performed for the indirect treatment comparisons. The primary analysis covered the wider population of patients with DMO (an overview is presented in this section, with full details presented in Appendix D). Full details of the exploratory (frequentist) analysis in the subgroup of patients with CSFT ≥400 µm at baseline are also presented in Appendix D. This analysis was initially considered during the feasibility assessment. However, due to limited data and lack of stratification in the studies, the wider DMO population was used as the primary analysis as it is more robust.

B.3.10.2 Primary analysis (wider DMO population)

Table 27 presents an overview of the included studies, and Figure 16 shows the network diagram.

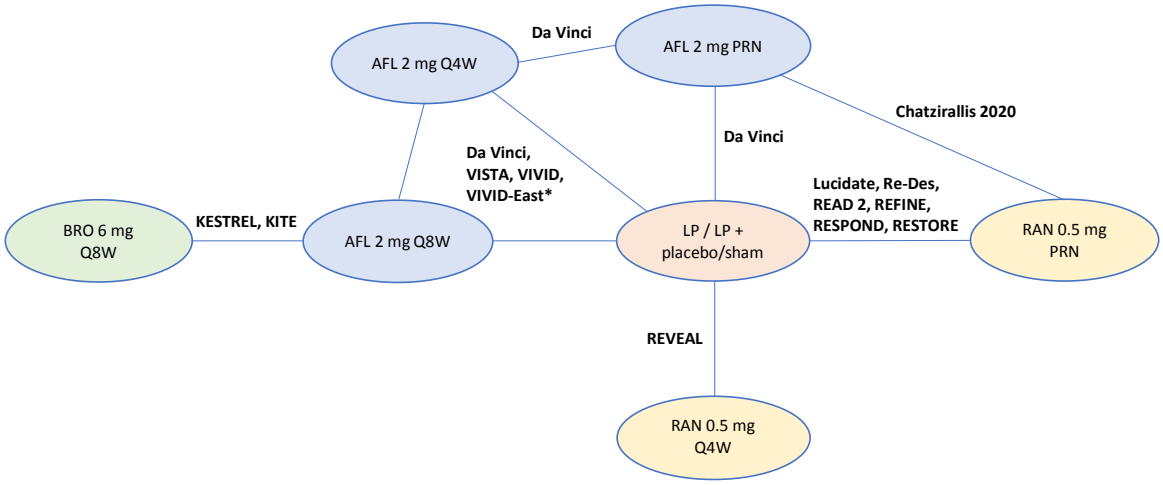
Table 27: Summary of the trials used to carry out the indirect treatment comparison

Trial	BEO 6 mg Q8W	AFL 2 mg Q4W	AFL 2 mg Q8W	AFL 2 mg PRN	RAN 0.5 mg Q4W	RAN 0.5 mg PRN	LP/LP+ placebo /sham
Chatzirallis				✓		✓	
Da Vinci		✓	✓	✓			✓
KESTREL	✓		✓				
KITE	✓		✓				
Lucidate						✓	✓
READ-2						✓	✓
Re-Des						✓	✓
REFINE						✓	✓
RESPOND						✓	✓
RESTORE						✓	✓
REVEAL					✓		✓
VISTA		✓	✓				✓
VIVID		✓	✓				✓
VIVID-East		✓	✓				✓

Abbreviations: AFL, aflibercept; BEO, brolucizumab; LP, laser photocoagulation; RAN, ranibizumab.

Studies reporting q4w, q8w and PRN treatment were treated as separate treatment nodes for all outcomes, although pooling by treatment was also considered as a scenario for inclusion in the cost-comparison model.

Figure 16: Network diagram



Abbreviations: AFL, aflibercept; BRO, brolucizumab; LP, laser photocoagulation; PRN, pro re nata (as needed) qXw, every X weeks; RAN, ranibizumab.

B.3.10.2.1 *Methods*

B.3.10.2.1.1 Continuous and dichotomous outcomes

For each of the outcomes, results are presented for a classical (frequentist) pairwise meta-analysis, which assessed heterogeneity across studies reporting the same treatment contrasts. Results are presented for both random effects models and fixed effect models. For count outcomes, the Mantel-Haenszel method was used for fixed effects, and the DerSimonian and Laird method was used for random effects. For continuous outcomes, τ^2 was estimated using the inverse variance for fixed effects and DerSimonian and Laird method for random effects.

B.3.10.2.1.2 Model selection and fit

Both fixed and random effect models were fit to all outcomes. When meta-analyses or NMA only had a small number of studies per treatment link (which is relevant for many of the analyses presented here), it was challenging to estimate the between-studies heterogeneity parameter. Therefore, decisions on best fit model were made on the basis of the deviance information criterion (DIC) (approximate difference of DIC ≥3 in favour of one model over another), as well as a comparison of the total residual deviance with the number of datapoints and findings from the direct pairwise analyses, which may point to heterogeneity where sufficient studies were included.

B.3.10.2.1.3 Programming language

The analyses followed NICE Decision Support Unit (DSU) Technical Support Document (TSD) 2 guidelines and were implemented using the publicly available WinBUGS code for each type of outcomes, as appropriate (89).

B.3.10.2.2 *Results*

B.3.10.2.2.1 BCVA

For the change from baseline in BCVA, licensed anti-VEGFs were found to be mostly comparable in terms of 1-year change from baseline in BCVA. Brolucizumab was favoured over laser photocoagulation and ranibizumab 0.5 mg q4w in gaining ETDRS letters over the course of 1 year of follow-up, with an additional [redacted] (95% credible interval [CrI]: [redacted]) and [redacted] (95% CrI: [redacted]) increase in letters, respectively. For treatments with Year 2 BCVA information, there appears to be no large change from Year 1 to Year 2, i.e. the change in visual acuity in Year 1 was maintained until Year 2.

B.3.10.2.2.2 BCVA categorical analysis

Another way of reporting change in BCVA is using a categorical approach, i.e. specifying how many patients lose or gain a specified numbers of letters (5, 10 or 15 letters). Categories were expressed in consecutive, mutually exclusive categories. Brolucizumab was found to be similar compared with the majority of anti-VEGF comparator regimens and favoured over laser treatment and ranibizumab 0.5 mg PRN, with relative effects estimated as z-scores; for brolucizumab vs ranibizumab 0.5 mg q4w the z-score was estimated to be [redacted] and compared with ranibizumab 0.5 mg PRN was [redacted]

B.3.10.2.2.3 Study discontinuation (all cause)

Discontinuation across treatments was similar, except for ranibizumab 0.5 mg q4w, which showed fewer overall discontinuations when compared with all other treatments. Although the fixed effect model may be preferred, the findings were consistent across fixed and random effects models.

B.3.10.2.2.4 Study discontinuation (adverse events)

Study discontinuation due to adverse events were similar across treatments. Although the fixed effect model may be preferred, the findings were consistent across fixed and random effects models for brolucizumab comparisons.

B.3.10.2.2.5 Serious ocular adverse events

The low frequency of serious ocular adverse events supports a favourable benefit/risk profile across all treatments, although this may result in unstable relative treatment effects. Brolucizumab showed similar hazards of experiencing an event compared with all other treatments. No treatment showed favourable outcomes over any other, with some credible intervals very wide even in the fixed effects model.

B.3.10.2.2.6 Serious non-ocular adverse events

All treatments were similar with respect to the frequency of serious non-ocular adverse events.

B.3.10.2.2.7 Change from baseline in DRSS

At 1 year, conclusions were broadly consistent across the fixed and random effects models for brolucizumab comparisons, with brolucizumab favoured over laser photocoagulation, and ranibizumab 0.5 mg PRN, in the fixed effect model. The surface under the cumulative ranking curve (SUCRA) and ranking suggest that brolucizumab may offer the greatest benefit in 2-step improvement in DRSS.

At 2 years, brolucizumab was favoured over laser photocoagulation in increasing the odds of experiencing a 2-step improvement in DRSS and was similar to aflibercept 2 mg. Brolucizumab was ranked best amongst the four treatments for this outcome.

B.3.10.2.2.8 Retinal thickness

Brolucizumab ranks highly for reduction in retinal thickness, being favoured over both laser photocoagulation and ranibizumab 0.5 mg PRN at 1 year. Estimated relative treatment effects were very similar across the fixed and random effects models. The SUCRA and ranking suggest that brolucizumab may offer the greatest benefit in decrease in retinal thickness.

At 2 years, the findings were similar, and no comparison with ranibizumab was possible, however brolucizumab was favoured over laser photocoagulation in decreasing retinal thickness and SUCRA and ranking suggest that brolucizumab may offer greater benefit compared with aflibercept 2 mg q4w and q8w.

B.3.10.2.3 *Uncertainties in the indirect and mixed treatment comparisons*

The findings of the NMA are limited by the small number of studies informing some connections, even in the best case, where all studies reported data. The sparsest data were available for the ranibizumab 0.5 mg q4w node, which was only informed by one study. In addition, the analyses were based on aggregate level data and not individual patient data, the latter could potentially have enabled further exploration of the subgroup with CRT ≥400 µm.

B.3.10.2.4 *Strengths of the analysis*

This analysis provides an up-to-date synthesis of available evidence for several efficacy and safety outcomes and is representative of the different therapeutic regimens used in practice. Comparison between brolucizumab and ranibizumab regimens was possible where this was not available from head-to-head trials. All NMAs followed the generalised linear modelling framework recommended by the NICE Decision Support Unit (89).

B.3.10.2.5 *Conclusions*

In the primary analysis of all enrolled patients included in the studies, brolucizumab is ranked amongst the best treatments for a number of outcomes including change in BCVA, improvement in DRSS and decrease in retinal thickness while maintaining a comparable adverse event profile. The comparative benefit of brolucizumab versus aflibercept and ranibizumab in the exploratory analysis (Appendix D) were comparable with the results of the more robust wider network. Therefore, the wider network and FAS population results from the KITE and KESTREL studies can be used as proxies for NICE decision making.

B.3.11 Adverse reactions

B.3.11.1 Patient exposure

The extent of exposure to study treatment is calculated as the number of study treatment IVT injections (active/sham) received. A summary of the number of active IVT injections received from baseline to Week 100 is presented in Table 28 for both studies (additional timepoints are presented in Appendix F).

From baseline to Week 100, in both KITE and KESTREL, [redacted]. In KITE, the mean number of injections received to Week 100 was [redacted] and [redacted] in the brolucizumab and aflibercept arms, respectively and in KESTREL, [redacted] and [redacted], respectively.

Table 28: Extent of exposure to study treatment: number of active injections from baseline to Week 96 (SAF)

Study name	KITE		KESTREL		
Number of active injections	Brolucizumab 6 mg (N=179)	Aflibercept 2 mg (N=181)	Brolucizumab 3 mg (N=190)	Brolucizumab 6 mg (N=189)	Aflibercept 2 mg (N=187)
n (%)					
n	[redacted]				
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
13					
14					

Study name	KITE		KESTREL		
Number of active injections	Brolucizumab 6 mg (N=179)	Aflibercept 2 mg (N=181)	Brolucizumab 3 mg (N=190)	Brolucizumab 6 mg (N=189)	Aflibercept 2 mg (N=187)
15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Descriptive statistics					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

n=number of patients with at least one active injection. Percentages (%) are calculated based on n.
Abbreviations: SAF, safety set.
Source: Data on file (79).

B.3.11.2 Adverse events

B.3.11.2.1 *Ocular adverse events to Week 100*

The overall rate of ocular AEs at Week 52 was comparable between the brolucizumab 6 mg and aflibercept 2 mg arm in both studies (KITE: 29.6% vs. 28.7%, respectively; KESTREL: 40.2% vs. 39.0%, respectively). Ocular AEs occurring in ≥2% of patients at Week 52 in any treatment arm in either study are presented in Appendix F.

A summary of the ocular AEs in the study eye up to Week 100 that occurred in ≥2% of patients in any treatment arm across either study is presented in Table 29.

[redacted] The majority of these were all [redacted] in severity (KITE: [redacted][brolucizumab 6 mg] vs [redacted] [aflibercept 2 mg]; KESTREL: [redacted][brolucizumab 6 mg] vs [redacted] [aflibercept 2 mg]).

Table 29: Ocular AEs occurring in ≥2% of patients in any arm of either study by MedDRA preferred term for the study eye up to Week 100 (SAF)

Study name	KITE		KESTREL		
Preferred term	**Brolucizumab 6mg (N=179) n (%)**	**Aflibercept 2mg (N=181) n (%)**	**Brolucizumab 3 mg (N=190) n (%)**	**Brolucizumab 6 mg (N=189) n (%)**	**Aflibercept 2 mg (N=187) n (%)**
Number of patients with ≥1 ocular AE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AEs with start date on or after the date of first study treatment administration are counted. AEs started after the subject discontinued study treatment and started alternative DME treatment in the study eye are censored. A patient with multiple occurrences of an AE for a preferred term is counted only once in each specific category. Abbreviations: MedDRA Version 24.0 (KITE) and 24.1 (KESTREL) has been used for the reporting of adverse events.
Abbreviations: AE, adverse event; MedDRA, medical dictionary for regulatory activities; SAF, safety set. Source: Data on file (79).

B.3.11.2.2 *Non-ocular adverse events*

The non-ocular AEs reported in KITE and KESTREL up to Week 52 were [redacted] In KITE, at Week 52, the incidence of non-ocular AEs was lower in the brolucizumab arm (60.3%) compared with the aflibercept arm (70.2%). In KESTREL, non-ocular AEs were reported with comparable frequencies across the brolucizumab 6 mg and aflibercept 2 mg arms (67.7% vs. 65.2%, respectively). Non-ocular AEs occurring in ≥2% of patients at Week 52 in any treatment arm in either study are presented in Appendix F.

Table 30 presents a summary of the non-ocular AEs in the study eye up to Week 100 that occurred in ≥2% of patients in any treatment arm across both studies. [redacted] These were all mainly [redacted] in severity (KITE: [redacted] [brolucizumab 6 mg] vs [redacted] [aflibercept 2 mg]; KESTREL: [redacted] [brolucizumab 6 mg] vs [redacted] [aflibercept 2 mg]).

Table 30: Non-ocular AEs occurring in ≥2% of patients in any arm in either study by MedDRA preferred term to Week 100 (SAF)

Trial name	KITE		KESTREL		
Preferred term	**Brolucizumab 6 mg (N=179) n (%)**	**Aflibercept 2 mg (N=181) n (%)**	**Brolucizumab 3 mg (N=190) n (%)**	**Brolucizumab 6 mg (N=189) n (%)**	**Aflibercept 2 mg (N=187) n (%)**
[redacted]					

Trial name	KITE		KESTREL		
Preferred term	Brolucizumab 6 mg (N=179) n (%)	Aflibercept 2 mg (N=181) n (%)	Brolucizumab 3 mg (N=190) n (%)	Brolucizumab 6 mg (N=189) n (%)	Aflibercept 2 mg (N=187) n (%)
[redacted]					

Trial name	KITE		KESTREL		
Preferred term	Brolucizumab 6 mg (N=179) n (%)	Aflibercept 2 mg (N=181) n (%)	Brolucizumab 3 mg (N=190) n (%)	Brolucizumab 6 mg (N=189) n (%)	Aflibercept 2 mg (N=187) n (%)
[redacted]					

Trial name	KITE		KESTREL		
Preferred term	Brolucizumab 6 mg (N=179) n (%)	Aflibercept 2 mg (N=181) n (%)	Brolucizumab 3 mg (N=190) n (%)	Brolucizumab 6 mg (N=189) n (%)	Aflibercept 2 mg (N=187) n (%)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AEs with start date on or after the date of first study treatment administration are counted.
AEs started after the patient discontinued study treatment and started alternative DMO treatment in the study eye are censored.
AEs started on the same day as the start of alternative DMO treatment are censored, unless this AE led to study drug withdrawal (in such a case, the AE is included in the analysis).
A patient with multiple occurrences of an AE for a preferred term is counted only once in each specific category.
MedDRA Version 24.0 (KITE) and 24.1 (KESTREL) were used for the reporting of AEs.
Abbreviations: AE, adverse event; DMO, diabetic macular oedema; MedDRA, medical dictionary for regulatory activities; SAF, safety set .
Source: Data on file (79).

B.3.11.2.3 *Deaths, serious adverse events and adverse events of special interest*

The number of deaths during each study (KITE, KESTREL) up to Week 100 are presented in Table 31. In addition, the number of patients experiencing ≥1 ocular serious adverse event (SAE) or ≥1 non-ocular SAE suspected to be related to study treatment, or the IVT injection procedure are presented. Further details and timepoints are provided as a data on file (79).

Up to Week 100, a total of [redacted] vs. [redacted] patients in KITE, and [redacted] vs. 4 [redacted] patients in KESTREL experienced an ocular adverse event of special interest (AESI) in the brolucizumab 6 mg and aflibercept 2 mg arms, respectively (Table 31). Additional timepoints are provided as a data on file (15, 16).

Table 31: Deaths, SAEs and ocular AESIs interest for the study eye by category and MedDRA preferred term to Week 100 (SAF)

Study name	KITE		KESTREL		
Category Preferred term	Brolucizumab 6 mg (N=179) n (%)	Aflibercept 2 mg (N=181) n (%)	Brolucizumab 3 mg (N=190) n (%)	Brolucizumab 6 mg (N=189) n (%)	Aflibercept 2 mg (N=187) n (%)
Deaths	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No of patients with ≥1 ocular	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Study name	KITE		KESTREL		
Category Preferred term	**Brolucizumab 6 mg (N=179) n (%)**	**Aflibercept 2 mg (N=181) n (%)**	**Brolucizumab 3 mg (N=190) n (%)**	**Brolucizumab 6 mg (N=189) n (%)**	**Aflibercept 2 mg (N=187) n (%)**
SAE suspected to be related to study treatment					
No of patients with ≥1 non-ocular SAE suspected to be related to study treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No of patients with ≥1 ocular SAE suspected to be related to IVT injection procedure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocular AESIs					
No. of patients with ≥1 ocular AESI	[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]	[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]

Study name	KITE		KESTREL		
Category Preferred term	**Brolucizumab 6 mg (N=179) n (%)**	**Aflibercept 2 mg (N=181) n (%)**	**Brolucizumab 3 mg (N=190) n (%)**	**Brolucizumab 6 mg (N=189) n (%)**	**Aflibercept 2 mg (N=187) n (%)**
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Deaths or AEs with start date on or after the date of first study treatment administration are counted.
Deaths or AEs started after the patient discontinued study treatment and started alternative DMO treatment in the study eye are censored.
AEs are identified using Novartis search definitions (RTH258 Case Retrieval Strategy).
A patient with multiple occurrences of an AE for a preferred term or category is counted only once in each specific category.
An AE can appear with more than one category.
Primary system organ classes (bold text) are presented alphabetically.
MedDRA Version 24.0 (KITE) and 24.1 (KESTREL) were used for the reporting of death events and AEs.
Abbreviations: AE, adverse event; AESI, adverse event of special interest; DMO, diabetic macular oedema; MedDRA; medical dictionary for regulatory activities; SAF, safety set.
Source: Data on file (79).

B.3.11.3 Conclusion of safety of the technology

[redacted] Ocular AEs were reported with similar frequency across treatment arms in both studies. [redacted] The proportion of patients with BCVA loss of ≥15 letters from baseline at Week 52 was low and comparable across all arms in both studies (KITE: 1.1% [brolucizumab 6 mg] vs. 1.7% [aflibercept 2 mg]; KESTREL: 0.0% [brolucizumab 6 mg] vs. 0.5% [aflibercept 2 mg]) [redacted]

B.3.12 Conclusions about comparable health benefits and safety

Evidence for the efficacy and safety of brolucizumab was derived from two pivotal phase 3 randomised controlled trials, KITE and KESTREL. In both studies, brolucizumab 6 mg was found to be non-inferior to aflibercept 2 mg for the primary endpoint (LSM change from baseline in BCVA at Week 52; p<0.001 in both studies). The key secondary endpoint of non-inferiority of brolucizumab 6 mg versus aflibercept 2 mg in the change from baseline in BCVA over the period of Weeks 40–52 was also met (p<0.001 in both studies). [redacted] In addition, more than 50% of patients in the brolucizumab 6 mg arm (in both KITE and KESTREL) were maintained on a q12w dosing regimen at Week 52 (patients receiving aflibercept were treated q8w). [redacted] despite fewer IVT injections administered in the brolucizumab arms. [redacted] In addition, in both studies, a greater reduction in the LSM change from baseline in the proportion of patients with retinal fluid was observed in the brolucizumab arms at Week 52 [redacted]

[redacted]

Subgroup analysis demonstrated that the relative health benefit of brolucizumab for patients with CRT ≥400 µm does not deviate from the comparable health benefits established for the KITE and KESTREL FAS population. In this subgroup, the LSM difference in the change from baseline in BCVA at Week 52 was [redacted] ([redacted]) in KITE and [redacted] ([redacted]) in KESTREL (Figure 15). Results suggest that the wider DMO population (in line with brolucizumab's expected license population) can be used as proxy for decision making. The head-to-head trial evidence provides the most robust comparison of brolucizumab versus NICE recommended comparator, aflibercept. Brolucizumab 6mg is expected to provide similar or greater health benefits compared to aflibercept 2mg for patients with DMO.

In the primary NMA analysis of all enrolled patients included in the studies, brolucizumab is ranked amongst the best treatments for several outcomes including change in BCVA, improvement in DRSS and decrease in retinal thickness while maintaining a comparable adverse event profile. The comparative benefit of brolucizumab versus aflibercept and ranibizumab in the exploratory analysis (Appendix D) were comparable with the results of the more robust wider network.

B.3.13 Ongoing studies

No further clinical effectiveness evidence for this indication is expected to become available during the appraisal. The KINGFISHER study is not considered relevant as part of the evidence base for this submission as it investigates a more frequent brolucizumab dosing regimen (once every 4 weeks). [redacted]

B.4 Cost-comparison analysis

The cost-comparison analysis shows that brolucizumab is expected to be cost-saving compared with both aflibercept and ranibizumab.

- A cost-comparison analysis was conducted comparing brolucizumab against aflibercept and ranibizumab for the treatment of patients with DMO who have CRT of ≥400 µm.
- Subgroup analyses presented in Sections B.3.8 and Appendix D demonstrated that the relative efficacy of brolucizumab versus aflibercept and ranibizumab in all patients with visual impairment caused by DMO was similar to that in the CRT ≥400 µm subgroup.

- It is therefore assumed that data from patients in the broader DMO population are representative of the CRT ≥400 µm subgroup and can be used as proxy for decision making.

- Where data for the NICE-recommended population of patients with a CRT ≥400 µm were unavailable or deemed uncertain, data aligned to all patients with visual impairment caused by DMO are used.
- The analysis considers costs associated with drug acquisition, administration, and monitoring for patients with unilateral and bilateral disease, and factors in treatment discontinuation; a scenario explores the inclusion of adverse events.
- Aflibercept was included in the analysis at the NHS list price; ranibizumab and brolucizumab were included at their confidential net prices to the NHS.
- In the base case, brolucizumab is shown to result in cost savings of [redacted] and [redacted] compared with aflibercept and ranibizumab, respectively.
- All considered scenario and sensitivity analyses result in cost savings versus both aflibercept and ranibizumab.

B.4.1 Changes in service provision and management

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

Studies identified in the literature review as well as real world data demonstrated that fewer injection and monitoring visits are required with brolucizumab versus aflibercept and ranibizumab (Section B.4.2.2.2).

B.4.2 Cost-comparison analysis inputs and assumptions

The objective of this analysis was to evaluate the costs associated with brolucizumab versus aflibercept and ranibizumab for the treatment of visual impairment caused by DMO (CRT ≥ 400 µm) from an England and Wales healthcare system perspective.

B.4.2.1 Features of the cost-comparison analysis

An overview of the features of the cost-comparison analysis is presented in Table 32.

Table 32: Features of the cost-comparison analysis

Component	Approach
Population	Adult patients with visual impairment caused by DMO, with a central retinal thickness of 400 µm or more at the start of treatment

Component	Approach
Intervention	Brolucizumab 6 mg • Administered five times, once every 6 weeks during the loading phase, then every 12 or 8 weeks
Comparator(s)	• Aflibercept 2 mg • Ranibizumab 0.5 mg
Outcomes	• Incremental per-patient costs • Total per-patient costs
Perspective	NHS and PSS in England and Wales
Time horizon	Lifetime (maximum age of 100 years).
Discounting	A 3.5% discount rate is used in the base case; this is considered appropriate because a lifetime time horizon is used. This approach was also taken in the NICE submission for brolucizumab in wAMD (TA672) (90). A scenario is considered in which no discounting is applied.

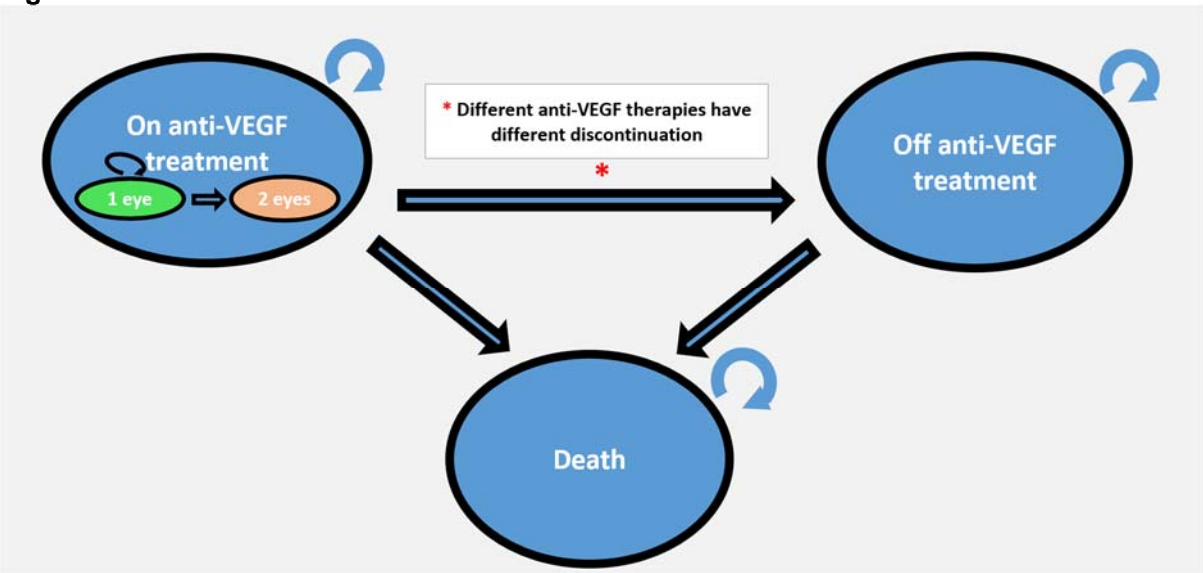
Abbreviations: DMO, diabetic macular oedema; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PSS, personal social services; TA, technology appraisal; wAMD, wet age-related macular degeneration.

B.4.2.1.1 *Model structure*

A cost-comparison model was developed in Microsoft Excel® using a Markov cohort approach to calculate the proportion of patients across three health states over time: “On anti-VEGF”, “Off anti-VEGF”, and “Death” (Figure 17).

In the “On anti-VEGF” state, patients can progress from unilateral to bilateral disease, and a proportion of patients are assumed to have bilateral disease at the start of the model. Once patients develop bilateral disease, they cannot revert to unilateral disease.

Figure 17: Model structure



Abbreviations: VEGF, vascular endothelial growth factor.

A cycle length of one year was adopted, reflecting the relatively slow rate of visual decline in this population. This approach was also taken in the NICE submission for brolucizumab in wAMD and was accepted by the committee (90). A half-cycle correction was applied, assuming that state transitions occur, on average, half-way through each model cycle.

B.4.2.1.2 *Baseline characteristics*

The baseline age and gender distribution were taken from the pooled KITE and KESTREL patient populations; these were used to determine the cohort life expectancy, affecting the number of predicted treatment and monitoring visits. Subgroup data were not used, as the trials were not stratified by the CRT ≥400 µm subgroup and the full analysis sets from KITE and KESTREL were considered to be more robust.

KITE and KESTREL did not report the number of patients with bilateral DMO at baseline; therefore, this value ([redacted]) was taken from the average of the estimates provided through clinical insight gathering conducted by Novartis (Appendix J).

Two scenario analyses were performed assuming:

- 46.5% of patients with bilateral disease at baseline; this figure was used in TA346 and was derived from a UK clinician survey (77), and
- 12.7% of patients with bilateral disease at baseline; this value was taken from the VISTA and VIVID trials (54).

Modelled population baseline characteristics are presented in Table 33.

Table 33: Modelled population baseline characteristics

Characteristic	Value	Source
Age at baseline (years)	[redacted]	KITE and KESTREL pooled analysis (15, 16)
Percentage of females	[redacted]	
Percentage with bilateral disease at baseline	[redacted] (base case)	Average from clinical insight gathering (Appendix J)
	46.5% (scenario)	NICE TA346 (77)
	12.7% (scenario)	VISTA and VIVID (54)

Abbreviations: NICE, National Institute for Health and Care Excellence; TA, technology appraisal.

B.4.2.1.3 *Incidence of bilateral DMO*

As stated above, patients in the "On anti-VEGF" health state can progress from unilateral to bilateral disease. Annual probabilities of DMO diagnosis in the fellow eye were taken from the VISTA and VIVID trials (54). It was assumed that the probability of developing DMO in the fellow eye is constant from Year 2 onwards, in the absence of other data. It was assumed that all patients developing DMO in the fellow eye would receive bilateral treatment.

Table 34: Incidence of bilateral DMO

Parameter		Value	Source
Annual probability of developing bilateral disease (developing DMO in fellow eye)	Year 1	37.6%†	VISTA and VIVID (54)
	Year 2+	13.5%‡	

†266 out of 755 patients had bilateral DMO at 48 weeks; converted from a 48-week probability to an annual probability; ‡66 out of 489 patients had bilateral DMO at 100 weeks.
Abbreviations: DMO, diabetic macular oedema.

B.4.2.1.4 *Mortality*

Mortality was modelled using the 2018–2020 national life tables for England and Wales as published by the Office for National Statistics (91).

Age- and gender-specific mortality rates were combined into a blended rate using the proportion of females and mean age set in the model to reflect the FAS patient population in the KITE and KESTREL trials. Patients can transition to the dead state at any point in the model.

B.4.2.1.5 *Bilateral disease cost multipliers*

In the base-case analysis, it was assumed that the treatment of bilateral DMO comprises 'one-stop' appointments, i.e. the cost of administration and monitoring is shared between eyes, in line with the approach adopted in the NICE TA672 (90) and NG82 (92).

As such, for the proportion of patients estimated to receive bilateral treatment, the cost of drug treatment was doubled (cost multiplier of 2) and the cost of administration was assumed to increase by 50% (cost multiplier of 1.5; i.e. doubled in 50% of the cases and shared in other cases). The cost of monitoring was assumed to be fully shared (cost multiplier of 1) (Table 35).

Table 35: Bilateral disease cost multipliers

Cost multiplier	Value	Assumptions	Source
Drug cost multiplier	2	Assumed use of two units	TA672 (90) and NG82 Appendix J (92)
Administration cost multiplier	1.5	Assumed that administration costs would only double in 50% of cases	
Monitoring cost multiplied	1	Assumed that monitoring costs are always shared	

Abbreviations: TA, technology appraisal.

B.4.2.2 Intervention and comparators' acquisition costs

A summary of the acquisition costs for brolucizumab, aflibercept and ranibizumab is presented in Table 36.

Brolucizumab and ranibizumab are available at simple confidential discount patient access scheme (PAS) prices; these prices are used in the cost-comparison analysis. The confidential PAS price for aflibercept is unknown, so the list price is used in the cost-comparison analysis, and is sourced from the British National Formulary (93).

Table 36: Acquisition costs of the intervention and comparator technologies

	Brolucizumab	Aflibercept	Ranibizumab
Pharmaceutical formulation	Solution for injection	Solution for injection	Solution for injection
(Anticipated) care setting	Hospital	Hospital	Hospital
Acquisition cost (excluding VAT)	List price: £816 per 120 mg PAS price: [redacted] per 120 mg	List price: £816 per 40 mg	List price: £551 per 10 mg PAS price: [redacted] per 10 mg

	Brolucizumab	Aflibercept	Ranibizumab
Method of administration	Intravitreal injection	Intravitreal injection	Intravitreal injection
Doses	6 mg (0.05 ml)	2 mg (0.05 ml)	0.5 mg (0.05 ml)

Abbreviations: PAS, patient access scheme; VAT, value added tax.

B.4.2.2.1 *Dosing regimens*

For brolucizumab, a 5xq6w loading phase → q8w/q12w dosing regimen was assumed, in line with the anticipated marketing authorisation.

For aflibercept and ranibizumab, a blend of dosing regimens used in the UK was assumed, using data from a UK real-world evidence study, Peto et al. 2021 (94). This was considered to best reflect anti-VEGF usage in UK clinical practice. [redacted]. A scenario analysis considers the Q8W dosing regimen for aflibercept, as per the KITE and KESTREL studies.

B.4.2.2.2 *Injection frequency*

Drug acquisition costs are applied based on the modelled injection frequency.

In the first and second years, the injection frequencies for brolucizumab are taken from pooled KITE and KESTREL data, and injection frequencies for other comparators are based on the UK real-world evidence (RWE) study (94). In the scenario analysis in which the Q8W regimen is considered for aflibercept, injection frequencies in the first and second years are taken from pooled KITE and KESTREL data.

Table 37: Injection frequency in Years 1 and 2

Comparator	Regimen	Source	Injection frequency	
			Year 1	Year 2
Brolucizumab	Q12W/Q8W (base case)	Pooled KITE & KESTREL	[redacted]	[redacted]
Aflibercept	Blend of dosing regimens used in the UK (base case)	UK RWE study (94)	7.70	5.60
	Q8W (scenario)	Pooled KITE & KESTREL	[redacted]	[redacted]
Ranibizumab	Blend of dosing regimens used in the UK (base case)	UK RWE study (94)	7.70	5.60

Abbreviations: qXw, every X weeks; RWE, real world evidence; UK, United Kingdom.

For Year 3 onwards, the injection frequency is taken from TA346 (77) and assumed to be equivalent across all comparators. In order to explore the sensitivity of the cost-comparison analysis results to injection frequencies in later years, a scenario analysis is considered in which

the Year 3+ injection frequency is assumed to correspond to the highest estimate provided as part of the clinical insight gathering conducted by Novartis (Appendix J; Table 38).

Table 38: Injection frequency in Year 3+

Year	Injection frequency	
	TA346 (77) (base case)	Estimate from clinical insight gathering (scenario)
3	2.30	[redacted]
4	1.20	[redacted]
5+	1.00	[redacted]

Abbreviations: TA, technology appraisal.

B.4.2.2.3 *Treatment discontinuation*

Treatment discontinuation was assumed to be constant over time. The discontinuation rate for aflibercept was calculated from the pooled KITE and KESTREL studies. Discontinuation rates for brolucizumab and ranibizumab were calculated by applying the hazard ratios from the NMA to the aflibercept rate (Appendix D)[3].

Three scenario analyses were considered:

- Scenario 1: the KITE/KESTREL rate was used for brolucizumab, and the rate for ranibizumab was assumed the same as the KITE/KESTREL aflibercept rate.
- Scenario 2: the KITE/KESTREL rate for brolucizumab was used for all comparators.
- Scenario 3: the UK RWE study (94) anti-VEGF rate was used for all comparators

The base case and alternative discontinuation scenarios considered are presented in Table 39.

Table 39: Discontinuation scenarios

Comparator	Annual probability of discontinuation			
	Base case	Scenario 1	Scenario 2	Scenario 3
Brolucizumab	[redacted]	[redacted]	[redacted]	15.03%
Aflibercept	[redacted]	[redacted]	[redacted]	15.03%
Ranibizumab	[redacted]	[redacted]	[redacted]	15.03%

B.4.2.3 Intervention and comparators' healthcare resource use and associated costs

An SLR was conducted to identify cost and resource use data relevant to the decision problem from the published literature as summarised in Appendix I. In total 106 studies were identified that met the pre-defined inclusion criteria. Of these, 10 studies included data from UK patients (eight full text publications, one conference abstract and one conference poster).

[3] Note that aflibercept was the common comparator in the NMA described in Section **Error! Reference source not found.**.

B.4.2.3.1 *Diagnosis*

A one-off cost of a fundus fluorescein angiography (FFA) examination was included for each affected eye at either Year 1 or diagnosis of new bilateral disease (Table 40).

Table 40: Diagnosis costs

Resource type	Value	Source
Fundus fluorescein angiography examination	£130.74	National Schedule of NHS Costs 2019–20. Weighted average of RD30Z, RD31Z and RD32Z (95).

Abbreviations: NHS, National Health Service.

B.4.2.3.2 *Administration*

Administration was assumed to require a retinal specialist visit; a scenario is considered in which administration is assumed to require a nurse visit (Table 41). This is aligned with the results of the clinical insight gathering conducted by Novartis (Appendix J).

Table 41: Administration costs

Resource type	Value	Source
Retinal specialist visit	£110.34	National Schedule of NHS Costs 2019–20. Outpatient attendances, consultant led, ophthalmology (95).
Nurse visit	£95.07	National Schedule of NHS Costs 2019–20. Outpatient attendances, non-consultant led, ophthalmology (95).

Abbreviations: NHS, National Health Service.

B.4.2.3.3 *Monitoring*

The cost of OCT testing was applied for each monitoring visit (Table 42).

Table 42: Monitoring costs

Resource type	Value	Source
Optical coherence tomography testing	£124.94	National Schedule of NHS Costs 2019–20. Retinal tomography, 19 years and over (BZ88A) (95).

Abbreviations: NHS, National Health Service.

In Years 1 and 2, monitoring frequency for brolucizumab is assumed to be the same as injection frequency (Section B.4.2.2.2); monitoring frequency for aflibercept and ranibizumab are taken from a UK RWE study (94), to align with injection frequency (Table 43).

Table 43: Base-case monitoring frequency in Years 1 and 2

Comparator	Monitoring frequency	
	Year 1	Year 2
Brolucizumab	[redacted]	[redacted]
Aflibercept	14.2	13.4
Ranibizumab	14.2	13.4

Monitoring frequency in Year 3 onwards is taken from TA346 and presented in Table 44; these values were validated by clinicians consulted as part of the clinical insights gathering conducted by Novartis (Appendix J). A scenario is considered in which monitoring frequency is taken from Glassman et al (96), and monitoring is assumed to be 4 times per year from Year 3 onwards.

Table 44: Base-case monitoring frequency in Year 3 onwards

Year	Monitoring frequency	Source
3	4	NICE TA346 (77)
4	4	
5+	2	

Abbreviations: NICE, National Institute for Health and Care Excellence; TA, technology appraisal.

B.4.2.4 Adverse reaction unit costs and resource use

Adverse event costs were not included in the base-case analysis; however, a scenario is presented in which these costs are included.

Modelled AEs include serious ocular events and stroke; stroke was included to align with the recommendations of the guideline committee in NG82 (92). 100-week adverse event rates for brolucizumab and aflibercept were taken from the pooled KITE and KESTREL studies; rates for ranibizumab were generated by applying the hazard ratios from the NMA to the aflibercept rates (Section B.3.9). Adverse event costs were derived from the National Schedule of NHS Costs 2019-20 (95) (assuming a weighted average of selected currency codes), with the exception of endophthalmitis and stroke, which were taken from NG82 (92) and inflated to 2020 prices using the Office for National Statistics (ONS) inflation indices (97). The 100-week probabilities of each event and the cost per event are presented in Table 45.

Table 45: Costs and probabilities for adverse events

Adverse event	Cost per event	Probability of adverse event		
		Brolucizumab	Aflibercept	Ranibizumab
Conjunctival cyst	£948.65†	[redacted]	[redacted]	[redacted]
Diabetic retinal oedema	£948.65†	[redacted]	[redacted]	[redacted]
Pterygium	£948.65†	[redacted]	[redacted]	[redacted]
Posterior capsule opacification	£948.65†	[redacted]	[redacted]	[redacted]
Vitreous floaters	£948.65†	[redacted]	[redacted]	[redacted]
Cataract	£985.62‡	[redacted]	[redacted]	[redacted]
Glaucoma	£608.27¶	[redacted]	[redacted]	[redacted]
Retinal artery occlusion	£948.65†	[redacted]	[redacted]	[redacted]
Uveitis	£948.65†	[redacted]	[redacted]	[redacted]
Visual acuity reduced	£948.65†	[redacted]	[redacted]	[redacted]
Retinal detachment	£1,566.90§	[redacted]	[redacted]	[redacted]
Retinal tear	£716.99††	[redacted]	[redacted]	[redacted]

Adverse event	Cost per event	Probability of adverse event		
		Brolucizumab	Aflibercept	Ranibizumab
Intraocular pressure increased	£948.65†	[redacted]	[redacted]	[redacted]
Ophthalmic herpes zoster	£948.65†	[redacted]	[redacted]	[redacted]
Endophthalmitis	£2,113.28‡‡	[redacted]	[redacted]	[redacted]
Stroke	£5,425.46‡‡ (one-off) £205.51‡‡ (annual)	[redacted]	[redacted]	[redacted]

† Weighted average cost of all non-elective short stay and day case codes for ophthalmology, excluding codes for patients aged 18 and under, and codes for oculoplastics (95);
‡ Weighted average cost of non-elective short stay and day case entries for BZ34A-C: Phacoemulsification Cataract Extraction and Lens Implant (95);
¶ Weighted average cost of currency codes for glaucoma (BZ90Z-BZ95Z) (95);
§ Weighted average cost of non-elective procedure (75%) and day case (25%) codes for BZ87A and BZ84B Vitreous Retinal Procedures, and 2 follow-up visits (WF01A, Consultant led - Ophthalmology) (95);
†† Weighted average cost of non-elective short stay and day case codes for Major Vitreous Retinal Procedures: BZ84A, BZ84B (95);
‡‡ NG82 prices inflated to 2021 prices using ONS inflation indices Table 23 D7FC (06.3 Hospital Services)
Abbreviations: NHS, National Health Service.

B.4.2.5 Miscellaneous unit costs and resource use

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

B.4.2.6 Clinical expert validation

Novartis developed key questions to gather clinical opinion regarding DMO in England and Wales to better understand current NHS treatment in support of the current technology appraisal.

A total of 8 consultant level medical retina experts were contacted. All 8 experts participated. Selection criteria included those with experience in DMO management and treatments. Previous participation in DMO-specific clinical trials, advisory boards and publications was also considered. The experts were selected from a number of locations, including large retina services throughout England and Wales in order to get a representative landscape of treatment patterns. The conversations with clinicians took place from 07 January 2022 to 01 February 2022.

A summary of all clinician responses is provided in Appendix J; all clinicians were provided the same questions and background as described in Appendix J. Conflicts of interest were also collected and no conflicts of concern were raised.

B.4.2.7 Uncertainties in the inputs and assumptions

A summary of the key assumptions in the base-case cost-comparison analysis is presented in Table 46.

Table 46: Key model assumptions

Assumption	Description
Equivalent efficacy across treatments	The cost-comparison model assumes equal efficacy between comparators. The KITE and KESTREL trials demonstrate non-inferiority in BCVA between brolucizumab and aflibercept. This is supported by the findings of the network meta-analysis which demonstrated that brolucizumab had at least similar efficacy compared with comparators (Section B.3.9).
Equivalent efficacy between the FAS and CRT ≥400 µm populations	Subgroup analysis demonstrated that the relative health benefit of brolucizumab for patients with CRT ≥400 µm does not deviate from the comparable health benefits established for the KITE and KESTREL FAS population and is aligned with brolucizumab's full marketing authorisation
General population mortality	It was assumed the cohort followed age and gender general population mortality rates. No increased mortality from bilateral disease or adverse events were considered.
Discontinuation probability	The probability of discontinuing from each treatment was considered constant over time and did not differ between those with unilateral and bilateral disease.
Treatment switching	It was assumed patients did not switch treatments.
Adverse events	The cost comparison model considers equal safety outcomes for all comparators therefore, the base case analysis does not consider AEs. The inclusion of costs for serious ocular AEs were explored in a scenario analysis based on week 104 data from KITE and KESTREL.
Costs for bilateral disease	Patients with bilateral disease were assumed to incur twice the cost of treatment, one and a half times the administration cost and the same monitoring costs as those with unilateral disease (Table 35), in line with NICE clinical guidance in NG82 (92).

Abbreviations: AE, adverse event; BCVA, Best Corrected Visual Acuity; CRT, central retinal thickness; DMO, diabetic macular oedema; FAS, full analysis set; FFA, Fundus fluorescein angiography; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; OCT, Optical Coherence Tomography

B.4.3 Base-case results

Base-case results are presented in Table 47. Brolucizumab is shown to result in cost savings of [redacted] and [redacted] compared with aflibercept and ranibizumab, respectively.

Table 47: Base-case results

Technology	Drug costs	Administration costs	Diagnosis & monitoring costs	Total costs	Incremental costs (versus brolucizumab)
Brolucizumab	[redacted]	£2,408	£3,077	[redacted]	–
Aflibercept	£25,815	£2,908	£5,599	£34,322	[redacted]
Ranibizumab	[redacted]	£3,338	£6,367	[redacted]	[redacted]

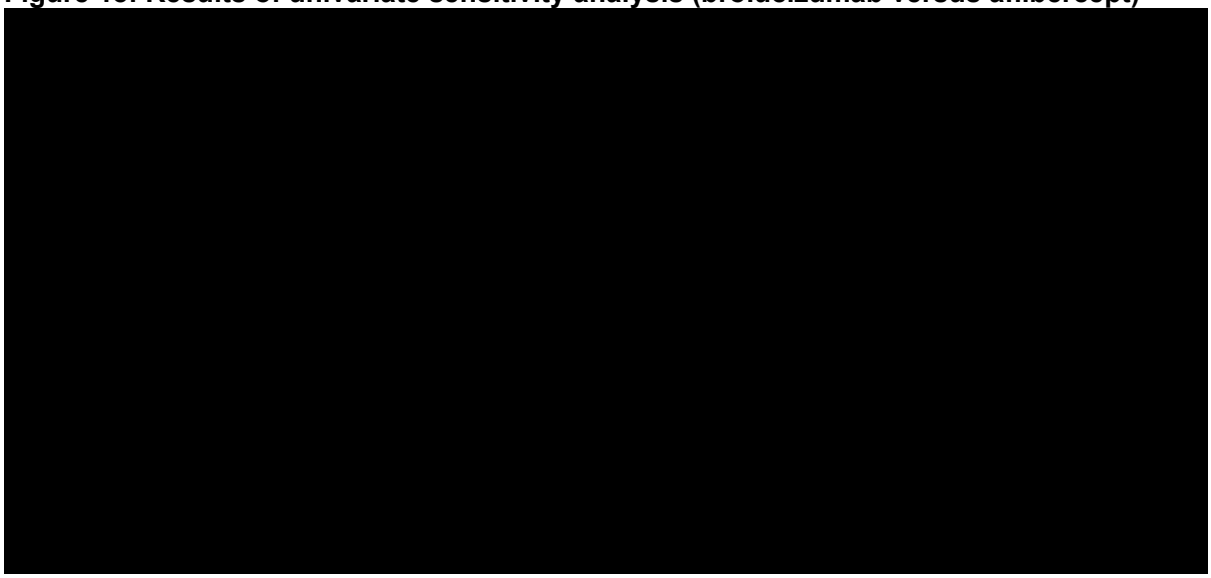
B.4.4 Sensitivity and scenario analyses

B.4.4.1 Univariate sensitivity analysis

Parameter uncertainty was tested using univariate sensitivity analysis, in which all model parameters are systematically and independently varied over a plausible range determined by either the 95% CI, or ±20% where no estimates of precision were available. The results of univariate sensitivity analysis are presented for the comparisons of brolucizumab against aflibercept and ranibizumab in Figure 18 and Figure 19, respectively. The most influential

parameters relate to discontinuation, the frequency of administration and the multiplier for drug costs; however, brolucizumab remains cost-saving for each considered parameter across the full range of plausible values.

Figure 18: Results of univariate sensitivity analysis (brolucizumab versus aflibercept)



Abbreviations: OCT, Optical Coherence Tomography.

Figure 19: Results of univariate sensitivity analysis (brolucizumab versus ranibizumab)

Abbreviations: OCT, Optical Coherence Tomography.

B.4.4.2 Scenario analysis

Scenario analyses were performed in which key structural assumptions were varied, and the results of each analysis reported. The results of scenario analyses are presented for the comparisons of brolucizumab against aflibercept and ranibizumab in Table 48; all scenarios are associated with cost savings for brolucizumab compared with aflibercept and ranibizumab.

Table 48: Scenario analyses

Scenario	Incremental costs (versus aflibercept)	Incremental costs (versus ranibizumab)
Base case	[redacted]	[redacted]
No discounting	[redacted]	[redacted]
Baseline % with bilateral disease: 46.50%	[redacted]	[redacted]
Baseline % with bilateral disease: 12.71%	[redacted]	[redacted]
Aflibercept Year 1/2 injection frequency: pooled KITE and KESTREL	[redacted]	[redacted]
Injection frequency in Year 3+: clinician estimate	[redacted]	[redacted]
Discontinuation rates: ranibizumab assumed equivalent to aflibercept	[redacted]	[redacted]
Discontinuation rates: aflibercept and ranibizumab assumed equivalent to brolucizumab	[redacted]	[redacted]
Discontinuation rates: Peto et al 2021	[redacted]	[redacted]
Administration costed as a nurse visit	[redacted]	[redacted]
Monitoring frequency in Year 3+: Glassman et al	[redacted]	[redacted]
Adverse events included	[redacted]	[redacted]

B.4.5 Subgroup analysis

No subgroup analyses were considered; however, this submission reflects a subgroup of the licensed population (i.e. those with CRT ≥400 µm; Section B.1.1).

B.4.6 Interpretation and conclusions of economic evidence

The aim of this analysis was to compare total costs associated with brolucizumab, aflibercept and ranibizumab in the treatment of adult patients with visual impairment due to DMO and CRT≥400 µm.

In the base case, brolucizumab is shown to result in cost savings of [redacted] and [redacted] compared with aflibercept and ranibizumab, respectively. All considered scenario and sensitivity analyses resulted in cost savings versus both aflibercept and ranibizumab. Brolucizumab is therefore expected to result in savings for the NHS while providing similar efficacy.

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Appendices

The following appendices are provided as separate documents to the submission:

Appendix C: Summary of product characteristics (SmPC) and UK public assessment report

Appendix D: Identification, selection, and synthesis of clinical evidence

Appendix E: Subgroup analysis

Appendix F: Adverse reactions

Appendix G: Cost and healthcare resource identification, measurement and valuation

Appendix H: Price details of treatments included in the submission

Appendix I: Checklist of confidential information

Appendix J: Clinical Insight for HTA: Treatment Patterns for Diabetic Macular Oedema in England

Appendix K: Other efficacy endpoints from KITE and KESTREL

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Brolucizumab for treating diabetic macular oedema [ID3902]

Clarification questions

March 2022

File name	Version	Contains confidential information	Date
ID3902 brolucizumab EAG Clarification letter to PM for company Fully redacted	1.0	Yes	25/04/22

Section A: Clarification on effectiveness data

Indirect treatment comparisons

A1. Priority question. As a scenario analysis, please conduct a network meta-analysis (NMA) for the 'wider DMO population' excluding the KITE study for the following outcomes:

The external assessment group (EAG) clarified with Novartis that the rationale for requesting the exclusion of the KITE study was based upon an imbalance of baseline characteristics. Specifically, mean baseline best-corrected visual acuity (BCVA) in the study eye and the proportion of patients presenting with ≤65 Early Treatment Diabetic Retinopathy Study (ETDRS) letters at baseline were noted. Novartis disagree with the exclusion of a pivotal trial as this is misaligned with National Institute for Health and Care Excellence (NICE) guidance to systematically include all available relevant evidence (1). Furthermore, both the KITE and KESTREL studies were deemed appropriate clinical trials for the regulatory approval of brolucizumab for the treatment of diabetic macular oedema (DMO) (2).

It is typical in the non-inferiority setting for two similarly designed studies to be used for regulatory submissions (3) and slightly imbalanced baseline characteristics can be expected in pivotal studies. Two non-inferiority studies were also used for the brolucizumab wet age-related macular degeneration (wAMD) indication utilising the HAWK and HARRIER studies for regulatory approval and NICE reimbursement (2, 4-6).

In KITE, the mean baseline BCVA in the study eye was 2.3 letters higher in the brolucizumab arm (66.0 letters) compared with the aflibercept arm (63.7 letters) (7). A difference of 2.3 ETDRS letters is not generally considered to be clinically significant as evidenced by several clinical trials which use 3.5 to 5 letters as the margin to demonstrate a significant difference between drugs (IVAN (8), CATT (9), HAWK and HARRIER (5), KITE and KESTREL (10)). In addition, the proportion of patients in KITE presenting ≤65 letters at baseline was lower in the brolucizumab arm (36.3%) compared with the aflibercept arm (50.3%) (7). Including KITE data represents a conservative approach; generally, the higher the baseline BCVA, the smaller the number of letters gained (due to the ceiling effect (11)). Although

provided as an additional scenario analysis for decision making, exclusion of KITE from the network meta-analyses (NMA) is not deemed appropriate by Novartis as it omits valid evidence from a pivotal trial and the results should be interpreted as such.

Some of the outcomes in the scenario analysis requested by the EAG were not included in the base-case analysis therefore, results including KITE are also presented alongside the results below to demonstrate the impact of removing KITE from the analysis. Unless otherwise stated, results including KITE are as per those presented in Company submission Appendix D. Please note that in three places, errors were found in the tables that were included in Company submission Appendix D (Table 1, Table 13, Table 29). These errors (highlighted using footnotes) have been corrected in this document and do not have any impact on the relative treatment effects.

It should be noted that treatments are labelled according to their maintenance phases. Due to the adjustable nature of brolucizumab's injection frequency, brolucizumab was labelled as every 8 weeks (q8w) in the company submission NMA results, although the physician may individualise treatment intervals based on disease activity as assessed by visual acuity and/or anatomical parameters after the once every six weeks (q6w) loading phase, and every 12 weeks (q12w) should be considered in patients without disease activity. In patients with disease activity, q8w should be considered. To ensure the description of the brolucizumab regimen is clearly aligned with dosing in the KESTREL and KITE trials, the labelling in the NMA results has been updated in the responses to the clarification questions to read brolucizumab 6 mg q12w/q8w.

a) Change from baseline in BCVA at 1 year

For change from baseline in BCVA at 1 year, the results for the random effects model were the better fit, whether including or excluding KITE from the analysis (Table 1).

Table 1: A1 – Model fit statistics for change from baseline in BCVA at 1 year (both BRO trials and excluding KITE)

	Model	DIC	pD	Totalresdev	Datapoints	SD (95% CrI)
KITE and KESTREL	Fixed effects	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Random effects	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Excluding KITE	Fixed effects	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Random effects	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

†This cell has been updated as there was an error in Company submission Appendix D.
Abbreviations: BCVA, best corrected visual acuity; CrI, credible interval; DIC, deviance information criterion; N/A, not applicable; pD, posterior mean of the deviance; SD, standard deviation; Totalresdev, total residual deviance.

For change from baseline in BCVA, the conclusions whether including or excluding KITE were unchanged in the random effects model; licensed anti-vascular endothelial growth factor (VEGF) therapies are mostly comparable in terms of 1-year change from baseline in BCVA (Table 2 and Table 3). Brolucizumab was favoured over laser photocoagulation and ranibizumab 0.5 mg q4w in gaining letters of BCVA over the course of one year of follow-up.

Table 2: A1 – Change from baseline in BCVA at 1 year, BRO 6 mg q12w/q8w vs comparator (both BRO trials and excluding KITE)

		KITE and KESTREL				Excluding KITE			
		Fixed effects		Random effects		Fixed effects		Random effects	
Intervention	Comparator	Median relative mean difference (95% CrI)	Mean relative mean difference (SD)	Median relative mean difference (95% CrI)	Mean relative mean difference (SD)	Median relative mean difference (95% CrI)	Mean relative mean difference (SD)	Median relative mean difference (95% CrI)	Mean relative mean difference (SD)
BRO 6 mg q12w/q8w	LP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Intervention	Comparator	KITE and KESTREL				Excluding KITE			
		Fixed effects		Random effects		Fixed effects		Random effects	
		Median relative mean difference (95% CrI)	Mean relative mean difference (SD)	Median relative mean difference (95% CrI)	Mean relative mean difference (SD)	Median relative mean difference (95% CrI)	Mean relative mean difference (SD)	Median relative mean difference (95% CrI)	Mean relative mean difference (SD)
BRO 6 mg q12w/q8w	AFL 2 mg q4w	[redacted]							
BRO 6 mg q12w/q8w	AFL 2 mg q8w	[redacted]							
BRO 6 mg q12w/q8w	AFL 2 mg PRN	[redacted]							
BRO 6 mg q12w/q8w	RAN 0.5 mg q4w	[redacted]							
BRO 6 mg q12w/q8w	RAN 0.5 mg PRN	[redacted]							

Font in bold and italics indicates one treatment is favoured over another.
Abbreviations: AFL, aflibercept; BCVA, best corrected visual acuity; BRO, brolucizumab; CrI, credible interval; LP, laser photocoagulation; PRN, pro re nata; qXw, every X weeks; RAN, ranibizumab; SD, standard deviation.

Table 3: A1 – Change from baseline in BCVA at 1 year, treatment effect matrix (relative mean difference [95% CrI]) – random effects model (both BRO trials and excluding KITE)

Intervention/ comparator	KITE and KESTREL							Excluding KITE						
	LP	AFL 2 mg q4w	AFL 2 mg q8w	AFL 2 mg PRN	BRO 6 mg q12w/q 8w	RAN 0.5 mg q4w	RAN 0.5 mg PRN	LP	AFL 2 mg q4w	AFL 2 mg q8w	AFL 2 mg PRN	BRO 6 mg q12w/q 8w	RAN 0.5 mg q4w	RAN 0.5 mg PRN
LP		[redacted]												
AFL 2 mg q4w														
AFL 2 mg q8w														

Intervention/ comparator	KITE and KESTREL							Excluding KITE						
	LP	AFL 2 mg q4w	AFL 2 mg q8w	AFL 2 mg PRN	BRO 6 mg q12w/q 8w	RAN 0.5 mg q4w	RAN 0.5 mg PRN	LP	AFL 2 mg q4w	AFL 2 mg q8w	AFL 2 mg PRN	BRO 6 mg q12w/q 8w	RAN 0.5 mg q4w	RAN 0.5 mg PRN
AFL 2 mg PRN														
BRO 6 mg q12w/q8w														
RAN 0.5 mg q4w														
RAN 0.5 mg PRN														

Font in bold and italics indicates one treatment is favoured over another.
Abbreviations: AFL, aflibercept; BCVA, best-corrected visual acuity; BRO, brolucizumab; CrI, credible interval; LP, laser photocoagulation; PRN, pro re nata; qXw, every X weeks; RAN, ranibizumab.

Table 4: A1 – Change from baseline in BCVA at 1 year, SUCRA and ranking table – random effects model (both BRO trials and excluding KITE)

Ranks	KITE and KESTREL							Excluding KITE						
	LP	AFL 2 mg q4w	AFL 2 mg q8w	AFL 2 mg PRN	BRO 6 mg q12w/ q8w	RAN 0.5 mg q4w	RAN 0.5 mg PRN	LP	AFL 2 mg q4w	AFL 2 mg q8w	AFL 2 mg PRN	BRO 6 mg q12w/ q8w	RAN 0.5 mg q4w	RAN 0.5 mg PRN
1														
2														
3														
4														
5														
6														
7														
SUCRA														

Abbreviations: AFL, aflibercept; BCVA, best-corrected visual acuity; BRO, brolucizumab; LP, laser photocoagulation; PRN, pro re nata; qXw, every X weeks; RAN, ranibizumab; SUCRA, surface under the cumulative ranking curve.

b) ≥10 letter improvement in BCVA at 1 year

In the company submission for this outcome (Company submission Appendix D) pairwise meta-analyses were conducted to compare the odds of gaining ≥10 letters per treatment. However, for the NMA in the Company submission, the results of all letter gain / letter loss categories for ≥5, ≥10 and ≥15 letters were included in a single BCVA categorical change model. To allow for the impact of the exclusion of the KITE to be observed when responding to the clarification question, new NMA results for ≥10 letter improvement in BCVA are presented both including and excluding KITE. The results for the random effects model were the better fit for this outcome as the deviance information criterion (DIC) was very similar between fixed and random effects models, however total residual deviance was better for the random effects model (Table 5).

Table 5: A1 – Model fit statistics for ≥10 letter improvement in BCVA at 1 year (both BRO trials and excluding KITE)

	Model	DIC	pD	Totalresdev	Datapoints	SD (95% CrI)
KITE and KESTREL	Fixed effects	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Random effects	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Excluding KITE	Fixed effects	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Random effects	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BCVA, best corrected visual acuity; CrI, credible interval; DIC, deviance information criterion; N/A, not applicable; pD, posterior mean of the deviance; SD, standard deviation; Totalresdev, total residual deviance.

As with the results for the ordered categorical model, brolucizumab is favoured vs laser photocoagulation (both fixed and random effects models) with higher odds of experiencing ≥10 letter improvement when KITE is included versus when it is excluded from the analysis (Table 6). For all remaining comparisons, licensed anti-VEGFs are similar in terms of ≥10 letter improvement from baseline in BCVA at 1 year follow-up when including and excluding KITE (Table 7).

Table 6: A1 – ≥10 letter improvement in BCVA at 1 year, BRO 6 mg q12w/q8w vs comparator (both BRO trials and excluding KITE)

		KITE and KESTREL				Excluding KITE			
		Fixed effects		Random effects		Fixed effects		Random effects	
Intervention	Comparator	Median OR (95% CrI)	Mean OR (SD)	Median OR (95% CrI)	Mean OR (SD)	Median OR (95% CrI)	Mean OR (SD)	Median OR (95% CrI)	Mean OR (SD)
BRO 6 mg q12w/q8w	LP	[redacted]							
BRO 6 mg q12w/q8w	AFL 2 mg q4w	[redacted]							
BRO 6 mg q12w/q8w	AFL 2 mg q8w	[redacted]							
BRO 6 mg q12w/q8w	AFL 2 mg PRN	[redacted]							
BRO 6 mg q12w/q8w	RAN 0.5 mg q4w	[redacted]							
BRO 6 mg q12w/q8w	RAN 0.5 mg PRN	[redacted]							

Font in bold and italics indicates one treatment is favoured over another.
Abbreviations: AFL, aflibercept; BCVA, best corrected visual acuity; BRO, brolucizumab; CrI, credible interval; LP, laser photocoagulation; OR, odds ratio; PRN, pro re nata; qXw, every X weeks; RAN, ranibizumab; SD, standard deviation.

Table 7: A1 – ≥10 letter improvement in BCVA at 1 year, treatment effect matrix (OR [95% CrI]) – random effects model (both BRO trials and excluding KITE)

	KITE and KESTREL							Excluding KITE						
Intervention /comparator	**LP**	**AFL 2 mg q4w**	**AFL 2 mg q8w**	**AFL 2 mg PRN**	**BRO 6 mg q12w/ q8w**	**RAN 0.5 mg q4w**	**RAN 0.5 mg PRN**	**LP**	**AFL 2 mg q4w**	**AFL 2 mg q8w**	**AFL 2 mg PRN**	**BRO 6 mg q12w/ q8w**	**RAN 0.5 mg q4w**	**RAN 0.5 mg PRN**
LP	[redacted]													
AFL 2 mg q4w														
AFL 2 mg q8w														
AFL 2 mg PRN														
BRO 6 mg q12w/q8w														
RAN 0.5 mg q4w														
RAN 0.5 mg PRN														

Font in bold and italics indicates one treatment is favoured over another.
Abbreviations: AFL, aflibercept; BCVA, best-corrected visual acuity; BRO, brolucizumab; CrI, credible interval; LP, laser photocoagulation; OR, odds ratio; PRN, pro re nata; qXw, every X weeks; RAN, ranibizumab.

Table 8: A1 – ≥10 letter improvement in BCVA at 1 year, SUCRA and ranking table – random effects model (both BRO trials and excluding KITE)

	KITE and KESTREL							Excluding KITE						
Ranks	LP	AFL 2 mg q4w	AFL 2 mg q8w	AFL 2 mg PRN	BRO 6 mg q12w/ q8w	RAN 0.5 mg q4w	RAN 0.5 mg PRN	LP	AFL 2 mg q4w	AFL 2 mg q8w	AFL 2 mg PRN	BRO 6 mg q12w/ q8w	RAN 0.5 mg q4w	RAN 0.5 mg PRN
1	[redacted]													
2	[redacted]													
3	[redacted]													
4	[redacted]													
5	[redacted]													
6	[redacted]													
7	[redacted]													
SUCRA	[redacted]													

Abbreviations: AFL, aflibercept; BCVA, best-corrected visual acuity; BRO, brolucizumab; LP, laser photocoagulation; PRN, pro re nata; qXw, every X weeks; RAN, ranibizumab; SUCRA, surface under the cumulative ranking curve.

c) ≥15 letter improvement in BCVA at 1 year

As with the analysis of ≥10 letter improvement in BCVA, in the company submission for this outcome (Company submission Appendix D) pairwise meta-analyses were conducted to compare the odds of gaining ≥15 letters per treatment. However, for the original NMA in the Company submission, the trial results were included in a BCVA categorical change model, which incorporated all available evidence for letter gain / letter loss categories for ≥5, ≥10 and ≥15 letters into a single outcome analysis. To allow for the impact of the exclusion of the KITE to be observed when responding to the clarification question, new NMA results for ≥15 letter improvement in BCVA are presented both including and excluding KITE. The model fit was very similar between models, with the fixed effects model having slightly smaller DIC, and total residual deviance almost identical between models (Table 9).

Table 9: A1 – Model fit statistics for ≥15 letter improvement in BCVA at 1 year (both BRO trials and excluding KITE)

	Model	DIC	pD	Totalresdev	Datapoints	SD (95% CrI)
KITE and KESTREL	Fixed effects	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Random effects	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Excluding KITE	Fixed effects	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Random effects	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BCVA, best corrected visual acuity; CrI, credible interval; DIC, deviance information criterion; N/A, not applicable; pD, posterior mean of the deviance; SD, standard deviation; Totalresdev, total residual deviance.

As with the results for the ordered categorical model, brolucizumab is favoured vs laser photocoagulation (both fixed and random effects models) with higher odds of experiencing ≥15 letter improvement (Table 10). For all remaining comparisons, licensed anti-VEGFs are similar in terms of ≥15 letter improvement from baseline in BCVA at 1 year follow-up (Table 11).

Table 10: A1 – ≥15 letter improvement in BCVA at 1 year, BRO 6 mg q12w/q8w vs comparator (both BRO trials and excluding KITE)

		KITE and KESTREL				Excluding KITE			
		Fixed effects		Random effects		Fixed effects		Random effects	
Intervention	Comparator	Median OR (95% CrI)	Mean OR (SD)	Median OR (95% CrI)	Mean OR (SD)	Median OR (95% CrI)	Mean OR (SD)	Median OR (95% CrI)	Mean OR (SD)
BRO 6 mg q12w/q8w	LP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BRO 6 mg q12w/q8w	AFL 2 mg q4w	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BRO 6 mg q12w/q8w	AFL 2 mg q8w	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BRO 6 mg q12w/q8w	AFL 2 mg PRN	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BRO 6 mg q12w/q8w	RAN 0.5 mg q4w	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BRO 6 mg q12w/q8w	RAN 0.5 mg PRN	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Font in bold and italics indicates one treatment is favoured over another.
Abbreviations: AFL, aflibercept; BCVA, best corrected visual acuity; BRO, brolucizumab; CrI, credible interval; LP, laser photocoagulation; OR, odds ratio; PRN, pro re nata; qXw, every X weeks; RAN, ranibizumab; SD, standard deviation.

Table 11: A1 – ≥15 letter improvement in BCVA at 1 year, treatment effect matrix (OR [95% CrI]) – fixed effects model (both BRO trials and excluding KITE)

	KITE and KESTREL							Excluding KITE						
Intervention /comparator	**LP**	**AFL 2 mg q4w**	**AFL 2 mg q8w**	**AFL 2 mg PRN**	**BRO 6 mg q12w/ q8w**	**RAN 0.5 mg q4w**	**RAN 0.5 mg PRN**	**LP**	**AFL 2 mg q4w**	**AFL 2 mg q8w**	**AFL 2 mg PRN**	**BRO 6 mg q12w/ q8w**	**RAN 0.5 mg q4w**	**RAN 0.5 mg PRN**
LP														
AFL 2 mg q4w														
AFL 2 mg q8w														
AFL 2 mg PRN														
BRO 6 mg q12w/q8w														
RAN 0.5 mg q4w														
RAN 0.5 mg PRN														

Font in bold and italics indicates one treatment is favoured over another.
Abbreviations: AFL, aflibercept; BCVA, best-corrected visual acuity; BRO, brolucizumab; CrI, credible interval; LP, laser photocoagulation; OR, odds ratio; PRN, pro re nata; qXw, every X weeks; RAN, ranibizumab.

Table 12: A1 – ≥15 letter improvement in BCVA at 1 year, SUCRA and ranking table – fixed effects model (both BRO trials and excluding KITE)

	KITE and KESTREL							Excluding KITE						
Ranks	LP	AFL 2 mg q4w	AFL 2 mg q8w	AFL 2 mg PRN	BRO 6 mg q12w/ q8w	RAN 0.5 mg q4w	RAN 0.5 mg PRN	LP	AFL 2 mg q4w	AFL 2 mg q8w	AFL 2 mg PRN	BRO 6 mg q12w/ q8w	RAN 0.5 mg q4w	RAN 0.5 mg PRN
1	[redacted]													
2	[redacted]													
3	[redacted]													
4	[redacted]													
5	[redacted]													
6	[redacted]													
7	[redacted]													
SUCRA	[redacted]													

Abbreviations: AFL, aflibercept; BCVA, best-corrected visual acuity; BRO, brolucizumab; LP, laser photocoagulation; PRN, pro re nata; qXw, every X weeks; RAN, ranibizumab; SUCRA, surface under the cumulative ranking curve.

d) discontinuations (all cause)

For this outcome, the results of the fixed effects model were considered the better fit compared with the random effects model, with a slightly smaller DIC value and total residual deviance slightly closer to the number of data points (Table 13).

Table 13: A1 – Model fit statistics for study discontinuation (all cause; no treatment pooling) (both BRO trials and excluding KITE)

	Model	DIC	pD	Totalresdev	Datapoints	SD (95% CrI)
KITE and KESTREL	Fixed effects	[redacted]				
	Random effects	[redacted]				
Excluding KITE	Fixed effects	[redacted]				
	Random effects	[redacted]				

†This cell has been updated as there was an error in Company submission Appendix D.
Abbreviations: CrI, credible interval; DIC, deviance information criterion; N/A, not applicable; pD, posterior mean of the deviance; SD, standard deviation; Totalresdev, total residual deviance.

Discontinuation across treatments was similar, with the exception of ranibizumab 0.5 mg q4w which showed fewer overall discontinuations when compared with all other treatments (Table 14 and Table 15). Excluding KITE made no difference to the overall conclusions, however the numerical values for the hazard ratios (HRs) did improve for brolucizumab. Although the fixed effect model may be preferred, the findings were consistent across fixed and random effects models.

Table 14: A1 – Study discontinuation (all cause; no treatment pooling), BRO 6 mg q12w/q8w vs comparator (both BRO trials and excluding KITE)

		KITE and KESTREL				Excluding KITE			
		Fixed effects		Random effects		Fixed effects		Random effects	
Intervention	Comparator	Median HR (95% CrI)	Mean (SD)	Median HR (95% CrI)	Mean (SD)	Median HR (95% CrI)	Mean HR (SD)	Median HR (95% CrI)	Mean HR (SD)
BRO 6 mg q12w/q8w	LP	[redacted]							
BRO 6 mg q12w/q8w	AFL 2 mg q4w								
BRO 6 mg q12w/q8w	AFL 2 mg q8w								
BRO 6 mg q12w/q8w	AFL 2 mg PRN								
BRO 6 mg q12w/q8w	RAN 0.5 mg q4w								
BRO 6 mg q12w/q8w	RAN 0.5 mg PRN								

Font in bold and italics indicates one treatment is favoured over another.
Abbreviations: AFL, aflibercept; BRO, brolucizumab; CrI, credible interval; HR, hazard ratio; LP, laser photocoagulation; PRN, pro re nata; qXw, every X weeks; RAN, ranibizumab; SD, standard deviation.

Table 15: A1 – Study discontinuation (all cause; no treatment pooling), treatment effect matrix (HR [95% CrI]) – fixed effects model (both BRO trials and excluding KITE)

Intervention /comparator	KITE and KESTREL							Excluding KITE						
	LP	AFL 2 mg q4w	AFL 2 mg q8w	AFL 2 mg PRN	BRO 6 mg q12w/ q8w	RAN 0.5 mg q4w	RAN 0.5 mg PRN	LP	AFL 2 mg q4w	AFL 2 mg q8w	AFL 2 mg PRN	BRO 6 mg q12w/ q8w	RAN 0.5 mg q4w	RAN 0.5 mg PRN
LP														
AFL 2 mg q4w														
AFL 2 mg q8w														
AFL 2 mg PRN														
BRO 6 mg q12w/q8w														
RAN 0.5 mg q4w														
RAN 0.5 mg PRN														

Font in bold and italics indicates one treatment is favoured over another.
Abbreviations: AFL, aflibercept; BRO, brolucizumab; CrI, credible interval; HR, hazard ratio; LP, laser photocoagulation; PRN, pro re nata; qXw, every X weeks; RAN, ranibizumab.

Table 16: A1 – Study discontinuation (all cause; no treatment pooling), SUCRA and ranking table – fixed effects model (both BRO trials and excluding KITE)

	KITE and KESTREL							Excluding KITE						
Ranks	LP	AFL 2 mg q4w	AFL 2 mg q8w	AFL 2 mg PRN	BRO 6 mg q12w/ q8w	RAN 0.5 mg q4w	RAN 0.5 mg PRN	LP	AFL 2 mg q4w	AFL 2 mg q8w	AFL 2 mg PRN	BRO 6 mg q12w/ q8w	RAN 0.5 mg q4w	RAN 0.5 mg PRN
1	[redacted]													
2	[redacted]													
3	[redacted]													
4	[redacted]													
5	[redacted]													
6	[redacted]													
7	[redacted]													
SUCRA	[redacted]													

Abbreviations: AFL, aflibercept; BRO, brolucizumab; LP, laser photocoagulation; PRN, pro re nata; qXw, every X weeks; RAN, ranibizumab; SUCRA, surface under the cumulative ranking curve.

A2. Priority question. As a scenario analysis, please conduct a NMA for the 'wider DMO population' excluding the KITE study and pooling results for each treatment in the network, regardless of treatment regimen, for the following outcomes:

For the outcomes presented in response to A2, results including KITE are also presented to demonstrate the impact of removing KITE on the analysis findings. Results including KITE for all-cause discontinuations are as per those presented in Company submission Appendix D; findings for other outcomes are newly reported in this response. As detailed in the response to question A1, Novartis do not agree with the exclusion of the KITE study from the analysis and consider its inclusion a conservative approach as the imbalance of baseline characteristics noted by the EAG may have introduced bias against brolucizumab.

a) change from baseline in BCVA at 1 year

The results for the random effects model were the better fit for both analyses (including and excluding KITE), with a slightly smaller DIC value compared with the fixed effect model and total residual deviance much closer to the number of data points (Table 17). This is consistent with the change from baseline BCVA analyses presented in the company submission without treatment pooling.

Table 17: A2 – Change from baseline in BCVA at 1 year (both BRO trials and excluding KITE; pooled by treatment)

	Model	DIC	pD	Totalresdev	Datapoints	SD (95% CrI)
KITE and KESTREL	Fixed effects	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Random effects	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Excluding KITE	Fixed effects	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Random effects	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BCVA, best corrected visual acuity; CrI, credible interval; DIC, deviance information criterion; N/A, not applicable; pD, posterior mean of the deviance; SD, standard deviation; Totalresdev, total residual deviance.

Licensed anti-VEGFs are mostly comparable in terms of 1-year change from baseline in BCVA (Table 18 and Table 19). Brolucizumab was favoured over laser photocoagulation and ranibizumab in gaining letters of BCVA over the course of one year of

follow-up when including both KESTREL and KITE studies. In the analysis excluding KITE, brolucizumab was again favoured over laser photocoagulation and ranked more highly than ranibizumab, with similar efficacy compared with aflibercept.

Table 18: A2 – Change from baseline in BCVA at 1 year, BRO vs comparator (both BRO trials and excluding KITE; pooled by treatment)

		KITE and KESTREL				Excluding KITE			
		Fixed effects		Random effects		Fixed effects		Random effects	
Intervention	Comparator	Median relative mean difference (95% CrI)	Mean relative difference (SD)	Median relative mean difference (95% CrI)	Mean relative difference (SD)	Median relative mean difference (95% CrI)	Mean relative difference (SD)	Median relative mean difference (95% CrI)	Mean relative difference (SD)
BRO	LP	[redacted]							
BRO	AFL	[redacted]							
BRO	RAN	[redacted]							

Font in bold and italics indicates one treatment is favoured over another.
Abbreviations: AFL, aflibercept; BCVA, best corrected visual acuity; BRO, brolucizumab; CrI, credible interval; LP, laser photocoagulation; RAN, ranibizumab; SD, standard deviation.

Table 19: A2 – Change from baseline in BCVA at 1 year, treatment effect matrix (relative mean difference [95% CrI]) – random effects model (both BRO trials and excluding KITE; pooled by treatment)

Intervention/ comparator	KITE and KESTREL				Excluding KITE			
	LP	AFL	BRO	RAN	LP	AFL	BRO	RAN
LP	[redacted]							
AFL	[redacted]							
BRO	[redacted]							
RAN	[redacted]							

Font in bold and italics indicates one treatment is favoured over another.
Abbreviations: AFL, aflibercept; BCVA, best-corrected visual acuity; BRO, brolucizumab; CrI, credible interval; LP, laser photocoagulation; RAN, ranibizumab.

Table 20: A2 – Change from baseline in BCVA at 1 year, SUCRA and ranking table – random effects model (both BRO trials and excluding KITE; pooled by treatment)

Ranks	KITE and KESTREL				Excluding KITE			
	LP	AFL	BRO	RAN	LP	AFL	BRO	RAN
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SUCRA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AFL, aflibercept; BCVA, best-corrected visual acuity; BRO, brolucizumab; LP, laser photocoagulation; RAN, ranibizumab; SUCRA, surface under the cumulative ranking curve.

b) ≥10 letter improvement in BCVA at 1 year

The results for the random effects model were the better fit for this outcome as the DIC was very similar between fixed and random effects models, however total residual deviance was better for the random effects model (Table 21).

Table 21: A2 – ≥10 letter improvement in BCVA at 1 year (both BRO trials and excluding KITE; pooled by treatment)

	Model	DIC	pD	Totalresdev	Datapoints	SD (95% CrI)
KITE and KESTREL	Fixed effects	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Random effects	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Excluding KITE	Fixed effects	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Random effects	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BCVA, best corrected visual acuity; CrI, credible interval; DIC, deviance information criterion; N/A, not applicable; pD, posterior mean of the deviance; SD, standard deviation; Totalresdev, total residual deviance.

As with the results for clarification question A1, brolucizumab is favoured vs laser photocoagulation (both fixed and random effects models) with higher odds of experiencing ≥10 letter improvement when KITE is included and when it is excluded from the analysis (Table 22). For all remaining comparisons, licensed anti-VEGFs are similar in terms of ≥10 letter improvement from baseline in BCVA at 1 year follow-up when including and excluding KITE (Table 23).

Table 22: A2 – ≥10 letter improvement in BCVA at 1 year, BRO vs comparator (both BRO trials and excluding KITE; pooled by treatment)

		KITE and KESTREL				Excluding KITE			
		Fixed effects		Random effects		Fixed effects		Random effects	
Intervention	Comparator	Median OR (95% CrI)	Mean OR (SD)	Median OR (95% CrI)	Mean OR (SD)	Median OR (95% CrI)	Mean OR (SD)	Median OR (95% CrI)	Mean OR (SD)
BRO	LP	[redacted]							
BRO	AFL	[redacted]							
BRO	RAN	[redacted]							

Font in bold and italics indicates one treatment is favoured over another.
Abbreviations: AFL, aflibercept; BCVA, best corrected visual acuity; BRO, brolucizumab; CrI, credible interval; LP, laser photocoagulation; OR< odds ratio; RAN, ranibizumab; SD, standard deviation.

Table 23: A2 – ≥10 letter improvement in BCVA at 1 year, treatment effect matrix (OR [95% CrI]) – random effects model (both BRO trials and excluding KITE; pooled by treatment)

Intervention/ comparator	KITE and KESTREL				Excluding KITE			
	LP	AFL	BRO	RAN	LP	AFL	BRO	RAN
LP	[redacted]							
AFL	[redacted]							
BRO	[redacted]							
RAN	[redacted]							

Font in bold and italics indicates one treatment is favoured over another.
Abbreviations: AFL, aflibercept; BCVA, best-corrected visual acuity; BRO, brolucizumab; CrI, credible interval; LP, laser photocoagulation; OR, odds ratio; RAN, ranibizumab.

Table 24: A2 – ≥10 letter improvement in BCVA at 1 year, SUCRA and ranking table – random effects model (both BRO trials and excluding KITE; pooled by treatment)

Ranks	KITE and KESTREL				Excluding KITE			
	LP	AFL	BRO	RAN	LP	AFL	BRO	RAN
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SUCRA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AFL, aflibercept; BCVA, best-corrected visual acuity; BRO, brolucizumab; LP, laser photocoagulation; RAN, ranibizumab; SUCRA, surface under the cumulative ranking curve.

c) ≥15 letter improvement in BCVA at 1 year

The results for the fixed effects model were the better fit for this outcome as the DIC was slightly smaller and total residual deviance was closer to the number of data points for the fixed effects model (Table 25).

Table 25: A2 – ≥15 letter improvement in BCVA at 1 year (both BRO trials and excluding KITE; pooled by treatment)

	Model	DIC	pD	Totalresdev	Datapoints	SD (95% CrI)
KITE and KESTREL	Fixed effects	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Random effects	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Excluding KITE	Fixed effects	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Random effects	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BCVA, best corrected visual acuity; CrI, credible interval; DIC, deviance information criterion; N/A, not applicable; pD, posterior mean of the deviance; SD, standard deviation; Totalresdev, total residual deviance.

As with the results for the ordered categorical model, brolucizumab is favoured vs laser photocoagulation (both fixed and random effects models) with higher odds of experiencing ≥15 letter improvement (Table 26). For all remaining comparisons, licensed anti-VEGFs are similar in terms of ≥15 letter improvement from baseline in BCVA at 1 year follow-up when including or excluding KITE from the analyses (Table 27).

Table 26: A2 – ≥15 letter improvement in BCVA at 1 year, BRO vs comparator (both BRO trials and excluding KITE; pooled by treatment)

		KITE and KESTREL				Excluding KITE			
		Fixed effects		Random effects		Fixed effects		Random effects	
Intervention	Comparator	Median OR (95% CrI)	Mean OR (SD)	Median OR (95% CrI)	Mean OR (SD)	Median OR (95% CrI)	Mean OR (SD)	Median OR (95% CrI)	Mean OR (SD)
BRO	LP	[redacted]							
BRO	AFL	[redacted]							
BRO	RAN	[redacted]							

Font in bold and italics indicates one treatment is favoured over another.
Abbreviations: AFL, aflibercept; BCVA, best corrected visual acuity; BRO, brolucizumab; CrI, credible interval; LP, laser photocoagulation; OR, odds ratio; RAN, ranibizumab; SD, standard deviation.

Table 27: A2 – ≥15 letter improvement in BCVA at 1 year, treatment effect matrix (OR [95% CrI]) – fixed effects model (both BRO trials and excluding KITE; pooled by treatment)

Intervention/ comparator	KITE and KESTREL				Excluding KITE			
	LP	AFL	BRO	RAN	LP	AFL	BRO	RAN
LP	[redacted]							
AFL	[redacted]							
BRO	[redacted]							
RAN	[redacted]							

Font in bold and italics indicates one treatment is favoured over another.
Abbreviations: AFL, aflibercept; BCVA, best-corrected visual acuity; BRO, brolucizumab; CrI, credible interval; LP, laser photocoagulation; OR, odds ratio; RAN, ranibizumab.

Table 28: A2 – ≥15 letter improvement in BCVA at 1 year, SUCRA and ranking table – fixed effects model (both BRO trials and excluding KITE; pooled by treatment)

Ranks	KITE and KESTREL				Excluding KITE			
	LP	AFL	BRO	RAN	LP	AFL	BRO	RAN
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SUCRA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AFL, aflibercept; BCVA, best-corrected visual acuity; BRO, brolucizumab; LP, laser photocoagulation; RAN, ranibizumab; SUCRA, surface under the cumulative ranking curve.

d) discontinuations (all cause)

For this outcome, the results of the fixed effects model were considered the better fit compared with the random effects model, with a smaller DIC value and total residual deviance slightly closer to the number of data points (Table 29).

Table 29: A2 – Model fit statistics for study discontinuation (all cause; pooled by treatment) (both BRO trials and excluding KITE)

	Model	DIC	pD	Totalresdev	Datapoints	SD (95% CrI)
KITE and KESTREL	Fixed effects	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Random effects	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Excluding KITE	Fixed effects	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Random effects	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

†This cell has been updated as there was an error in Company submission Appendix D.
Abbreviations: CrI, credible interval; DIC, deviance information criterion; N/A, not applicable; pD, posterior mean of the deviance; SD, standard deviation; Totalresdev, total residual deviance.

Discontinuation across treatments was similar, with the exception of ranibizumab 0.5 mg q4w which showed fewer overall discontinuations when compared with all other treatments in the analysis including KITE (Table 30 and Table 31). When KITE was excluded from the analysis, ranibizumab was no longer favoured over brolucizumab, with both treatments showing similar hazard rate for discontinuation due to all causes.

Table 30: A2 – Study discontinuation (all cause; pooled by treatment), BRO vs comparator (both BRO trials and excluding KITE)

		KITE and KESTREL				Excluding KITE			
		Fixed effects		Random effects		Fixed effects		Random effects	
Intervention	Comparator	Median HR (95% CrI)	Mean (SD)	Median HR (95% CrI)	Mean (SD)	Median HR (95% CrI)	Mean HR (SD)	Median HR (95% CrI)	Mean HR (SD)
BRO	LP	[redacted]							
BRO	AFL	[redacted]							
BRO	RAN	[redacted]							

Font in bold and italics indicates one treatment is favoured over another.
Abbreviations: AFL, aflibercept; BRO, brolucizumab; CrI, credible interval; HR, hazard ratio; LP, laser photocoagulation; RAN, ranibizumab; SD, standard deviation.

Table 31: A2 – Study discontinuation (all cause; pooled by treatment), treatment effect matrix (HR [95% CrI]) – fixed effects model (both BRO trials and excluding KITE)

	KITE and KESTREL				Excluding KITE			
Intervention/ comparator	LP	AFL	BRO	RAN	LP	AFL	BRO	RAN
LP	[redacted]							
AFL	[redacted]							
BRO	[redacted]							
RAN	[redacted]							

Font in bold and italics indicates one treatment is favoured over another.
Abbreviations: AFL, aflibercept; BRO, brolucizumab; CrI, credible interval; LP, laser photocoagulation; RAN, ranibizumab.

Table 32: A2 – Study discontinuation (all cause; pooled by treatment), SUCRA and ranking table – fixed effects model (both BRO trials), random effects model (excluding KITE)

	KITE and KESTREL				Excluding KITE			
Ranks	**LP**	**AFL**	**BRO**	**RAN**	**LP**	**AFL**	**BRO**	**RAN**
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SUCRA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AFL, aflibercept; BRO, brolucizumab; LP, laser photocoagulation; RAN, ranibizumab; SUCRA, surface under the cumulative ranking curve.

A3. Priority question. As a scenario analysis, please conduct a NMA including only the following treatment regimens: aflibercept 2 mg Q8W, brolucizumab 6mg Q6W, ranibizumab 0.5 mg Q4W and laser photocoagulation (+/- placebo/sham). Please exclude the KITE study from the network and provide results for the following outcomes:

For the outcomes presented in response to A3, NMA results including KITE are also presented to demonstrate the impact of removing KITE on the findings. Results for all outcomes in this section are newly reported as part of the clarification question response.

Of note, question A3 asks for brolucizumab 6mg q6w which is not in line with the company submission. Novartis assumed that the EAG meant the same regimen that is presented in the company submission. As noted in the response to question A1, the labelling for brolucizumab in the NMA results is based on the maintenance phase. This label has been updated in the response document to q12w/q8w to represent the same treatment group as was previously defined as q8w in the Company submission Appendix D. This change is to clarify that all patients from KESTREL and KITE were included in the main NMA analyses.

a) change from baseline in BCVA at 1 year

As with all the alternative scenarios presented for this outcome, the results for the random effects model were the better fit when including KITE in the NMA, with very similar DIC value compared with the fixed effect model and total residual deviance much closer to the number of data points (Table 33). However, in the NMA excluding KITE, there was nothing to chose between the models and so for consistency and to enable comparison with the other scenarios, the random effects are presented for this analysis too.

Table 33: A3 – Model fit statistics for change from baseline in BCVA at 1 year (both BRO trials and excluding KITE)

	Model	DIC	pD	Totalresdev	Datapoints	SD (95% CrI)
KITE and KESTREL	Fixed effects	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Random effects	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Excluding KITE	Fixed effects	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Random effects	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BCVA, best corrected visual acuity; CrI, credible interval; DIC, deviance information criterion; N/A, not applicable; pD, posterior mean of the deviance; SD, standard deviation; Totalresdev, total residual deviance.

For change from baseline in BCVA, licensed anti-VEGFs are mostly comparable in terms of 1-year change from baseline in BCVA (Table 34 and Table 35). The conclusions of the analysis were identical when including or excluding KITE, although the actual numerical values are slightly different for the comparisons with brolucizumab. Brolucizumab was favoured over laser coagulation in gaining letters of BCVA over the course of one year of follow-up and ranked more highly than ranibizumab 0.5 mg q4w. In summary, the exclusion of KITE results in no change to the conclusion of similar treatment effect for brolucizumab versus aflibercept.

Table 34: A3 – Change from baseline in BCVA at 1 year, BRO 6 mg q12w/q8w vs comparator (both BRO trials and excluding KITE)

		KITE and KESTREL				Excluding KITE			
		Fixed effects		Random effects		Fixed effects		Random effects	
Intervention	Comparator	Median relative mean difference (95% CrI)	Mean relative difference (SD)	Median relative mean difference (95% CrI)	Mean relative difference (SD)	Median relative mean difference (95% CrI)	Mean relative difference (SD)	Median relative mean difference (95% CrI)	Mean relative difference (SD)
BRO 6 mg q12w/q8w	LP	[redacted]							
BRO 6 mg q12w/q8w	AFL 2 mg q8w	[redacted]							
BRO 6 mg q12w/q8w	RAN 0.5 mg q4w	[redacted]							

Font in bold and italics indicates one treatment is favoured over another.
Abbreviations: AFL, aflibercept; BCVA, best corrected visual acuity; BRO, brolucizumab; CrI, credible interval; LP, laser photocoagulation; PRN, pro re nata; qXw, every X weeks; RAN, ranibizumab; SD, standard deviation.

Table 35: A3 – Change from baseline in BCVA at 1 year, treatment effect matrix (relative mean difference [95% CrI]) – random effects model (both BRO trials and excluding KITE)

	KITE and KESTREL				Excluding KITE			
Intervention/ comparator	LP	AFL 2 mg q8w	BRO 6 mg q12w/q8w	RAN 0.5 mg q4w	LP	AFL 2 mg q8w	BRO 6 mg q12w/q8w	RAN 0.5 mg q4w
LP		[redacted]						
AFL 2 mg q8w								
BRO 6 mg q12w/q8w								
RAN 0.5 mg q4w								

Font in bold and italics indicates one treatment is favoured over another.
Abbreviations: AFL, aflibercept; BCVA, best-corrected visual acuity; BRO, brolucizumab; CrI, credible interval; LP, laser photocoagulation; PRN, pro re nata; qXw, every X weeks; RAN, ranibizumab.

Table 36: A3 – Change from baseline in BCVA at 1 year, SUCRA and ranking table – random effects model (both BRO trials and excluding KITE)

Ranks	KITE and KESTREL				Excluding KITE			
	LP	AFL 2 mg q8w	BRO 6 mg q12w/q8w	RAN 0.5 mg q4w	LP	AFL 2 mg q8w	BRO 6 mg q12w/q8w	RAN 0.5 mg q4w
1	[redacted]							
2	[redacted]							
3	[redacted]							
4	[redacted]							
SUCRA	[redacted]							

Abbreviations: AFL, aflibercept; BCVA, best-corrected visual acuity; BRO, brolucizumab; LP, laser photocoagulation; PRN, pro re nata; qXw, every X weeks; RAN, ranibizumab; SUCRA, surface under the cumulative ranking curve.

b) ≥10 letter improvement in BCVA at 1 year

For the NMA, the random effects model appeared to have a better fit as the total residual deviance was closer to the number of data points (Table 37), however the model did not converge well for all treatment comparisons, with very large values for mean odds ratio (sitting outside the 95% credible interval) and large associated standard deviation. This was true for analyses both including and excluding the KITE study. Therefore, only the findings for the fixed effect model are presented.

Table 37: A3 – Model fit statistics for ≥10 letter improvement in BCVA at 1 year (both BRO trials and excluding KITE)

	Model	DIC	pD	Totalresdev	Datapoints	SD (95% CrI)
KITE and KESTREL	Fixed effects	[redacted]				
	Random effects	[redacted]				
Excluding KITE	Fixed effects	[redacted]				
	Random effects	[redacted]				

Abbreviations: BCVA, best corrected visual acuity; CrI, credible interval; DIC, deviance information criterion; N/A, not applicable; pD, posterior mean of the deviance; SD, standard deviation; Totalresdev, total residual deviance.

As with all alternative scenario results for this outcome, brolucizumab is favoured vs laser photocoagulation with higher odds of experiencing ≥10 letter improvement (Table 38). For all remaining comparisons, licensed anti-VEGFs are similar in terms of ≥10 letter improvement from baseline in BCVA at 1 year follow-up when including or excluding KITE from the analyses (Table 39).

Table 38: A3 – ≥10 letter improvement in BCVA at 1 year, BRO 6 mg q12w/q8w vs comparator (both BRO trials and excluding KITE)

		KITE and KESTREL		Excluding KITE	
		Fixed effects		Fixed effects	
Intervention	Comparator	Median OR (95% CrI)	Mean OR (SD)	Median OR (95% CrI)	Mean OR (SD)
BRO 6 mg q12w/q8w	LP	[redacted]	[redacted]	[redacted]	[redacted]
BRO 6 mg q12w/q8w	AFL 2 mg q8w	[redacted]	[redacted]	[redacted]	[redacted]
BRO 6 mg q12w/q8w	RAN 0.5 mg q4w	[redacted]	[redacted]	[redacted]	[redacted]

Font in bold and italics indicates one treatment is favoured over another.
Abbreviations: AFL, aflibercept; BCVA, best corrected visual acuity; BRO, brolucizumab; CrI, credible interval; LP, laser photocoagulation; OR, odds ratio; PRN, pro re nata; qXw, every X weeks; RAN, ranibizumab; SD, standard deviation.

Table 39: A3 – ≥10 letter improvement in BCVA at 1 year, treatment effect matrix (OR [95% CrI]) – fixed effects model (both BRO trials and excluding KITE)

	KITE and KESTREL				Excluding KITE			
Intervention/ comparator	LP	AFL 2 mg q8w	BRO 6 mg q12w/q8w	RAN 0.5 mg q4w	LP	AFL 2 mg q8w	BRO 6 mg q12w/q8w	RAN 0.5 mg q4w
LP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AFL 2 mg q8w	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BRO 6 mg q12w/q8w	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RAN 0.5 mg q4w	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Font in bold and italics indicates one treatment is favoured over another.
Abbreviations: AFL, aflibercept; BCVA, best-corrected visual acuity; BRO, brolucizumab; CrI, credible interval; LP, laser photocoagulation; OR, odds ratio; PRN, pro re nata; qXw, every X weeks; RAN, ranibizumab.

Table 40: A3 – ≥10 letter improvement in BCVA at 1 year, SUCRA and ranking table – fixed effects model (both BRO trials and excluding KITE)

Ranks	KITE and KESTREL				Excluding KITE			
	LP	AFL 2 mg q8w	BRO 6 mg q12w/q8w	RAN 0.5 mg q4w	LP	AFL 2 mg q8w	BRO 6 mg q12w/q8w	RAN 0.5 mg q4w
1	[redacted]							
2	[redacted]							
3	[redacted]							
4	[redacted]							
SUCRA	[redacted]							

Abbreviations: AFL, aflibercept; BCVA, best-corrected visual acuity; BRO, brolucizumab; LP, laser photocoagulation; PRN, pro re nata; qXw, every X weeks; RAN, ranibizumab; SUCRA, surface under the cumulative ranking curve.

c) ≥15 letter improvement in BCVA at 1 year

Similar to the analysis of ≥10 letter improvement in BCVA at 1 year, the random effects model appeared to have a better fit to the data for ≥15 letter improvement as the total residual deviance was closer to the number of data points (Table 41). However, the model did not converge well for all treatment comparisons, with very large values for mean odds ratio (sitting outside the 95% credible interval [CrI]) and large associated standard deviation. This was true for analyses both including and excluding the KITE study. Therefore, only the findings for the fixed effect model are presented.

Table 41: A3 – Model fit statistics for ≥15 letter improvement in BCVA at 1 year (both BRO trials and excluding KITE)

	Model	DIC	pD	Totalresdev	Datapoints	SD (95% CrI)
KITE and KESTREL	Fixed effects	[redacted]				
	Random effects	[redacted]				
Excluding KITE	Fixed effects	[redacted]				
	Random effects	[redacted]				

Abbreviations: BCVA, best corrected visual acuity; CrI, credible interval; DIC, deviance information criterion; N/A, not applicable; pD, posterior mean of the deviance; SD, standard deviation; Totalresdev, total residual deviance.

As with all alternative scenario results for this outcome, brolucizumab is favoured vs laser photocoagulation with higher odds of experiencing ≥15 letter improvement (Table 42). For all remaining comparisons, licensed anti-VEGFs are similar in terms of ≥15 letter improvement from baseline in BCVA at 1 year follow-up when including or excluding KITE from the analyses (Table 43).

Table 42: A3 – ≥15 letter improvement in BCVA at 1 year, BRO 6 mg q12w/q8w vs comparator (both BRO trials and excluding KITE)

		KITE and KESTREL		Excluding KITE	
		Fixed effects		Fixed effects	
Intervention	Comparator	Median OR (95% CrI)	Mean OR (SD)	Median OR (95% CrI)	Mean OR (SD)
BRO 6 mg q12w/q8w	LP	[redacted]	[redacted]	[redacted]	[redacted]
BRO 6 mg q12w/q8w	AFL 2 mg q8w	[redacted]	[redacted]	[redacted]	[redacted]
BRO 6 mg q12w/q8w	RAN 0.5 mg q4w	[redacted]	[redacted]	[redacted]	[redacted]

Font in bold and italics indicates one treatment is favoured over another.
Abbreviations: AFL, aflibercept; BCVA, best corrected visual acuity; BRO, brolucizumab; CrI, credible interval; LP, laser photocoagulation; OR, odds ratio; PRN, pro re nata; qXw, every X weeks; RAN, ranibizumab; SD, standard deviation.

Table 43: A3 – ≥15 letter improvement in BCVA at 1 year, treatment effect matrix (OR [95% CrI]) – fixed effects model (both BRO trials and excluding KITE)

	KITE and KESTREL				Excluding KITE			
Intervention/ comparator	LP	AFL 2 mg q8w	BRO 6 mg q12w/q8w	RAN 0.5 mg q4w	LP	AFL 2 mg q8w	BRO 6 mg q12w/q8w	RAN 0.5 mg q4w
LP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AFL 2 mg q8w	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BRO 6 mg q12w/q8w	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RAN 0.5 mg q4w	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Font in bold and italics indicates one treatment is favoured over another.
Abbreviations: AFL, aflibercept; BCVA, best-corrected visual acuity; BRO, brolucizumab; CrI, credible interval; LP, laser photocoagulation; OR, odds ratio; PRN, pro re nata; qXw, every X weeks; RAN, ranibizumab.

Table 44: A3 – ≥15 letter improvement in BCVA at 1 year, SUCRA and ranking table – fixed effects model (both BRO trials and excluding KITE)

Ranks	KITE and KESTREL				Excluding KITE			
	LP	AFL 2 mg q8w	BRO 6 mg q12w/q8w	RAN 0.5 mg q4w	LP	AFL 2 mg q8w	BRO 6 mg q12w/q8w	RAN 0.5 mg q4w
1	[redacted]							
2	[redacted]							
3	[redacted]							
4	[redacted]							
SUCRA	[redacted]							

Abbreviations: AFL, aflibercept; BCVA, best-corrected visual acuity; BRO, brolucizumab; LP, laser photocoagulation; PRN, pro re nata; qXw, every X weeks; RAN, ranibizumab; SUCRA, surface under the cumulative ranking curve.

d) discontinuations (all cause)

The model fit for both fixed and random effects models were similar (Table 45), however, the random effects model did not converge well for all treatment comparisons, with very large values for mean hazard ratio (sitting outside the 95% CrI) and large associated standard deviation. This was true for analyses both including and excluding the KITE study; therefore, only the findings for the fixed effect model are presented.

Table 45: A3 – Model fit statistics for study discontinuation (all cause; no treatment pooling) (both BRO trials and excluding KITE)

	Model	DIC	pD	Totalresdev	Datapoints	SD (95% CrI)
KITE and KESTREL	Fixed effects	[redacted]				
	Random effects					
Excluding KITE	Fixed effects					
	Random effects					

Abbreviations: CrI, credible interval; DIC, deviance information criterion; N/A, not applicable; pD, posterior mean of the deviance; SD, standard deviation; Totalresdev, total residual deviance.

Discontinuation across treatments was similar, with the exception of ranibizumab 0.5 mg q4w which showed fewer overall discontinuations when compared with all other treatments (Table 46 and Table 47).

Table 46: A3 – Study discontinuation (all cause; no treatment pooling), BRO 6 mg q12w/q8w vs comparator (both BRO trials and excluding KITE)

Intervention	Comparator	KITE and KESTREL		Excluding KITE	
		Fixed effects		Fixed effects	
		Median HR (95% CrI)	Mean HR (SD)	Median HR (95% CrI)	Mean HR (SD)
BRO 6 mg q12w/q8w	LP	[redacted]	[redacted]	[redacted]	[redacted]
BRO 6 mg q12w/q8w	AFL 2 mg q8w	[redacted]	[redacted]	[redacted]	[redacted]
BRO 6 mg q12w/q8w	RAN 0.5 mg q4w	[redacted]	[redacted]	[redacted]	[redacted]

Font in bold and italics indicates one treatment is favoured over another.
Abbreviations: AFL, aflibercept; BRO, brolucizumab; CrI, credible interval; HR, hazard ratio; LP, laser photocoagulation; PRN, pro re nata; qXw, every X weeks; RAN, ranibizumab; SD, standard deviation.

Table 47: A3 – Study discontinuation (all cause; no treatment pooling), treatment effect matrix (HR [95% CrI]) – fixed effects model (both BRO trials and excluding KITE)

Intervention/ comparator	KITE and KESTREL				Excluding KITE			
	LP	AFL 2 mg q8w	BRO 6 mg q12w/q8w	RAN 0.5 mg q4w	LP	AFL 2 mg q8w	BRO 6 mg q12w/q8w	RAN 0.5 mg q4w
LP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AFL 2 mg q8w	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BRO 6 mg q12w/q8w	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RAN 0.5 mg q4w	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Font in bold and italics indicates one treatment is favoured over another.
Abbreviations: AFL, aflibercept; BRO, brolucizumab; CrI, credible interval; HR, hazard ratio; LP, laser photocoagulation; PRN, pro re nata; qXw, every X weeks; RAN, ranibizumab.

Table 48: A3 – Study discontinuation (all cause; no treatment pooling), SUCRA and ranking table – fixed effects model (both BRO trials and excluding KITE)

Ranks	KITE and KESTREL				Excluding KITE			
	LP	AFL 2 mg q8w	BRO 6 mg q12w/q8w	RAN 0.5 mg q4w	LP	AFL 2 mg q8w	BRO 6 mg q12w/q8w	RAN 0.5 mg q4w
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SUCRA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BRO, brolucizumab; LP, laser photocoagulation; PRN, pro re nata; qXw, every X weeks; RAN, ranibizumab; SUCRA, surface under the cumulative ranking curve.

A4. Priority question. Please conduct an indirect treatment comparison for the subgroup of patients with baseline central subfield foveal thickness ≥400 µm excluding the KITE study for the following outcomes:

a) **change from baseline in BCVA at 52 weeks;**

b) **change from baseline in BCVA at 100/104 weeks;**

c) **≥10 letter improvement in BCVA at 52 weeks;**

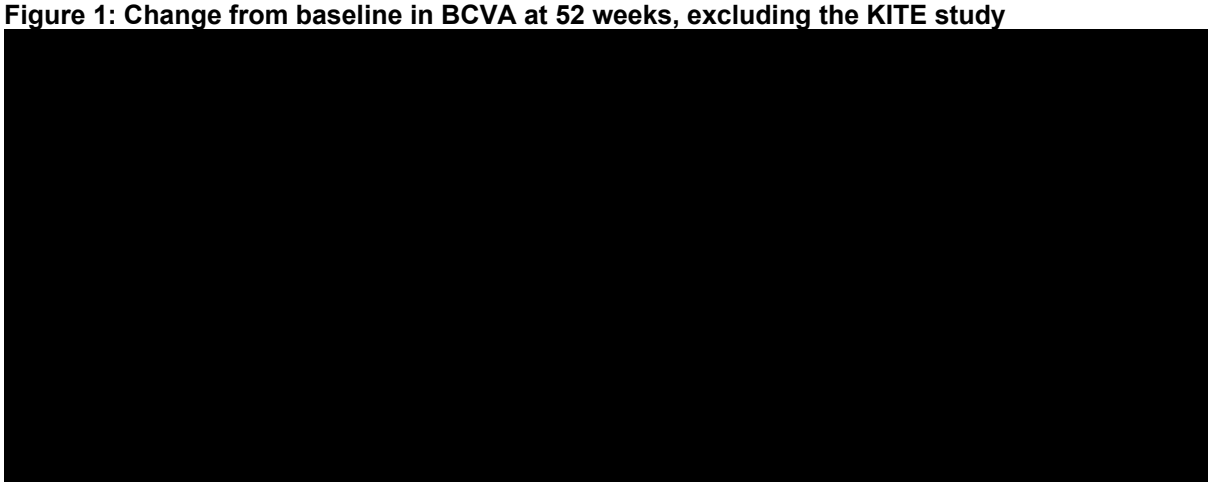
d) **≥15 letter improvement in BCVA at 52 weeks; and**

e) **discontinuations (all cause).**

The results of the indirect treatment comparisons for the subgroup of patients with baseline central retinal thickness (CRT) ≥400 µm excluding the KITE study for change from baseline in BCVA at 52 weeks, and at 100/104 weeks are presented in Figure 1 and Figure 2, respectively.

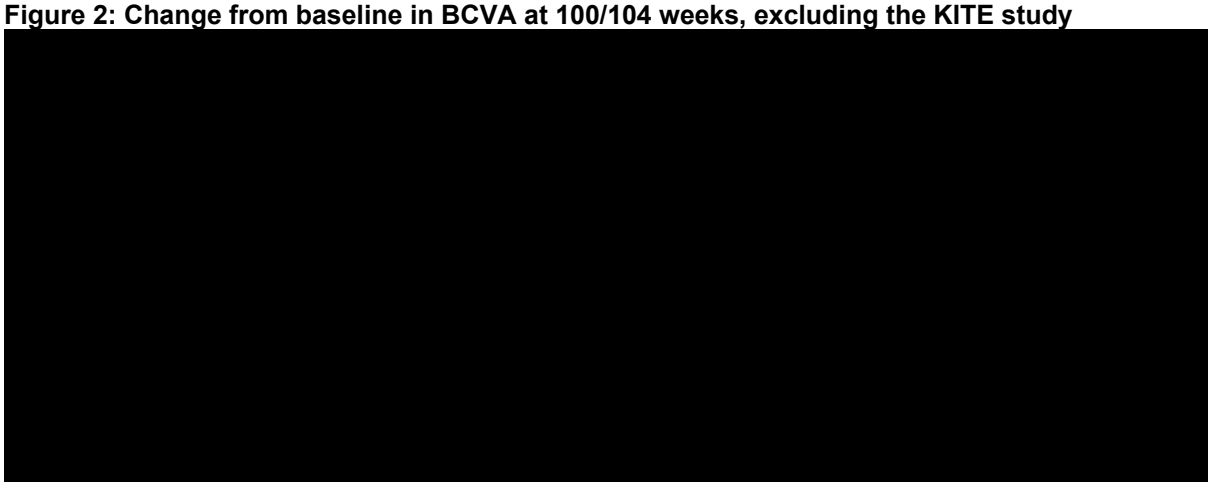
The outcomes ≥10 letter, and ≥15 letter improvement in BCVA at 52 weeks, and discontinuations (all cause) cannot be provided, as data for the subgroup of patients with baseline CRT ≥400 µm were not identified by the company systematic literature review for extraction (Company submission Appendix D).

Figure 1: Change from baseline in BCVA at 52 weeks, excluding the KITE study



Abbreviations: AFL, aflibercept; BCVA, best-corrected visual acuity; BEO, brolucizumab; CI, confidence interval; MD, mean difference; RAN, ranibizumab.

Figure 2: Change from baseline in BCVA at 100/104 weeks, excluding the KITE study



Abbreviations: AFL, aflibercept; BCVA, best-corrected visual acuity; BEO, brolucizumab; CI, confidence interval; MD, mean difference; RAN, ranibizumab.

A5. Please provide an assessment of formal assessment of consistency for each of the NMAs presented in the company submission, the company submission appendices (for example, by assessing loop inconsistency (12) or by using a design-by-treatment interaction model (13)), and those requested in questions A1 to A4 above.

As there was only a single loop of independent studies in the network diagram in the original submission, consistency was evaluated using the simple Bucher method, as described by Dias et al, 2014 (14). This approach requires separate synthesis of the evidence in each pair-wise contrast and then a test of whether direct and indirect evidence are consistent.

The only outcome in the company submission appendices for which a calculation of consistency was required was change in BCVA at 1-year of follow-up. No other outcome had a loop of independent studies. The loop of evidence included three treatment nodes: laser photocoagulation; ranibizumab 0.5 mg pro re nata (PRN) and aflibercept 2 mg PRN. As the KESTREL and KITE studies do not form part of the loop, the findings are identical when including or excluding KITE. The results of the treatment comparisons for the relevant loop on the natural scale are reported in Table 49.

Table 49: Pairwise estimates of weighted mean difference and associated standard error

Direct comparison	WMD, change from baseline BCVA	SE of WMD
RAN 0.5 mg PRN vs AFL 2 mg PRN (1 study)	0.40	1.908
AFL 2 mg PRN vs LP (1 study)	13.3	3.536
RAN 0.5 mg PRN vs LP (5 studies)	6.02	0.694

Abbreviations: AFL, aflibercept; LP, laser photocoagulation; PRN, pro re nata; RAN, ranibizumab; SE, standard error; WMD, weighted mean difference.

Comparing the indirect and direct estimates of ranibizumab 0.5mg PRN vs laser photocoagulation, the inconsistency estimate, ω, is –7.68 with variance 17.09, leading to a z-statistic value of –1.858 indicating there is evidence of inconsistency ($p<0.05$). From the assessment of heterogeneity in the pairwise meta-analysis of studies directly comparing ranibizumab 0.5 mg PRN vs laser photocoagulation (Company submission Appendix D) all five studies demonstrated similar findings ($I^2 = 0\%$). For each of the remaining sides of the loop, there is only one study informing the treatment comparison, making it difficult to ascertain which comparison may be the outlier from the raw data. However, from the NMA residual deviance output by study, neither the Chatzirallis 2020 study (ranibizumab 0.5 mg PRN vs aflibercept 2 mg PRN) nor DA VINCI study (aflibercept 2 mg PRN vs laser photocoagulation) are a particularly good fit.

Comparing BCVA at baseline, these two studies enrolled patients with slightly lower mean BCVA compared with the five studies informing the direct comparison of ranibizumab 0.5 mg PRN vs laser photocoagulation (<60 vs. >60 ETDRS letters, respectively, for all studies except REFINE). Mean BCVA was particularly high in Lucidate and there was a small imbalance between the arms, however this is likely due to the small sample size in that study. Baseline BCVA ETDRS letters across studies are presented in Table 50.

Table 50: Mean BCVA (ETDRS letters) at baseline for studies in the network loop

Study	Treatment arm	Number of eyes	Mean BVCA (ETDRS letters), SD
Chatzirallis 2020 (15)	RAN 0.5 mg PRN	54	56.3 (6.2)
	AFL 2 mg PRN	58	58.9 (9.3)
DA VINCI (16, 17)	AFL 2 mg PRN	45	59.6 (11.1)
	LP	44	57.6 (12.5)
Lucidate (18-20)	RAN 0.5 mg PRN	22	70.4 (4.9)
	LP	11	63.8 (5.7)
Re-Des (21)	RAN 0.5 mg PRN	40	NR
	LP	43	NR

REFINE (22)	RAN 0.5 mg PRN	307	59.6 (10.53)
	LP	77	58.2 (9.43)
RESPOND (23, 24)	RAN 0.5 mg PRN	75	63.1 (10.6)
	LP	72	61.9 (10.6)
RESTORE (25)	RAN 0.5 mg PRN	115	64.8 (10.11)
	LP	110	62.4 (11.11)

Abbreviations: AFL, aflibercept; BCVA, best corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; LP, laser photocoagulation; PRN, pro re nata; RAN, ranibizumab; SD, standard deviation

An analysis to exclude either Chatzirallis 2020 or DA VINCI will not show meaningful resolution of the inconsistency as the loop would then be broken.

Note that the consistency calculation is identical for change from baseline in BCVA at 1 year for clarification question A1, as removing KITE from the analysis has no impact on the network loop. For clarification questions A2 and A3, there are no loops to assess for any outcome.

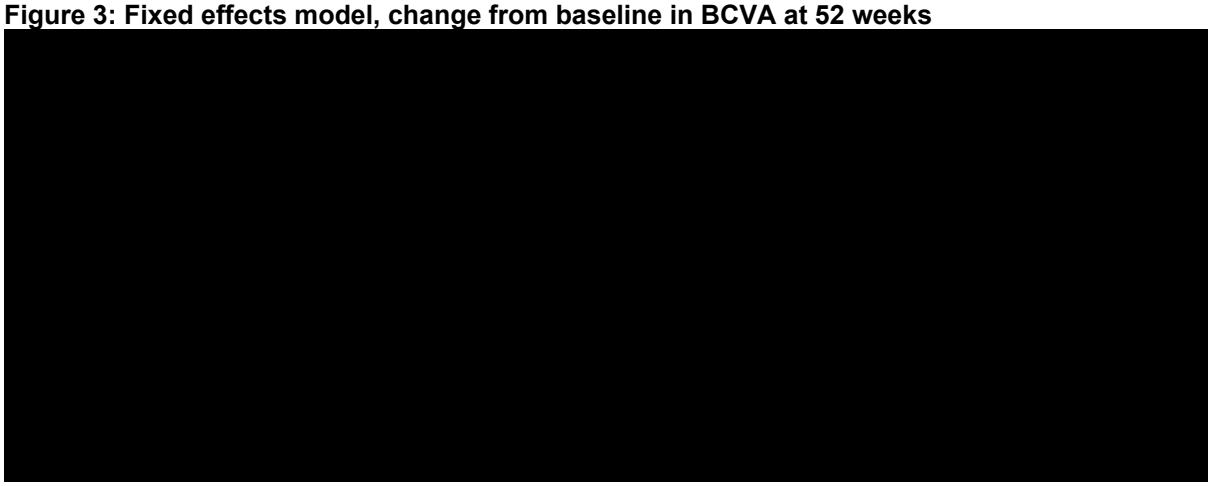
A6. Please provide the NMA results using the fixed effects model for the exploratory NMA for the subgroup of patients with baseline central subfield foveal thickness ≥400 µm for the following outcomes:

a) change from baseline in BCVA at 52 weeks; and

b) change from baseline in BCVA at 100/104 weeks.

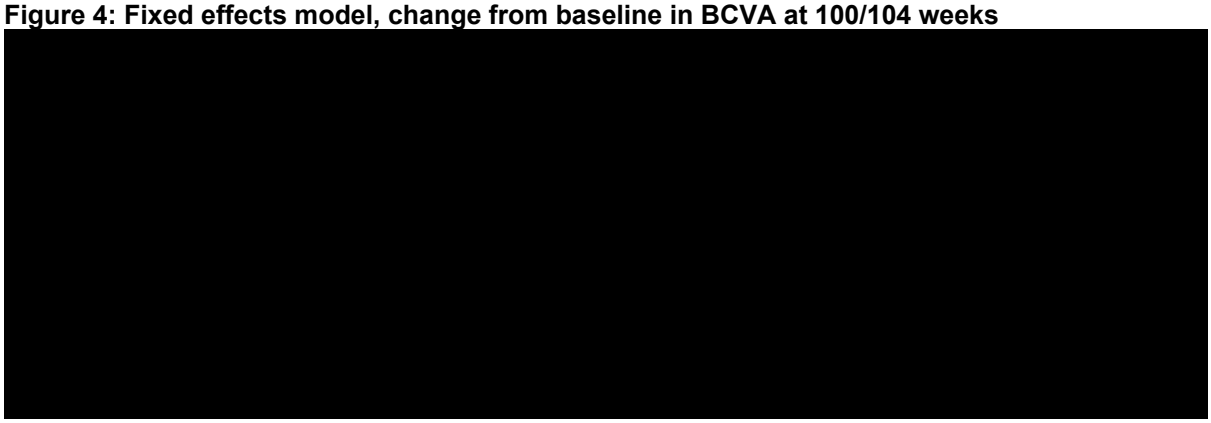
The results using the fixed effects model for the exploratory NMA for the subgroup of patients with baseline CRT ≥400 µm are presented in Figure 3 and Figure 4.

Figure 3: Fixed effects model, change from baseline in BCVA at 52 weeks



Abbreviations: AFL, aflibercept; BCVA, best-corrected visual acuity; BEO, brolucizumab; CI, confidence interval; MD, mean difference; RAN, ranibizumab.

Figure 4: Fixed effects model, change from baseline in BCVA at 100/104 weeks



Abbreviations: AFL, aflibercept; BCVA, best-corrected visual acuity; BEO, brolucizumab; CI, confidence interval; MD, mean difference; RAN, ranibizumab.

A7. Priority question. Please provide the rationale for not including PROTOCOL T in the primary NMAs for the wider DMO population.

PROTOCOL T did not include the posology used in UK clinical practice. Ranibizumab 0.3 mg was studied in PROTOCOL T, whilst the current UK dose is ranibizumab 0.5 mg (26). It was therefore considered inappropriate to include PROTOCOL T in the primary NMA for the wider DMO population. This is in line with the committee's preference in NICE TA346 (27).

As detailed in Company submission Appendix D, the NMA for the subgroup of patients with baseline CRT ≥400 µm was performed as an exploratory analysis. After NMA feasibility assessment, PROTOCOL T was the only study that could potentially provide an indirect treatment comparison of brolucizumab versus ranibizumab. Novartis acknowledge the limitation of the incorrect posology, however, when considered in context with the results from the NMAs for the wider DMO population, the exploratory analysis provides relevant supportive information for decision making. The results suggest that the relative benefit of brolucizumab versus ranibizumab are comparable with the results of NMAs for the wider DMO population. This supports the assumption that the results from the analyses for the wider DMO population can be used as proxies for NICE decision making.

A8. Priority question. Please provide the rationale for only including PROTOCOL T to inform ranibizumab and aflibercept in the exploratory NMAs for the subgroup of patients with baseline central subfield foveal thickness

≥400 µm and not also including the subgroup data from other studies such as VISTA-DME and VIVID-DME (28).

The VISTA-DME and VIVID-DME studies presented BCVA data for the subgroup of patients with baseline central subfield foveal thickness ≥400 µm, however, both trials included laser photocoagulation as comparator. This is not a comparator of interest, so additional studies linking laser photocoagulation to ranibizumab needed to be identified. As the systematic literature review did not identify additional studies to link the subpopulation of interest, only PROTOCOL T could be included in the subgroup analysis.

KITE and KESTREL

A9. Priority question. Please provide a table with a breakdown of the reasons for discontinuations in each of the KITE and KESTREL studies along with the proportion of patients in each study discontinuing for each reason.

The proportion of patients discontinuing up to Week 100 and reasons for discontinuation are provided in Table 51.

Table 51: Study discontinuations in KITE and KESTREL to Week 100 (all enrolled set)

Disposition Reason	KITE		KESTREL		
	Brolucizumab 6 mg n (%)	Aflibercept 2 mg n (%)	Brolucizumab 3 mg n (%)	Brolucizumab 6 mg n (%)	Aflibercept 2 mg n (%)
All randomised	179	181	190	189	187
Randomised and treated	179 (100)	181 (100)	190 (100)	189 (100)	187 (100)
Completed study	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued study	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Physician decision	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progressive disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Protocol deviation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patient decision	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Percentages are calculated based on 'n' from 'all randomised' category.
Abbreviations: AE, adverse event.
Source: Data on file (29).

A10. Please provide the rationale for not conducting pooled analyses of the KITE and KESTREL studies.

KITE and KESTREL were non-inferiority trials. According to regulatory guidelines, in the non-inferiority setting, consistent results should be demonstrated in two similarly designed and adequately powered studies (3). While superiority testing of the primary endpoint would be more powerful after pooling, this adds complexity for Type I error control. In addition, the result of pooling KITE and KESTREL was intuitive given the similarity of the two studies. Therefore, presenting study results individually was considered most appropriate for the purpose of establishing the clinical efficacy of brolucizumab. For the cost-comparison analysis, injection frequencies, discontinuation, and adverse event rates were pooled to represent the combined data for brolucizumab, which allowed for a larger sample size.

Treatment pathway

A11. Priority question. The EAG's clinical experts reported that due to safety concerns with brolucizumab, it may potentially be used in clinical practice for diabetic macular oedema as a second line treatment. In order to facilitate a cost comparison, please provide an assessment of clinical equivalence for brolucizumab versus appropriate second line comparators.

Novartis maintain that brolucizumab is a first line treatment option for the treatment of visual impairment caused by DMO.

Additional insight from six UK clinical experts was gathered from 8th–12th April 2022 (30). Seven clinicians were originally contacted and six agreed to participate. In line with previous clinical insight gathered for ID3902, selection considered previous participation in DMO-specific clinical trials, advisory boards, and publications. All participants were given the same background information and asked an identical list of questions. Conflicts of interest were also recorded. Further detail of the clinical insight gathering is provided for the EAG and NICE as part of the reference pack (30).

All six clinicians stated that brolucizumab would be considered as a first line treatment for DMO in UK clinical practice, thus the decision problem presented by the company is correct. All six clinicians also confirmed that in current clinical

practice, DMO patients not responding or experiencing a suboptimal response to first line anti-VEGF treatment are switched to another anti-VEGF treatment, and if approved, brolucizumab would be considered amongst existing anti-VEGF treatment options for these patients. The appropriate second line comparators for brolucizumab would therefore be aflibercept and ranibizumab.

Novartis are unable to provide assessment of equivalence specifically for second line patients. The KITE and KESTREL studies did not include second line patients and such evidence is similarly not available from randomised control trials for the comparators. Although some clinicians noted that brolucizumab may be used after treatment with aflibercept or ranibizumab, this is in line with current use of existing anti-VEGFs recommended by NICE. Brolucizumab was confirmed as a first line treatment option, therefore the company base case versus comparators aflibercept and ranibizumab is most appropriate for the NICE decision problem.

A12. Both ranibizumab and aflibercept have a treat and extend option for maintenance treatment. Please clarify whether the maintenance treatment for brolucizumab also includes treat and extend as an option.

Brolucizumab has received European Medicines Agency (EMA) approval (2), but Medicine and Healthcare products Regulatory Agency (MHRA) approval is still pending.

[redacted].

Two-year results from the KITE study show that [redacted] of patients were on a 16-week treatment interval at week 100 (16-week intervals were allowed from week 72) (Company submission Section B.5.7.3.3).

Subgroup analyses

A13. Priority question. Please provide the results from KITE and KESTREL for the subgroup of patients with a baseline central subfield foveal thickness ≥400 µm for all outcomes of relevance to the NICE final scope.

Results for the post-hoc subgroup analyses are presented in Table 52–Table 62 and Figure 5–Figure 9. Although KITE and KESTREL were not powered to perform such analyses, overall results for each endpoint were similar whether analysing the subgroup or the full analysis set (FAS) population, supporting the use of the latter as proxies for decision making.

Key secondary endpoint: Average change in BCVA from baseline over the period Week 40–Week 52

Table 52: ANOVA results for change from baseline in BCVA (letters read) over Weeks 40–52 for the study eye (baseline CRT ≥400 µm subgroup – LOCF)

Trial name	KITE		KESTREL		
Baseline CRT ≥400 µm subgroup	**Brolucizumab 6 mg (N=119)**	**Aflibercept 2 mg (N=125)**	**Brolucizumab 3 mg (N=111)**	**Brolucizumab 6 mg (N=110)**	**Aflibercept 2 mg (N=125)**
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Brolucizumab 3 mg vs. aflibercept 2 mg					
LSM (SE)		–	[redacted]	–	[redacted]
95% CI for LSM	–	–		–	
Brolucizumab 6 mg vs. aflibercept 2 mg					
LSM (SE)	[redacted]	[redacted]	–	[redacted]	[redacted]
95% CI for LSM			–		
Brolucizumab – aflibercept					
LSM difference - (SE)	[redacted]	–	[redacted]	[redacted]	–
95% CI for treatment difference	[redacted]	–	[redacted]	[redacted]	–

Patients with baseline CRT <400 are excluded from this analysis. Results for the FAS can be found in Table 15 of Company submission Document B, Section B.5.7.2.1.
n=number of patients with data used in the model.
Analysed using the ANOVA model with baseline BCVA categories (≤65, >65 letters), age categories (<65, ≥65 years), and treatment as fixed effect factors.
BCVA assessment after the start of alternative DMO treatment in the study eye are censored and replaced by the last value prior to the start of the alternative treatment.
Abbreviations: ANOVA, analysis of variance; BCVA, best-corrected visual acuity; CI, confidence interval; FAS, full analysis set; LOCF, last observation carried forward; LSM, least squares mean; SE, standard error.
Source: Data on file (31).

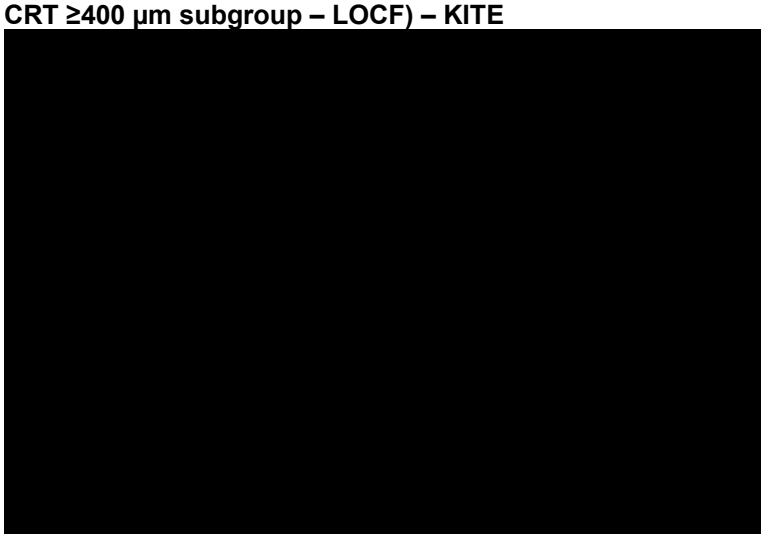
Other secondary endpoints – functional outcomes: Change from baseline in BCVA up to Week 100

Table 53: ANOVA results for change from baseline in BCVA (letters read) at Week 52 and Week 100 for the study eye (baseline CRT ≥400 µm subgroup – LOCF)

Week	Trial name	KITE		KESTREL		
	Baseline CRT ≥400 µm subgroup	**Brolucizumab 6 mg (N=119)**	**Aflibercept 2 mg (N=125)**	**Brolucizumab 3 mg (N=111)**	**Brolucizumab 6 mg (N=110)**	**Aflibercept 2 mg (N=125)**
52	n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Brolucizumab 3 mg vs. aflibercept 2 mg					
	LSM (SE)	–	–	[redacted]	–	[redacted]
	95% CI for LSM	–	–	[redacted]	–	[redacted]
	Brolucizumab 6 mg vs. aflibercept 2 mg					
	LSM (SE)	[redacted]	[redacted]	–	[redacted]	[redacted]
	95% CI for LSM	[redacted]	[redacted]	–	[redacted]	[redacted]
	Brolucizumab – aflibercept					
	LSM difference (SE)	[redacted]	–	[redacted]	[redacted]	–
	95% CI for treatment difference	[redacted]	–	[redacted]	[redacted]	–
100	n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Brolucizumab 3 mg vs. aflibercept 2 mg					
	LSM (SE)	–	–	[redacted]	–	[redacted]
	95% CI for LSM	–	–	[redacted]	–	[redacted]
	Brolucizumab 6 mg vs. aflibercept 2 mg					
	LSM (SE)	[redacted]	[redacted]	–	[redacted]	[redacted]
	95% CI for LSM	[redacted]	[redacted]	–	[redacted]	[redacted]
	Brolucizumab – aflibercept					
	LSM difference (SE)	[redacted]	–	[redacted]	[redacted]	–
	95% CI for treatment difference	[redacted]	–	[redacted]	[redacted]	–

Patients with baseline CRT <400 are excluded from this analysis. Results for the FAS can be found in Company submission Appendix K, Section K1.1.
n=the number of patients with data used in the model. Analysed using the ANOVA model with baseline BCVA categories (≤65, >65 letters), age categories (<65, ≥65 years) and treatment as fixed effect factors. BCVA assessment after the start of alternative DMO treatment in the study eye are censored and replaced by the last value prior to the start of the alternative treatment.
Abbreviations: ANOVA, analysis of variance; BCVA, best-corrected visual acuity; CI, confidence interval; CRT, central retinal thickness; FAS, full analysis set; LOCF, last observation carried forward; LSM, least squares mean; SE, standard error.
Source: Data on file (31).

Figure 5: LSM change from baseline (±SE) in BCVA for the study eye up to Week 100 (baseline CRT ≥400 µm subgroup – LOCF) – KITE



Patients with baseline CRT <400 are excluded from this analysis. Results for the FAS can be found in Figure 1 of Company submission Appendix K, Section K1.1.
LSM and SE estimates are based on an ANOVA model with baseline BCVA categories (≤65, >65 letters), age categories (<65, ≥65 years) and treatment as fixed effect factors. BCVA assessment after the start of alternative DMO treatment in the study eye are censored and replaced by the last value prior to the start of the alternative treatment.
Abbreviations: ANOVA, analysis of variance; BCVA, best-corrected visual acuity; CRT, central retinal thickness; FAS, full analysis set; LOCF, last observation carried forward; LSM, least squares mean; SE, standard error. Source: Data on file (31).

Figure 6: LSM change from baseline (±SE) in BCVA for the study eye up to Week 100 (baseline CRT ≥400 µm subgroup† – LOCF) – KESTREL

Patients with baseline CRT <400 are excluded from this analysis. Results for the FAS can be found in Figure 2 of Company submission Appendix K, Section K1.1
LSM and SE estimates are based on an ANOVA model with baseline BCVA categories (≤65, >65 letters), age categories (<65, ≥65 years) and treatment as fixed effect factors. BCVA assessment after the start of alternative DMO treatment in the study eye are censored and replaced by the last value prior to the start of the alternative treatment.
Abbreviations: ANOVA, analysis of variance; BCVA, best-corrected visual acuity; CRT, central retinal thickness; FAS, full analysis set; LOCF, last observation carried forward; LSM, least squares mean; SE, standard error. Source: Data on file (31).

Other secondary endpoints: Anatomical outcomes

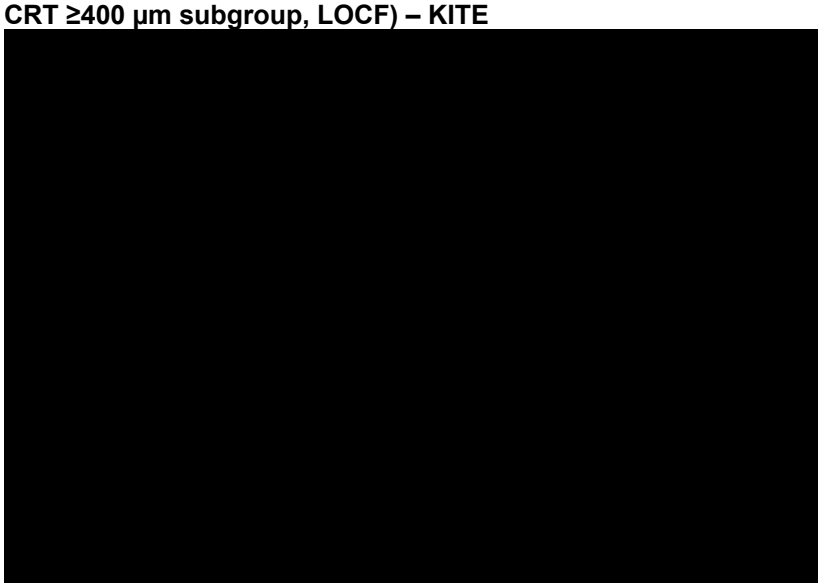
Change from baseline in central subfield thickness (CSFT) to Week 100

Table 54: ANOVA results for change from baseline in CSFT (µm) at Week 52 and Week 100 for the study eye (baseline CRT ≥400 µm subgroup – LOCF)

Week	Trial name	KITE		KESTREL		
	Baseline CRT ≥400 µm subgroup	**Brolucizumab 6 mg (N=119)**	**Aflibercept 2 mg (N=125)**	**Brolucizumab 3 mg (N=111)**	**Brolucizumab 6 mg (N=110)**	**Aflibercept 2 mg (N=125)**
52	n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Brolucizumab 3 mg vs. aflibercept 2 mg					
	LSM (SE)	–	–	[redacted]	–	[redacted]
	95% CI for LSM	–	–	[redacted]	–	[redacted]
	Brolucizumab 6 mg vs. aflibercept 2 mg					
	LSM (SE)	[redacted]	[redacted]	–	[redacted]	[redacted]
	95% CI for LSM	[redacted]	[redacted]	–	[redacted]	[redacted]
	Brolucizumab – aflibercept					
	LSM difference (SE)	[redacted]	–	[redacted]	[redacted]	–
	95% CI for treatment difference	[redacted]	–	[redacted]	[redacted]	–
100	n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Brolucizumab 3 mg vs. aflibercept 2 mg					
	LSM (SE)	–	–	[redacted]	–	[redacted]
	95% CI for LSM	–	–	[redacted]	–	[redacted]
	Brolucizumab 6 mg vs. aflibercept 2 mg					
	LSM (SE)	[redacted]	[redacted]	–	[redacted]	[redacted]
	95% CI for LSM	[redacted]	[redacted]	–	[redacted]	[redacted]
	Brolucizumab – aflibercept					
	LSM difference (SE)	[redacted]	–	[redacted]	[redacted]	–
	95% CI for treatment difference	[redacted]	–	[redacted]	[redacted]	–

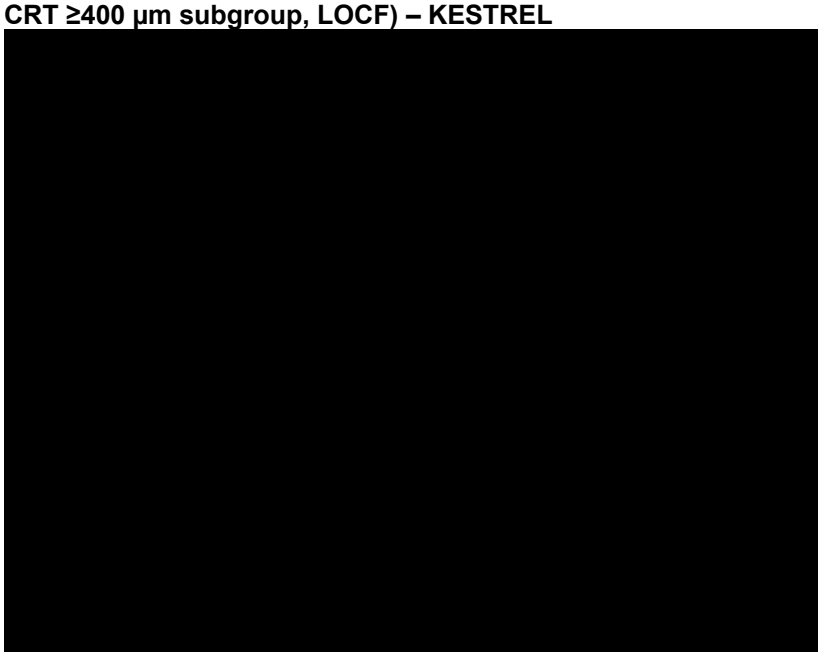
Patients with baseline CRT <400 are excluded from this analysis. Results for the FAS can be found in Table 22 of Company submission Document B, Section B.5.7.5.1.1. n=the number of patients with data used in the model. Analysed using ANOVA model with baseline CSFT categories (<450, ≥450–<650, ≥650 µm), age categories (<65, ≥65 years) and treatment as fixed effect factors. CSFT assessments after start of alternative DMO treatment in the study eye are censored and replaced by the last value prior to start of this alternative treatment.
Abbreviations: ANOVA, analysis of variance; CI, confidence interval; CRT, central retinal thickness; CSFT, central subfield thickness; FAS, full-analysis set; LOCF, last observation carried forward; LSM, least squares mean; SE, standard error.
Source: Data on file (31).

Figure 7: LSM change from baseline (±SE) in CSFT (µm) by visit for the study eye (baseline CRT ≥400 µm subgroup, LOCF) – KITE



Patients with baseline CRT <400 are excluded from this analysis. Results for the FAS can be found in Figure 9 of Company submission Document B, Section B.5.7.5.1.1. Analysed using ANOVA model with baseline CSFT categories (<450, ≥450–<650, ≥650 µm), age categories (<65, ≥65 years) and treatment as fixed effect factors. CSFT assessments after start of alternative DMO treatment in the study eye are censored and replaced by the last value prior to start of this alternative treatment. Abbreviations: ANOVA, analysis of variance; CRT, central retinal thickness; CSFT, central subfield thickness; FAS, full analysis set; LOCF, last observation carried forward; LSM, least squares mean; SE, standard error. Source: Data on file (31).

Figure 8: LSM change from baseline (±SE) in CSFT (µm) by visit for the study eye (baseline CRT ≥400 µm subgroup, LOCF) – KESTREL



Patients with baseline CRT <400 are excluded from this analysis. Results for the FAS can be found in Figure 10 of Company submission Document B, Section B.5.7.5.1.1. Analysed using ANOVA model with baseline CSFT categories (<450, ≥450–<650, ≥650 µm), age categories (<65, ≥65 years) and treatment as fixed effect factors. CSFT assessments after start of alternative DMO treatment in the study eye are censored and replaced by the last value prior to start of this alternative treatment. Abbreviations: ANOVA, analysis of variance; CRT, central retinal thickness; CSFT, central subfield thickness; FAS, full analysis set; LOCF, last observation carried forward; LSM, least squares mean; SE, standard error. Source: Data on file (31).

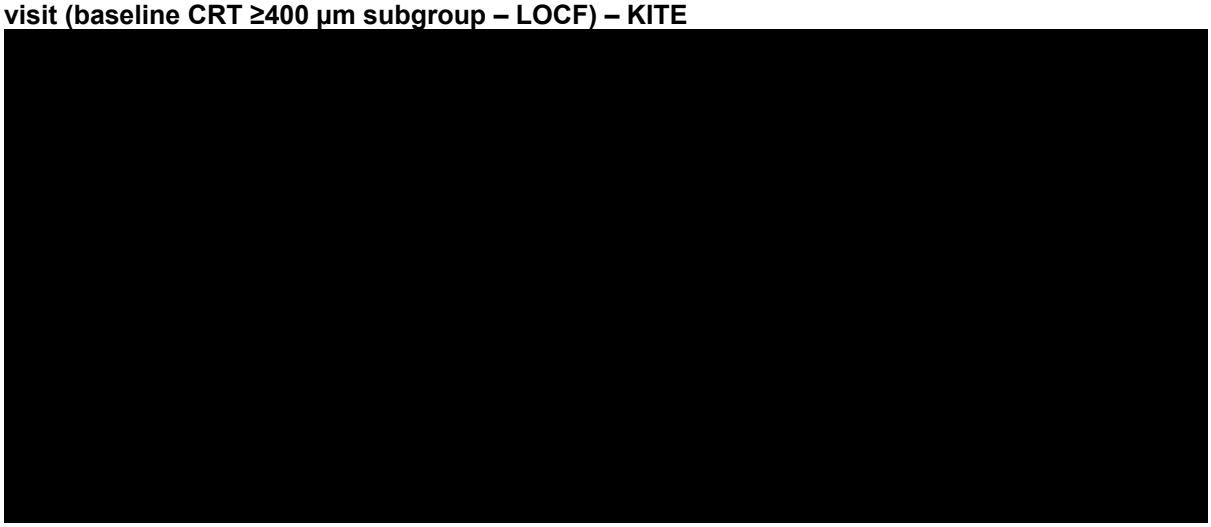
Proportion of patients with CSFT <280 µm

Table 55: The proportion of patients (%) with CSFT <280 µm in the study eye at Week 52 and Week 100 (baseline CRT ≥400 µm subgroup – LOCF)

Week	Study name	KITE		KESTREL		
	Baseline CRT ≥400 µm subgroup	**Brolucizumab 6 mg (N=119)**	**Aflibercept 2 mg (N=125)**	**Brolucizumab 3 mg (N=111)**	**Brolucizumab 6 mg (N=110)**	**Aflibercept 2 mg (N=125)**
52	n/M (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	95% CI†	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Comparison of brolucizumab 3 mg vs. aflibercept 2 mg‡					
	Proportion estimates, %	–	–	[redacted]	–	[redacted]
	Difference, %	–	–	[redacted]	–	–
	95 % CI¶ for treatment difference	–	–	[redacted]	–	–
	Comparison of brolucizumab 6 mg vs. aflibercept 2 mg‡					
	Proportion estimates, %	[redacted]	[redacted]	–	[redacted]	[redacted]
	Difference, %	[redacted]	–	–	[redacted]	–
	95 % CI¶ for treatment difference	[redacted]	–	–	[redacted]	–
100	n/M (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	95% CI†	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Comparison of brolucizumab 3 mg vs. aflibercept 2 mg‡					
	Proportion estimates, %	–	–	[redacted]	–	[redacted]
	Difference, %	–	–	[redacted]	–	–
	95 % CI¶ for treatment difference	–	–	[redacted]	–	–
	Comparison of brolucizumab 6 mg vs. aflibercept 2 mg‡					
	Proportion estimates, %	[redacted]	[redacted]	–	[redacted]	[redacted]
	Difference, %	[redacted]	–	–	[redacted]	–
	95 % CI¶ for treatment difference	[redacted]	–	–	[redacted]	–

Patients with baseline CRT <400 are excluded from this analysis. Results for the FAS can be found in Company submission Document B, Section B.5.7.5.1.2.
n=number of patients satisfying the criteria of the response variable. M=number of patients with an assessment of the criterion.
CSFT assessment after the start of alternative DMO treatment in the study eye are censored and replaced by the last value prior to start of this alternative treatment.
†95% CI for binomial proportions is based on Clopper-Pearson exact method; ‡Statistical model used logistic regression adjusting for baseline CSFT categories (<450, ≥450–<650, ≥650 um), age categories (<65, ≥65 years) and treatment as fixed effect factors. 95% CI for the treatment difference estimated using bootstrap method.
Abbreviations: CI, confidence interval; CRT, central retinal thickness; FAS, full analysis set; CSFT, central subfield thickness; LOCF, last observation carried forward.
Source: Data on file (31).

Figure 9: Proportion of patients (%) with CSFT <280 µm in the study eye at each post-baseline visit (baseline CRT ≥400 µm subgroup – LOCF) – KITE



Patients with baseline CRT <400 are excluded from this analysis. Results for the FAS can be found in Figure 11 of Company submission Document B, Section B.5.7.5.1.2.
CSFT assessment after the start of alternative DMO treatment in the study eye are censored and replaced by the last value prior to start of this alternative treatment.
Abbreviations: CRT, central retinal thickness; CSFT, central subfield thickness; LOCF, last observation carried forward.
Source: Data on file (31).

Figure 10: Proportion of patients (%) with CSFT <280 µm in the study eye at each post-baseline visit (baseline CRT ≥400 µm subgroup – LOCF) – KESTREL

Patients with baseline CRT <400 are excluded from this analysis. Results for the FAS can be found in Figure 12 of Company submission Document B, Section B.5.7.5.1.2.
CSFT assessment after the start of alternative DMO treatment in the study eye are censored and replaced by the last value prior to start of this alternative treatment.
Abbreviations: CRT, central retinal thickness; CSFT, central subfield thickness; LOCF, last observation carried forward.
Source: Data on file (31).

The proportion of patients with presence of subretinal fluid (SRF) and/or intraretinal fluid (IRF) (central subfield) in the study eye at each post-baseline visit up to Week 100

Table 56: Proportion of patients (%) with presence of SRF and/or IRF in the study eye (CRT ≥400 µm subgroup – LOCF)

Visit	Study name	KITE		KESTREL		
	FAS population	Brolucizumab 6 mg (N=119)	Aflibercept 2 mg (N=125)	Brolucizumab 3 mg (N=111)	Brolucizumab 6 mg (N=110)	Aflibercept 2 mg (N=125)
Week 52	n/M (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	95% CI†	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Comparison of brolucizumab 3 mg vs. aflibercept 2 mg‡					
	Proportion estimates, %	–	–	[redacted]	–	[redacted]
	Difference, %	–	–	[redacted]	–	–
	95 % CI¶ for treatment difference	–	–	[redacted]	–	–
	Comparison of brolucizumab 6 mg vs. aflibercept 2 mg‡					
	Proportion estimates, %	[redacted]	[redacted]	–	[redacted]	[redacted]
	Difference, %	[redacted]	–	–	[redacted]	–
	95 % CI¶ for treatment difference	[redacted]	–	–	[redacted]	–
Week 100	n/M (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	95% CI†	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Proportion estimates, %	–	–	[redacted]	–	[redacted]
	Difference, %	–	–	[redacted]	–	–
	95 % CI¶ for treatment difference	–	–	[redacted]	–	–
	Comparison of brolucizumab 6 mg vs. aflibercept 2 mg‡					
	Proportion estimates, %	[redacted]	[redacted]	–	[redacted]	[redacted]
	Difference, %	[redacted]	–	–	[redacted]	–
	95 % CI¶ for treatment difference	[redacted]		–	[redacted]	–

Patients with baseline CRT <400 are excluded from this analysis. Results for the FAS can be found in Table 4 of Company submission Appendix K, Section K1.3.2.1. n=number of patients satisfying the criteria of the response variable. M=number of patients with an assessment of the criterion. Fluid status

assessments after start of alternative DMO treatment in the study eye are censored and replaced by the last value prior to start of this alternative treatment. †95% CI for binomial proportions is based on Clopper-Pearson exact method; ‡Statistical model used logistic regression adjusting for baseline fluid status (SRF and/or IRF), age categories (<65, ≥65 years) and treatment as fixed effect factors; ¶95% CI for the treatment difference estimated using bootstrap method. Abbreviations: CI, confidence interval; CRT, central retinal thickness; DMO, diabetic macular oedema; FAS, full analysis set; IRF, intraretinal fluid; LOCF, last observation carried forward; SRF, subretinal fluid.
Source: Data on file (31).

Other secondary endpoints: Disease severity outcomes

Proportion of patients with ≥2- or ≥3-step improvement in ETDRS Diabetic Retinopathy Severity Scale (DRSS) score from baseline

Table 57: Proportion of patients (%) with ≥2 or ≥3-step improvement from baseline in DRSS score at each assessment visit for the study eye (baseline CRT ≥400 µm subgroup – LOCF)

Visit	Study name	KITE		KESTREL		
	Baseline CRT ≥400 µm subgroup	**Brolucizumab 6 mg (N=119)**	**Aflibercept 2 mg (N=125)**	**Brolucizumab 3 mg (N=111)**	**Brolucizumab 6 mg (N=110)**	**Aflibercept 2 mg (N=125)**
≥2-step improvement from baseline						
Week 28	Proportion of patients, n/M (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	95% CI†	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Comparison of brolucizumab 3 mg vs. aflibercept 2 mg					
	Proportion estimates‡, %	–	–	[redacted]	–	[redacted]
	Difference‡, %	–	–	[redacted]	–	–
	95% CI for treatment difference‡,¶	–	–	[redacted]	–	–
	Comparison of brolucizumab 6 mg vs. aflibercept 2 mg					
	Proportion estimates‡, %	[redacted]	[redacted]	–	[redacted]	[redacted]
	Difference‡, %	[redacted]	–	–	[redacted]	–
	95% CI for treatment difference‡,¶	[redacted]	–	–	[redacted]	–
Week 52	Proportion of patients, n/M (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	95% CI†	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Comparison of brolucizumab 3 mg vs. aflibercept 2 mg					
	Proportion estimates‡, %	–	–	[redacted]	–	[redacted]
	Difference‡, %	–	–	[redacted]	–	–
	95% CI for treatment difference‡,¶	–	–	[redacted]	–	–

Visit	Study name	KITE		KESTREL		
	Baseline CRT ≥400 µm subgroup	**Brolucizumab 6 mg (N=119)**	**Aflibercept 2 mg (N=125)**	**Brolucizumab 3 mg (N=111)**	**Brolucizumab 6 mg (N=110)**	**Aflibercept 2 mg (N=125)**
	Comparison of brolucizumab 6 mg vs. aflibercept 2 mg					
	Proportion estimates‡, %	[redacted]	[redacted]	–	[redacted]	[redacted]
	Difference‡, %	[redacted]	–	–	[redacted]	–
	95% CI for treatment difference‡,¶	[redacted]	–	–	[redacted]	–
Week 76	Proportion of patients, n/M (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	95% CI†	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Comparison of brolucizumab 3 mg vs. aflibercept 2 mg					
	Proportion estimates‡, %	–	–	[redacted]	–	[redacted]
	Difference‡, %	–	–	[redacted]	–	–
	95% CI for treatment difference‡,¶	–	–	[redacted]	–	–
	Comparison of brolucizumab 6 mg vs. aflibercept 2 mg					
	Proportion estimates‡, %	[redacted]	[redacted]	–	[redacted]	[redacted]
	Difference‡, %	[redacted]	–	–	[redacted]	–
	95% CI for treatment difference‡,¶	[redacted]	–	–	[redacted]	–
Week 100	Proportion of patients, n/M (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	95% CI†	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Comparison of brolucizumab 3 mg vs. aflibercept 2 mg					
	Proportion estimates‡, %	–	–	[redacted]	–	[redacted]
	Difference‡, %	–	–	[redacted]	–	–
	95% CI for treatment difference‡,¶	–	–	[redacted]	–	–
	Comparison of brolucizumab 6 mg vs. aflibercept 2 mg					
	Proportion estimates‡, %	[redacted]	[redacted]	–	[redacted]	[redacted]
	Difference‡, %	[redacted]	–	–	[redacted]	–
	95% CI for treatment difference‡,¶	[redacted]	–	–	[redacted]	–

Visit	Study name	KITE		KESTREL		
	Baseline CRT ≥400 µm subgroup	Brolucizumab 6 mg (N=119)	Aflibercept 2 mg (N=125)	Brolucizumab 3 mg (N=111)	Brolucizumab 6 mg (N=110)	Aflibercept 2 mg (N=125)
≥3-step improvement from baseline						
Week 28	Proportion of patients, n/M (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	95% CI[†]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Comparison of brolucizumab 3 mg vs. aflibercept 2 mg					
	Proportion estimates[‡], %	–	–	[redacted]	–	[redacted]
	Difference[‡], %	–	–	[redacted]	–	–
	95% CI for treatment difference[‡,¶]	–	–	[redacted]	–	–
	Comparison of brolucizumab 6 mg vs. aflibercept 2 mg					
	Proportion estimates[‡], %	[redacted]	[redacted]	–	[redacted]	[redacted]
	Difference[‡], %	[redacted]	–	–	[redacted]	–
	95% CI for treatment difference[‡,¶]	[redacted]	–	–	[redacted]	–
Week 52	Proportion of patients, n/M (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	95% CI[†]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Comparison of brolucizumab 3 mg vs. aflibercept 2 mg					
	Proportion estimates[‡], %	–	–	[redacted]	–	[redacted]
	Difference[‡], %	–	–	[redacted]	–	–
	95% CI for treatment difference[‡,¶]	–	–	[redacted]	–	–
	Comparison of brolucizumab 6 mg vs. aflibercept 2 mg					
	Proportion estimates[‡], %	[redacted]	[redacted]	–	[redacted]	[redacted]
	Difference[‡], %	[redacted]	–	–	[redacted]	–
	95% CI for treatment difference[‡,¶]	[redacted]	–	–	[redacted]	–

Visit	Study name	KITE		KESTREL		
	Baseline CRT ≥400 µm subgroup	**Brolucizumab 6 mg (N=119)**	**Aflibercept 2 mg (N=125)**	**Brolucizumab 3 mg (N=111)**	**Brolucizumab 6 mg (N=110)**	**Aflibercept 2 mg (N=125)**
Week 76	Proportion of patients, n/M (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	95% CI†	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Comparison of brolucizumab 3 mg vs. aflibercept 2 mg					
	Proportion estimates‡, %	–	–	[redacted]	–	[redacted]
	Difference‡, %	–	–	[redacted]	–	–
	95% CI for treatment difference‡,¶	–	–	[redacted]	–	–
	Comparison of brolucizumab 6 mg vs. aflibercept 2 mg					
	Proportion estimates‡, %	[redacted]		–	[redacted]	[redacted]
	Difference‡, %	[redacted]	–	–	[redacted]	–
	95% CI for treatment difference‡,¶	[redacted]	–	–	[redacted]	–
Week 100	Proportion of patients, n/M (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	95% CI†	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Comparison of brolucizumab 3 mg vs. aflibercept 2 mg					
	Proportion estimates‡, %	–	–	[redacted]	–	[redacted]
	Difference‡, %	–	–	[redacted]	–	–
	95% CI for treatment difference‡,¶	–	–	[redacted]	–	–
	Comparison of brolucizumab 6 mg vs. aflibercept 2 mg					
	Proportion estimates‡, %	[redacted]	[redacted]	–	[redacted]	[redacted]
	Difference‡, %	[redacted]	–	–	[redacted]	–
	95% CI for treatment difference‡,¶	[redacted]	–	–	[redacted]	–

Patients with baseline CRT <400 are excluded from this analysis. Results for the FAS can be found in Table 5 of Company submission Appendix K, Section K1.4.1. n=number of patients satisfying the criteria of the response variable; M=number of patients with an assessment of the criterion. DRSS assessments after start of alternative DMO treatment in the study eye are censored and replaced by the last value prior to start of this alternative treatment. †95% CI for binomial proportions is based on Clopper-Pearson exact method; ‡Statistical model used logistic regression adjusting for baseline DRSS score categories (≤4, ≥5), age categories (<65, ≥65 years) and treatment as fixed effect factors; ¶95% CI for the treatment difference estimated using bootstrap method.
Abbreviations: CI, confidence interval; CRT, central retinal thickness; FAS, full analysis set; DRSS, Diabetic Retinopathy Severity Scale; ETDRS, Early Treatment Diabetic Retinopathy Study; FAS, full analysis set; LOCF, last observation carried forward.
Source: Data on file (31).

Proportion of patients with ≥2- or ≥3-step worsening in ETDRS DRSS score from baseline

Table 58: Proportion of patients (%) with ≥2 or ≥3-step worsening from baseline in DRSS score at each assessment visit for the study eye (baseline CRT ≥400 µm subgroup – LOCF)

Visit	Study name	KITE		KESTREL		
	Baseline CRT ≥400 µm subgroup	Brolucizumab 6 mg (N=119)	Aflibercept 2 mg (N=125)	Brolucizumab 3 mg (N=111)	Brolucizumab 6 mg (N=110)	Aflibercept 2 mg (N=125)
≥2-step worsening from baseline						
Week 28	Proportion of patients, n/M (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	95% CI†	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Comparison of brolucizumab 3 mg vs. aflibercept 2 mg					
	Proportion estimates‡, %	–	–	[redacted]	–	[redacted]
	Difference‡, %	–	–	[redacted]	–	–
	95% CI for treatment difference‡,¶	–	–	[redacted]	–	–
	Comparison of brolucizumab 6 mg vs. aflibercept 2 mg					
	Proportion estimates‡, %	[redacted]	[redacted]	–	[redacted]	[redacted]
	Difference‡, %	[redacted]	–	–	[redacted]	–
	95% CI for treatment difference‡,¶	[redacted]	–	–	[redacted]	–
Week 52	Proportion of patients, n/M (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	95% CI†	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Comparison of brolucizumab 3 mg vs. aflibercept 2 mg					
	Proportion estimates‡, %	–	–	[redacted]	–	[redacted]
	Difference‡, %	–	–	[redacted]	–	–
	95% CI for treatment difference‡,¶	–	–	[redacted]	–	–
	Comparison of brolucizumab 6 mg vs. aflibercept 2 mg					
	Proportion estimates‡, %	[redacted]	[redacted]	–	[redacted]	[redacted]
	Difference‡, %	[redacted]	–	–	[redacted]	–
	95% CI for treatment difference‡,¶	[redacted]	–	–	[redacted]	–

Visit	Study name	KITE		KESTREL		
	Baseline CRT ≥400 µm subgroup	**Brolucizumab 6 mg (N=119)**	**Aflibercept 2 mg (N=125)**	**Brolucizumab 3 mg (N=111)**	**Brolucizumab 6 mg (N=110)**	**Aflibercept 2 mg (N=125)**
Week 76	Proportion of patients, n/M (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	95% CI[†]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Comparison of brolucizumab 3 mg vs. aflibercept 2 mg					
	Proportion estimates[‡], %	–	–	[redacted]	–	[redacted]
	Difference[‡], %	–	–	[redacted]	–	–
	95% CI for treatment difference[‡,¶]	–	–	[redacted]	–	–
	Comparison of brolucizumab 6 mg vs. aflibercept 2 mg					
	Proportion estimates[‡], %	[redacted]	[redacted]	–	[redacted]	[redacted]
	Difference[‡], %	[redacted]	–	–	[redacted]	–
	95% CI for treatment difference[‡,¶]	[redacted]	–	–	[redacted]	–
Week 100	Proportion of patients, n/M (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	95% CI[†]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Comparison of brolucizumab 3 mg vs. aflibercept 2 mg					
	Proportion estimates[‡], %	–	–	[redacted]	–	[redacted]
	Difference[‡], %	–	–	[redacted]	–	–
	95% CI for treatment difference[‡,¶]	–	–	[redacted]	–	–
	Comparison of brolucizumab 6 mg vs. aflibercept 2 mg					
	Proportion estimates[‡], %	[redacted]	[redacted]	–	[redacted]	[redacted]
	Difference[‡], %	[redacted]	–	–	[redacted]	–
	95% CI for treatment difference[‡,¶]	[redacted]	–	–	[redacted]	–

Visit	Study name	KITE		KESTREL		
	Baseline CRT ≥400 µm subgroup	Brolucizumab 6 mg (N=119)	Aflibercept 2 mg (N=125)	Brolucizumab 3 mg (N=111)	Brolucizumab 6 mg (N=110)	Aflibercept 2 mg (N=125)
≥3-step worsening from baseline						
Week 28	Proportion of patients, n/M (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	95% CI[†]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Comparison of brolucizumab 3 mg vs. aflibercept 2 mg					
	Proportion estimates[‡], %	–	–	[redacted]	–	[redacted]
	Difference[‡], %	–	–	[redacted]	–	–
	95% CI for treatment difference[‡,¶]	–	–	[redacted]	–	–
	Comparison of brolucizumab 6 mg vs. aflibercept 2 mg					
	Proportion estimates[‡], %	[redacted]	[redacted]	–	[redacted]	[redacted]
	Difference[‡], %	[redacted]	–	–	[redacted]	–
	95% CI for treatment difference[‡,¶]	[redacted]	–	–	[redacted]	–
Week 52	Proportion of patients, n/M (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	95% CI[†]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Comparison of brolucizumab 3 mg vs. aflibercept 2 mg					
	Proportion estimates[‡], %	–	–	[redacted]	–	[redacted]
	Difference[‡], %	–	–	[redacted]	–	–
	95% CI for treatment difference[‡,¶]	–	–	[redacted]	–	–
	Comparison of brolucizumab 6 mg vs. aflibercept 2 mg					
	Proportion estimates[‡], %	[redacted]	[redacted]	–	[redacted]	[redacted]
	Difference[‡], %	[redacted]	–	–	[redacted]	–
	95% CI for treatment difference[‡,¶]	[redacted]	–	–	[redacted]	–

Visit	Study name	KITE		KESTREL		
	Baseline CRT ≥400 µm subgroup	**Brolucizumab 6 mg (N=119)**	**Aflibercept 2 mg (N=125)**	**Brolucizumab 3 mg (N=111)**	**Brolucizumab 6 mg (N=110)**	**Aflibercept 2 mg (N=125)**
Week 76	Proportion of patients, n/M (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	95% CI†	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Comparison of brolucizumab 3 mg vs. aflibercept 2 mg					
	Proportion estimates‡, %	–	–	[redacted]	–	[redacted]
	Difference‡, %	–	–	[redacted]	–	–
	95% CI for treatment difference‡,¶	–	–	[redacted]	–	–
	Comparison of brolucizumab 6 mg vs. aflibercept 2 mg					
	Proportion estimates‡, %	[redacted]	[redacted]	–	[redacted]	[redacted]
	Difference‡, %	[redacted]	–	–	[redacted]	–
	95% CI for treatment difference‡,¶	[redacted]	–	–	[redacted]	–
Week 100	Proportion of patients, n/M (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	95% CI†	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Comparison of brolucizumab 3 mg vs. aflibercept 2 mg					
	Proportion estimates‡, %	–	–	[redacted]	–	[redacted]
	Difference‡, %	–	–	[redacted]	–	–
	95% CI for treatment difference‡,¶	–	–	[redacted]	–	–
	Comparison of brolucizumab 6 mg vs. aflibercept 2 mg					
	Proportion estimates‡, %	[redacted]	[redacted]	–	[redacted]	
	Difference‡, %	[redacted]	–	–	[redacted]	–
	95% CI for treatment difference‡,¶	[redacted]	–	–	[redacted]	–

Patients with baseline CRT <400 are excluded from this analysis. Results for the FAS can be found in Company submission Appendix K, Section K1.4.2.
n=number of patients satisfying the criteria of the response variable; M=number of patients with an assessment of the criterion. DRSS assessments after start of alternative DMO treatment in the study eye are censored and replaced by the last value prior to start of this alternative treatment. †95% CI for binomial proportions is based on Clopper-Pearson exact method; ‡Statistical model used logistic regression adjusting for baseline DRSS score categories (≤4, ≥5), age categories (<65, ≥65 years) and treatment as fixed effect factors; ¶95% CI for the treatment difference estimated using bootstrap method.
Abbreviations: CI, confidence interval; CRT, central retinal thickness; DRSS, Diabetic Retinopathy Severity Scale; ETDRS, Early Treatment Diabetic Retinopathy Study; FAS, full analysis set; LOCF, last observation carried forward.
Source: Data on file (31).

Other secondary endpoints: Patient reported outcomes

Change in patient reported outcomes (visual functioning questionnaire [VFQ]-25) total scores from baseline to Week 100

Table 59: ANCOVA results for change from baseline in VFQ-25 overall score by visit (baseline CRT ≥400 µm subgroup – Observed)

Visit	Study name	KITE		KESTERL		
	Baseline CRT ≥400 µm subgroup	Brolucizumab 6 mg (N=119)	Aflibercept 2 mg (N=125)	Brolucizumab 3 mg (N=111)	Brolucizumab 6 mg (N=110)	Aflibercept 2 mg (N=125)
Week 28	n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	LSM estimate (brolucizumab 3 mg)	–	–	[redacted]	–	[redacted]
	LSM estimate (brolucizumab 6 mg)	[redacted]	[redacted]	–	[redacted]	[redacted]
	LSM difference (brolucizumab – aflibercept)	[redacted]	–	[redacted]	[redacted]	–
	95% CI for LSM difference	[redacted]	–	[redacted]	[redacted]	–
Week 52	n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	LSM estimate (brolucizumab 3 mg)	–	–	[redacted]	–	[redacted]
	LSM estimate (brolucizumab 6 mg)	[redacted]	[redacted]	–	[redacted]	[redacted]
	LSM difference (brolucizumab – aflibercept)	[redacted]	–	[redacted]	[redacted]	–
	95% CI for LSM difference	[redacted]	–	[redacted]	[redacted]	–
Week 76	n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	LSM estimate (brolucizumab 3 mg)	–	–	[redacted]	–	[redacted]
	LSM estimate (brolucizumab 6 mg)	[redacted]	[redacted]	–	[redacted]	[redacted]
	LSM difference (brolucizumab – aflibercept)	[redacted]	–	[redacted]	[redacted]	–
	95% CI for LSM difference	[redacted]		[redacted]	[redacted]	–
Week 100	n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	LSM estimate (brolucizumab 3 mg)	–	–	[redacted]	–	[redacted]
	LSM estimate (brolucizumab 6 mg)	[redacted]	[redacted]	–	[redacted]	[redacted]
	LSM difference (brolucizumab – aflibercept)	[redacted]		[redacted]	[redacted]	–
	95% CI for LSM difference	[redacted]	–	[redacted]	[redacted]	–

Patients with baseline CRT <400 are excluded from this analysis. Results for the FAS can be found in Table 24 of Company submission Document B, Section B.5.7.7.1. n=number of patients with a non-missing value at baseline and the corresponding post-baseline visit. Analysed using the ANCOVA model with treatment as a fixed effect factor and corresponding baseline value of the endpoint as a covariate. Data after start of alternative DMO treatment in the study eye are censored and are not included in this analysis. Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; CRT, central retinal thickness; FAS, full analysis set; LSM; least squares mean; VFQ-25, visual functioning questionnaire-25.
Source: Data on file (31).

Adverse reactions

Ocular Adverse events to Week 100

Table 60: Ocular AEs occurring in ≥2% of patients in any arm of either study by MedDRA preferred term for the study eye up to Week 100, within patients with CRT ≥400 µm (SAF)

Study name	KITE		KESTREL		
Preferred term	Brolucizumab 6mg (N=119) n (%)	Aflibercept 2mg (N=125) n (%)	Brolucizumab 3 mg (N=111) n (%)	Brolucizumab 6 mg (N=110) n (%)	Aflibercept 2 mg (N=125) n (%)
Number of patients with ≥1 ocular AE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Study name	KITE		KESTREL		
Preferred term	Brolucizumab 6mg (N=119) n (%)	Aflibercept 2mg (N=125) n (%)	Brolucizumab 3 mg (N=111) n (%)	Brolucizumab 6 mg (N=110) n (%)	Aflibercept 2 mg (N=125) n (%)
[redacted]					

Patients with baseline CRT <400 µm are excluded from this analysis. Results for the FAS can be found in Table 29 of Company submission Document B, Section B.5.11.2.1.
AEs with start date on or after the date of first study treatment administration are counted.
AEs started after the patient discontinued study treatment and started alternative DMO treatment in the study eye are censored.
A patient with multiple occurrences of an AE for a preferred term is counted only once in each specific category.
MedDRA Version 24.0 has been used for the reporting of AEs in KITE and MedDRA version 24.1 in KESTREL.
Abbreviations: AE, adverse event; CRT, central retinal thickness; FAS, full analysis set; MedDRA, medical dictionary for regulatory activities; SAF, safety set.
Source: Data on file (31).

Non-ocular Adverse events to Week 100

Table 61: Non-ocular AEs occurring in ≥2% of patients in any arm of either study by MedDRA preferred term for the study eye up to Week 100, within patients with CRT ≥400 µm (SAF)

Study name	KITE		KESTREL		
Preferred term	Brolucizumab 6mg (N=119) n (%)	Aflibercept 2mg (N=125) n (%)	Brolucizumab 3 mg (N=111) n (%)	Brolucizumab 6 mg (N=110) n (%)	Aflibercept 2 mg (N=125) n (%)
Number of patients with ≥1 non-ocular AE	[redacted]				
[redacted]					

Study name	KITE		KESTREL		
Preferred term	Brolucizumab 6mg (N=119) n (%)	Aflibercept 2mg (N=125) n (%)	Brolucizumab 3 mg (N=111) n (%)	Brolucizumab 6 mg (N=110) n (%)	Aflibercept 2 mg (N=125) n (%)
[redacted]					

Study name	KITE		KESTREL		
Preferred term	Brolucizumab 6mg (N=119) n (%)	Aflibercept 2mg (N=125) n (%)	Brolucizumab 3 mg (N=111) n (%)	Brolucizumab 6 mg (N=110) n (%)	Aflibercept 2 mg (N=125) n (%)
[redacted]					

Study name	KITE		KESTREL		
Preferred term	Brolucizumab 6mg (N=119) n (%)	Aflibercept 2mg (N=125) n (%)	Brolucizumab 3 mg (N=111) n (%)	Brolucizumab 6 mg (N=110) n (%)	Aflibercept 2 mg (N=125) n (%)
[redacted]					

Patients with baseline CRT <400 µm are excluded from this analysis. Results for the FAS can be found in Table 30 of Company submission Document B, Section B.5.11.2.2
AEs with start date on or after the date of first study treatment administration are counted.
AEs started after the patient discontinued study treatment and started alternative DMO treatment in the study eye are censored.
A patient with multiple occurrences of an AE for a preferred term is counted only once in each specific category.
MedDRA Version 24.0 has been used for the reporting of AEs in KITE and MedDRA version 24.1 in KESTREL.
Abbreviations: AE, adverse event; CRT, central retinal thickness; FAS, full analysis set; MedDRA, medical dictionary for regulatory activities; SAF, safety set.
Source: Data on file (31).

Deaths, serious adverse events and adverse events of special interest

Table 62: Deaths, and ocular AESIs for the study eye by category and MedDRA preferred term to Week 100, within patients with baseline CRT ≥400 µm (SAF)

Study name	KITE		KESTREL		
Category Preferred term	Brolucizumab 6 mg (N=119) n (%)	Aflibercept 2 mg (N=125) n (%)	Brolucizumab 3 mg (N=111) n (%)	Brolucizumab 6 mg (N=110) n (%)	Aflibercept 2 mg (N=125) n (%)
Deaths	[redacted]				
Ocular AESIs					
No. of patients with ≥1 ocular AESI	[redacted]				
[redacted]					

Study name	KITE		KESTREL		
Category Preferred term	**Brolucizumab 6 mg (N=119) n (%)**	**Aflibercept 2 mg (N=125) n (%)**	**Brolucizumab 3 mg (N=111) n (%)**	**Brolucizumab 6 mg (N=110) n (%)**	**Aflibercept 2 mg (N=125) n (%)**
[redacted]					

Patients with baseline CRT <400 µm are excluded from this analysis. Results for the FAS can be found in Table 31 of Company submission Document B, Section B.5.11.2.3 AEs with start date on or after the date of first study treatment administration are counted.
AEs started after the patient discontinued study treatment and started alternative DMO treatment in the study eye are censored. A patient with multiple occurrences of an AE for a preferred term is counted only once in each specific category.
MedDRA Version 24.0 has been used for the reporting of AEs in KITE and MedDRA version 24.1 in KESTREL.
Abbreviations: AE, adverse event; CRT, central retinal thickness; FAS, full analysis set; MedDRA, medical dictionary for regulatory activities; SAF, safety set.
Source: Data on file (31).

Adverse events

A14. Priority question. The EAG notes that for neovascular (wet) age-related macular degeneration (AMD) maintenance doses of brolucizumab (after the first 3 doses) should not be given at intervals of less than 8 weeks apart due to the risk of intraocular inflammation. (https://www.gov.uk/drug-safety-update/brolucizumab-beovuv-risk-of-intraocular-inflammation-and-retinal-vascular-occlusion-increased-with-short-dosing-intervals#evidence-that-retinal-vasculitis-and-retinal-vascular-occlusion-are-immune-mediated-events). The EAG also notes that the brolucizumab initial treatment regimen in diabetic macular oedema (DMO) differs from that in neovascular AMD, although the recommended maintenance dose and regimen is also a minimum of 8 weeks. Please can the company clarify:

a) **what additional monitoring (compared to aflibercept or ranibizumab) is expected to be required for patients on brolucizumab; and**

The brolucizumab EPAR and risk management plan (RMP) do not state that additional monitoring visits are required. Additionally, risk minimisation measures such as UK patient educational materials and patient support programs are available for brolucizumab to support self-monitoring at home (32-35).

As described above in the response to A11, clinical insight gathering was performed, consisting of input from six clinicians across England. All six clinicians confirmed that no additional visits would be required for brolucizumab compared with aflibercept or ranibizumab (30). Three clinicians said that there would be no difference in either the quality or quantity of monitoring assessments compared with aflibercept and ranibizumab. Two clinicians mentioned additional monitoring assessments for brolucizumab using anterior segment and fundus examination performed at the injection visit. However, these assessments were suggested as part of good clinical practice for anti-VEGFs (36-39) and they are routinely performed in most centres to monitor treatment effectiveness and make re-treatment decisions. Another clinician noted that for wAMD their centre currently uses non-specialist phone calls to monitor patients receiving brolucizumab as it does not cause further resource burden. Patient education and awareness was described as the most beneficial way to address safety signalling.

b) **how intraocular inflammation and retinal vascular occlusion adverse effects with brolucizumab in DMO are expected to compare with the incidence of adverse events in neovascular AMD.**

Novartis continues to monitor the safety of brolucizumab using well established pharmacovigilance measures. This includes the DMO population. The data from KITE and KESTREL studies are in line with what we know about the safety profile of brolucizumab in wAMD, and we cannot currently say that the safety profile in DMO is different. However, the safety data from KITE and KESTREL shows no evidence that underlying diabetes has a negative impact on the brolucizumab-related incidence of intraocular inflammation (IOI).

Section B: Clarification on cost-effectiveness data

For any scenarios requested in Section B, please ensure these are implemented as user selectable options in the economic model ("Specifications" tab). If scenarios cannot be implemented as user selectable options, please supply instructions on how to replicate the scenario. Furthermore, if the company chooses to update its base case analysis, please ensure that cost-effectiveness results, sensitivity and scenario analyses incorporating the revised base case assumptions are provided with the response along with a log of changes made to the company base case.

Model structure

B1. Priority question: The EAG noted that the model structure allows for fellow eye DMO incidence to occur only in patients remaining on anti-VEGF treatment. As a result treatment effectiveness has been introduced into the cost-comparison model as patients discontinue brolucizumab, aflibercept, and ranibizumab at different rates, the higher discontinuation rate for

brolucizumab results in a greater proportion of patients avoiding bilateral DMO.

The EAG's clinical experts considered the assumption that patients would not be at risk of developing bilateral DMO after discontinuation inappropriate, and noted that the risk would be similar whether on or off anti-VEGF treatment.

The EAG notes that the inclusion of the 'fellow eye DMO avoidance' treatment effect within the model is not consistent with the cost-comparison approach. Should the company wish to capture any form of direct or indirect treatment effect, a cost-utility model will be required.

a) **Please adapt the model such that the same rate of DMO incidence is applied to patients both on and off anti-VEGF treatment. The EAG believes that this change should ensure no indirect treatment effect is captured by the cost-comparison model.**

Although it is acknowledged that incidence of DMO in the fellow eye would continue beyond discontinuation, it is expected that the incident eye would not receive the same treatment that had been discontinued previously. Modelling of incident bilateral DMO beyond discontinuation would therefore require a sequencing model, for which insufficient data are available.

Two scenarios were presented in the original submission in which discontinuation was set to be equal between the three comparators (Table 63); any bias associated with bilateral DMO incidence beyond discontinuation would be eliminated in these scenarios.

In both scenarios, brolucizumab remains cost-saving versus both aflibercept and ranibizumab.

Table 63: Equal discontinuation scenarios

Time horizon	Incremental costs	
	vs aflibercept	vs ranibizumab
Base case	[redacted]	[redacted]
Equal discontinuation rates (brolucizumab patients in pooled KITE & KESTREL)	[redacted]	[redacted]
Equal discontinuation rates (Peto et al)	[redacted]	[redacted]

B2. The EAG notes that TA274 for ranibizumab treatment of DMO adopted a 10-year time horizon. The EAG's clinical experts also estimated that DMO patients are treated with anti-VEGFs for between 5 and 10 years.

a) **Please conduct scenario analyses wherein the model time horizon is reduced to 5, 10, and 15 years.**

Incremental results for the cost-comparison analysis when applying time horizons of 5, 10, and 15 years are presented in Table 64. All scenarios result in cost savings associated with brolucizumab.

Table 64: Model time horizons of 5, 10 and 15 years

Time horizon	Incremental costs					
	vs aflibercept			vs ranibizumab		
Base case (37 years)		[redacted]			[redacted]	
5 years		[redacted]			[redacted]	
10 years		[redacted]			[redacted]	
15 years		[redacted]			[redacted]	

NICE guidance states that the time horizon should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. The base case of 37 years was chosen to reflect a maximum age of 100 years; this approach was also taken in TA672 for brolucizumab in wet age-related macular degeneration.

Line of therapy

B3. Priority question: As discussed in question A11, the EAG's clinical experts believe brolucizumab may be used as second line treatment for DMO. If clinical equivalence can be demonstrated for brolucizumab and appropriate second line comparators, please provide a cost-comparison scenario analysis versus these second line comparators.

Please refer to the response to A11 above. In the clinical insight gathering, all six clinicians confirmed that brolucizumab will be considered a first line treatment option for DMO (30). In the context of second line treatment, all six clinicians also confirmed that in current clinical practice, another anti-VEGF treatment is considered next for DMO patients for patients with no response or suboptimal response to initial treatment with an anti-VEGF and if approved, brolucizumab would be considered

amongst existing anti-VEGF treatment options. The appropriate second line comparators for brolucizumab would therefore be aflibercept and ranibizumab.

Adapting the model to show a pre-treated DMO scenario requires inputs for second line injection frequencies and monitoring frequencies (among various other inputs specific to second line) which are not available. The added complexity and lack of data prohibit a second line cost-comparison of brolucizumab versus aflibercept and ranibizumab. However, since the appropriate comparators are considered, the first line comparison can be used as proxy for a second line comparison. Novartis maintain that the first line comparison is the appropriate comparison for the NICE decision problem for brolucizumab for the treatment of DMO in the UK.

Mortality

B4. The EAG notes that general population mortality was applied in the base case. However, previous submissions for DMO (TA346, TA349 and TA613) applied a relative risk of mortality of 1.95 associated with diabetes patients (sourced from Preis *et al.* 2009(40)).

a) Please conduct a scenario analysis adjusting the general population mortality used in the model for the relative risk of mortality associated with diabetes patients (1.95).

Incremental results for the cost-comparison analysis when applying a relative risk of 1.95 to general population mortality are presented in Table 65. In this scenario, brolucizumab remains cost-saving versus both aflibercept and ranibizumab.

Table 65: Applying a relative risk of 1.95 to general population mortality

Scenario	Incremental costs	
	Vs Aflibercept	Vs Ranibizumab
Base case (no relative risk applied)	[redacted]	[redacted]
Relative risk of 1.95 applied to general population mortality	[redacted]	[redacted]

Injection frequency

B5. Priority question: The EAG notes that the injection frequencies applied in the base case for the first 2 years of treatment reflect clinical trial dosing (KITE

and KESTREL) for the brolucizumab arm but not the aflibercept arm, which utilised data from the Peto *et al.* 2021(41) real world evidence study.

a) **Please clarify why real world evidence was preferred to KITE and KESTREL data for the aflibercept arm addressing; 1) the potential for bias when comparing clinical trial dosing with that observed in clinical practice and 2) the underlying assumption of equivalent clinical effectiveness between the two dosing frequencies for aflibercept.**

The treatment regimen for aflibercept in KITE and KESTREL included a loading phase of 5xq4w dosing followed by a fixed q8w dosing regimen. Clinical opinion suggested 21% of patients follow a q8w dosing schedule and flexible treatment regimens, such as PRN and TREX regimens, are more likely to be utilised in clinical practice (Company submission Appendix J). Real world evidence data, derived from Peto et al 2021 (41), are therefore more likely to accurately reflect the combination of treatment regimens used in the UK. This was also considered to be a conservative assumption, given that the injection frequency for aflibercept in KITE and KESTREL was slightly higher than reported by Peto et al (Table 66).

Table 66: Injection frequency for aflibercept in KITE, KESTREL and Peto et al

	Injection frequency for aflibercept		
	KITE	**KESTREL**	**Peto et al (41)**
Year 1	8.55	8.52	7.7
Year 2	5.21	5.26	5.6
Total (first two years)	13.76	13.78	13.3

There are a limited number of studies comparing the clinical effectiveness of aflibercept administered following fixed (every 8-weeks) vs flexible (TREX) regimens. It was recently reported that the TREX regimen of aflibercept in DMO showed 2-year efficacy comparable to that of fixed dosing regimens (42).

b) **Please conduct scenario analyses wherein the unpooled injection frequency data from KESTREL and KITE are separately used to inform the economic model, utilising the aflibercept injection frequencies for both the aflibercept and ranibizumab arms. Please also utilise annual discontinuation rates estimated from each trial to inform the respective**

scenarios, assuming that ranibizumab has the same discontinuation rate as aflibercept.

Injection frequency and discontinuation were pooled in the cost-comparison analysis to increase the sample size and best represent the available data for brolucizumab. Novartis consider the pooled KITE and KESTREL injection frequency and discontinuation inputs to be more representative of the outcomes that will be seen for brolucizumab in clinical practice than the unpooled inputs. Results for the scenarios using injection frequencies and discontinuation rates from the individual KITE and KESTREL trials (assuming equivalence between aflibercept and ranibizumab) are presented in Table 67. A scenario using injection frequencies and discontinuation rates from the pooled KITE and KESTREL trials (assuming equivalence between aflibercept and ranibizumab) is also presented; this only differs from the base case in terms of the injection frequency assumptions for aflibercept and ranibizumab. Novartis consider the pooled analysis to represent the best use of available data. In all scenarios, brolucizumab remains cost-saving versus both aflibercept and ranibizumab.

Table 67: Unpooled injection frequency and discontinuation rates

Source of data	Incremental costs	
	Vs Aflibercept	Vs Ranibizumab
Base case[†]	[redacted]	[redacted]
KESTREL	[redacted]	[redacted]
KITE	[redacted]	[redacted]
Pooled KITE and KESTREL	[redacted]	[redacted]

[†]Injection frequency taken from pooled KITE and KESTREL for brolucizumab, and Peto et al for aflibercept and ranibizumab; discontinuation rate for aflibercept taken from pooled KITE and KESTREL, with hazard ratios applied from the NMA for brolucizumab and ranibizumab.
Abbreviations: NMA, network meta-analysis.

Treatment monitoring

B6. Priority question: The EAG's clinical experts did not consider the monitoring frequency estimates applied in the base case reflective of current UK clinical practice. The Peto *et al.* 2021(41) real world evidence study estimates were roughly twice the injection frequencies in years 1 and 2. However, the EAG's clinical experts noted that monitoring, for the most part,

was conducted at injection appointments. This was also the assumption accepted for TA346.

a) **Please provide a scenario analysis wherein monitoring frequency is assumed equal to injection frequency for the aflibercept and ranibizumab arms.**

Results for the scenario in which monitoring frequency is set equal to injection frequency[1] are presented in Table 68. In this scenario, brolucizumab remains cost-saving versus both aflibercept and ranibizumab. The additional monitoring in the base case is observed data from Peto et al 2021 (41), therefore additional monitoring visits for aflibercept and ranibizumab are occurring in UK clinical practice. However, it is acknowledged that care varies across the UK.

Table 68: Monitoring frequency set equal to injection frequency

Scenario	Incremental costs	
	Vs Aflibercept	Vs Ranibizumab
Base case	[redacted]	[redacted]
Monitoring frequency set equal to injection frequency	[redacted]	[redacted]

b) **Please provide scenario analyses combining the above assumption with the assumptions in B5(b) (applying unpooled injection frequency and discontinuation data from KESTREL and KITE, separately, and assuming ranibizumab has equal injection frequency and discontinuation to aflibercept).**

Results for the following combined scenarios are presented in Table 69:

- Injection frequencies and discontinuation rates taken from the KITE, KESTREL or pooled KITE and KESTREL trials (assuming equivalence between aflibercept and ranibizumab); and
- Monitoring frequency set equal to injection frequency.

[1] Note that this applies to Year 1 and 2 only; in Year 3 onwards, injection frequency and monitoring frequency are assumed equal between the three comparators and aligned with the assumptions in TA346, as in the model base case.

In all scenarios, brolucizumab remains cost-saving versus both aflibercept and ranibizumab.

Table 69: Unpooled injection frequency and discontinuation rates, equal monitoring

Source of data	Incremental costs	
	Vs Aflibercept	Vs Ranibizumab
Base case†	[redacted]	[redacted]
KESTREL	[redacted]	[redacted]
KITE	[redacted]	[redacted]
Pooled KITE and KESTREL	[redacted]	[redacted]

†Injection frequency taken from pooled KITE and KESTREL for brolucizumab, and Peto et al for aflibercept and ranibizumab; discontinuation rate for aflibercept taken from pooled KITE and KESTREL, with hazard ratios applied from the NMA for brolucizumab and ranibizumab. Monitoring frequency taken from Peto et al for aflibercept and ranibizumab.
Abbreviations: NMA, network meta analysis.

B7. Priority question: The EAG's clinical experts noted that, in addition to optical coherence tomography testing, wide field fundus photography would be conducted at each monitoring visit for anti-VEGF therapy.

a) Please conduct a scenario analysis wherein the costs associated with wide field fundus photography are applied at each monitoring visit.

The cost of conducting wide field fundus photography is assumed to be £137.43[2]. Results for the scenario in which this cost is included for each monitoring visit are presented in Table 70. In this scenario, brolucizumab remains cost-saving versus both aflibercept and ranibizumab.

Table 70: Including the cost of wide field fundus photography for monitoring visits

Scenario	Incremental costs	
	Vs Aflibercept	Vs Ranibizumab
Base case	[redacted]	[redacted]
Including the cost of wide field fundus photography for monitoring visits	[redacted]	[redacted]

B8. Priority question: As mentioned in previous questions, the EAG's clinical experts are concerned about the increased risk of inflammation with brolucizumab treatment and consider that additional monitoring would be required. Namely, monitoring would be conducted, in clinic, once a month

[2] National Schedule of NHS Costs 2019-20. Outpatient procedures, BZ89A, Digital Retinal Photography, 19 years and over, Ophthalmology.

during the first six months of treatment with brolucizumab. During the additional monitoring visits, the EAG's clinical experts advised that, in addition to an OCT test and wide field fundus photography, an eye examination with an ophthalmologist at a slit lamp would also occur (ophthalmologist appointment length is typically 10 minutes).

a) **Please explain if there is any additional information around managing the risk of inflammation with brolucizumab treatment in clinical practice and ensure any guidance is reflected in the cost comparison model.**

The brolucizumab EPAR and RMP do not state that additional monitoring visits are required. Risk minimisation measures such as UK patient educational materials and patient support programs are available for brolucizumab (32-35). As described in the response to A14, clinical insights confirmed that no additional visits are required for the monitoring of DMO patients treated with brolucizumab, and the majority stated that monitoring for brolucizumab would not differ to monitoring performed for aflibercept and ranibizumab (30).

b) **Please conduct a scenario including the cost of monthly monitoring visits with the additional cost of an ophthalmologist visit included for the first six months of brolucizumab treatment**

Novartis do not believe this is a plausible scenario for the management of DMO patients treated with brolucizumab. All six of the clinicians that participated in the clinical insight gathering stated that there would be no additional monitoring visits for brolucizumab compared to existing anti-VEGF therapies aflibercept and ranibizumab (30). However, as B8 is a priority question, the scenario has been implemented as per the EAG request. Results for the following scenario analysis are presented in Table 71:

- Six monitoring visits are applied in the first 6 months for brolucizumab; the base case monitoring frequency is assumed thereafter.
- The cost of an ophthalmologist visit is applied for the additional visits modelled in the first 6 months; note that Novartis do not believe that it is necessary to include an additional ophthalmologist cost for monitoring visits

that coincide with injection visits, as injection visits are assumed to be led by an ophthalmologist in the model base case.

In this scenario, brolucizumab remains cost-saving versus both aflibercept and ranibizumab.

Table 71: Monthly monitoring for 6 months (including ophthalmologist visit) for brolucizumab

Scenario	Incremental costs	
	Vs Aflibercept	Vs Ranibizumab
Base case	[redacted]	[redacted]
Monthly monitoring for 6 months (including ophthalmologist visit) for brolucizumab	[redacted]	[redacted]

c) Please conduct an additional scenario wherein the additional cost of an ophthalmologist visit is applied for all monitoring visits throughout brolucizumab treatment.

In the brolucizumab arm of the model, monitoring is assumed to occur at injection visits; this in line with findings from the clinical insight gathering (see response to A11). Given that all injection visits are assumed to be led by an ophthalmologist, the base-case model already assumes that the cost of an ophthalmologist visit is applied for all monitoring visits. No further scenario analyses were therefore conducted.

Bilateral treatment

B9. Priority question: The EAG's clinical experts estimated that in current UK clinical practice, between 80% and 90% of bilateral DMO patients treated with aflibercept or ranibizumab would have both eyes treated in a single appointment. Furthermore, the EAG's clinical experts noted that due to the increased risk of intraocular inflammation in patients treated with brolucizumab would not be treated bilaterally in the same appointment.

The aflibercept and ranibizumab summary of product characteristics state that there are limited data on bilateral use (including same-day administration). There is a paucity of data for the percent of bilateral DMO patients treated with aflibercept or ranibizumab that have both eyes treated in a single appointment.

a) **Please provide a scenario analysis wherein the additional administration costs associated with a second appointment for bilateral DMO treatment with aflibercept or ranibizumab is applied for 15% of bilateral injections, rather than the 50% assumed in the base case (i.e. apply a bilateral administration cost multiplier of 1.15).**

Results for the scenario in which the bilateral administration cost multiplier is 1.15 for aflibercept and ranibizumab are presented in Table 72. In this scenario, brolucizumab remains cost-saving versus both aflibercept and ranibizumab.

Table 72: Bilateral administration cost multiplier of 1.15 for aflibercept and ranibizumab

Scenario	Incremental costs	
	Vs Aflibercept	Vs Ranibizumab
Base case	[redacted]	[redacted]
Bilateral administration cost multiplier of 1.15 for aflibercept and ranibizumab	[redacted]	[redacted]

b) **Please provide a scenario analysis wherein the additional administration costs associated with a second appointment for bilateral DMO brolucizumab treatment are applied for all bilateral injections (i.e. for brolucizumab, apply a bilateral administration cost multiplier of 2).**

Results for the scenario in which the bilateral administration cost multiplier is 2 for brolucizumab are presented in Table 73. In this scenario, brolucizumab remains cost-saving versus both aflibercept and ranibizumab.

Table 73: Bilateral administration cost multiplier of 2 for brolucizumab

Scenario	Incremental costs	
	Vs Aflibercept	Vs Ranibizumab
Base case	[redacted]	[redacted]
Bilateral administration cost multiplier of 2 for brolucizumab	[redacted]	[redacted]

Section C: Textual clarification and additional points

Exploratory NMA data

C1. The EAG notes from Table S8 of the supplementary material for Wells *et al*. 2015 (43) that the SD for the change in visual acuity letter score from baseline to 1 Year in the ranibizumab arm is reported as 9.0 whereas the SD reported in

Table 85 of Appendix D is 9.4. Please can the company clarify where they have extracted the value of 9.0 from, or if appropriate, update the exploratory NMA using the correct SD value for ranibizumab and provide the updated results.

There was an error inputting the standard deviation (SD) for the change in visual acuity letter score from baseline to 1 Year in the ranibizumab arm. There is also an error in Question C1; the second sentence should start 'Please can the company clarify where they have extracted the value of **9.4** from'.

The value of 9.4 was from an incorrect row in Table S8 of the supplementary materials for Wells et al, 2015 (43). Novartis have amended the analysis using the correct value of 9.0 for the SD for ranibizumab. The scenarios for A4 and A6 have been run with the corrected value. There is no change to the conclusion of the analyses.

Figure 11: Random effects mode – 52 weeks

Abbreviations: AFL, aflibercept; BEO, brolucizumab; CI confidence interval; MD, mean difference; RAN, ranibizumab.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Brolucizumab for treating diabetic macular oedema [ID3902]

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	Diabetes UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Diabetes UK is the country's leading diabetes charity representing the 4.9 million people living with diabetes in the UK. We help people manage their diabetes effectively by providing information, advice and support. We campaign with people with diabetes and healthcare professionals to improve the quality of diabetes care across the UK's health services. We fund pioneering research into care, cure and prevention for all types of diabetes. We are a growing community with more than 300,000 supporters nationwide – including people with diabetes, their friends and families – and more than 100,000 lay and healthcare professional members.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant	Roche: Aug 2021 - £100K for Engaging Communities (project delivery) Sanofi: 2021 - £72k for improving Inpatient Care program Novartis: 2021 – for sponsorship of Diabetes UK Professional Conference

manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	• Conversations, interviews and surveys of people living with diabetes • Information shared by other relevant patient organisations • Our online forum and Helpline service
Living with the condition	
6. What is it like to live with the condition? What do carers	Diabetes is one of the leading causes of preventable sight loss in the UK and more than 1,700 people have their sight seriously affected by their diabetes every year in the UK - more than 30 people every week. Diabetic macular oedema (DMO) is a serious eye condition which can lead to sight loss as a result of fluid leaking from the small blood vessels in the eye. There are an estimated 300,000 people living with the

experience when caring for someone with the condition?	condition in the UK. 7% of people with diabetes, or 1 in 14, develop DMO which results in a noticeable loss of vision. <u>Onset and escalation of DMO can be very sudden and shocking</u> The onset of symptoms of DMO can be very sudden and shocking for patients, especially as many are aware of the potential eye complications that can develop as a result of consistently higher blood glucose levels but unaware or unclear about how these can escalate and cause sight loss. In our case study interviews a man with DMO in his 50s who had diabetes for over 10 years and found it difficult to adjust to managing the condition for many years following diagnosis. He became aware of "floaters" in his eyes and after speaking to an optician was only told that this was related to his diabetes control but not told about retinopathy. He was referred for laser treatment for DMO but sadly lost his sight during treatment and is now registered blind. Similarly, a woman in her 40s who had diabetes since an infant was referred for laser treatment after signs of DMO were picked up in a regular screening and, whilst waiting for treatment, noticed her eyesight become cloudy in a shop one day and woke up without any sight the next morning. <u>Uncertainty and worry about further deterioration of eyesight</u> There is a high level of anxiety amongst people with the condition about further deterioration of their eyesight and potential blindness because of DMO – particularly given the lack of clear information many patients are offered at the point of diagnosis and the limited treatment options. A person with diabetes we've spoken to who had symptoms of DMO identified early and managed to have much of their eyesight stabilised with regular laser treatment for over a decade still says they are "terrified" their sight will degenerate further. This person also developed cataracts during their laser treatment and, though treated early and successfully, was unaware this was a common side-effect of their treatment – highlighting how unclear explanations and discussions with healthcare professionals can heighten uncertainty for people with DMO.

	People with diabetes are twice as likely to suffer from depression and are more likely to be depressed for longer and more frequent periods. Furthermore, people with macular disease are seven times more likely to feel distressed or depressed. The psychological effects of losing sight are acute and uncertainty and worry caused by DMO can have a major impact on mental wellbeing. <u>Employment issues due to DMO</u> DMO can be life-changing and a significant effect of people with diabetes and their livelihoods – forcing them to make adjustments to their employment or in some cases stop altogether. We have spoken to people with DMO who have had to stop working entirely due to the condition and this can place a devastating financial pressure on people and their loved ones. For example, we spoke to a man in middle age whose profession was as a full-time driver. This individual had to relinquish their licence because of sight loss and stop work – which left them feeling "literally suicidal". Although their partner was able to start work full-time, he "finds this hard to come to terms with and also finds the lack of routine challenging". His partner also had to adjust to becoming the primary source of income for the household – which included two young children and an elderly dependent parent – and the knock-on effects of DMO on carers and the wider family dynamic are important to note. In cases where people can continue in their current employment there is often additional attention that needs to be paid to manage the effects of DMO like limiting work that requires close focus like reading or typing as this can cause headaches. <u>Other issues impacting day-to-day life and wellbeing</u> Aside from employment DMO affects many other aspects of day-to-day life. One man we spoke to who had DMO said that "his loss of sight affects every area of his life but he says it is the small things that are most difficult. If he cooks for himself and he takes the lid off a jar and puts it down, it takes ages to find it again."

	DMO also makes it much harder for people with diabetes to manage blood glucose levels through regular tasks like taking readings, injecting insulin and using medical tech devices such as CGM and pumps. Whilst there are innovations that can help, like a talking meter, people with diabetes and DMO still need to code their reading and often require additional assistance from someone else to complete these tasks. Good management of diabetes is also essential to stopping complications like DMO worsening and this has the potential to create a very difficult situation for people with DMO: dependent on good management to help prevent further sight loss but faced with practical challenges as a result of their complication that hinders their ability to do so.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	There are two drugs in routine use for treating DMO currently: Lucentis (ranibizumab) and Eylea (aflibercept). These are both anti-VEGF drugs used as a first line response and the frequency and number of injections depends on how a patient responds to the drug. Some people are also given steroid injections if they do not respond well to anti-VEGF injections but these are limited as they can cause cataracts as a side-effect. The nature of the treatments currently available to stabilise vision and halt the progression of DMO make many people worried in the first instance as they are often already highly sensitive to their developing sight loss. Injections directly into or behind the eye are unusual for most and very unappealing, even when people are keen to undergo treatment and address the issue. <u>Confusing and worrying</u> Some of the people with DMO we have spoken to also relate a confusing series of appointments with different health professionals offering varying advice when they start treatment and one particular man – who was already uneasy about injections – recounted being referred from his optician to a doctor at a local hospital who discussed injections and laser with him but decided against starting these treatments before eventually seeking help at Moorfields Eye Hospital and beginning laser treatment. Unfortunately,

	this treatment did not stop their vision deteriorating, gave them a phobia of laser treatment and resulted in a loss of confidence in the potential for other treatments to help. The healthcare professionals who were treating this person were no doubt offering the best advice they could at the time but the inconsistency of the care ultimately left him "terrified that any further treatment on his eyes will result in further sight loss and confused by the treatment options available." As laser treatment only stops vision from deteriorating further and eye injections cannot restore sight if there is already significant damage to the macula, there is an element of resignation or even fatalism from and towards some people with DMO. For example in one case we heard from a taxi driver who had signs of DMO who was asked what he did for a living by their doctor and after telling them the doctor replied "not anymore, you're not". We know from our insight and campaigning work for that 7 of 10 people with diabetes feel overwhelmed by the demands of living with it and emotional support is a key of their care three quarters say they need more. The experience of the taxi driver above highlights the lack of consideration for psychological effects sometimes experienced by people with DMO. <u>Further disruption and uncertainty due to lockdown and backlog</u> The disruption to eye screening and other healthcare services during the COVID-19 pandemic has had a damaging impact on treatment, with eye screening reduced and people being forced to miss their usual face-to-face appointments. These missed appointments have huge real world effects. In a response to our survey of over 4000 people with diabetes about their care during the pandemic one respondent reported that their eye appointment was cancelled during lockdown and whilst waiting for another, they lost sight in one eye. Though services are working hard to recover it is likely that many thousands will not have had their regular eye screening check in the last 24 months and now be at higher risk of DMO.

8. Is there an unmet need for patients with this condition?	Yes, though there is no cure for DMO currently, stabilisation of the condition is vital and can be life-changing for people.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	• We welcome the added guidance and new technologies being considered to treat this sensitive and potentially life-changing condition. • The need for fewer injections compared to the anti-VEGF treatments available at the moment, due to the potential for longer intervals between injections. • Reducing appointments will have a positive impact for many patients who are worried about the treatment, find the practicalities of attending appointments difficult, or both. • The potential for new monoclonal antibody treatments such as this and Faricimab being made available – subject to NICE appraisal – also offers the benefit of more options for clinicians to choose the best matched option for an individual in terms of outcomes and treatment acceptability.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	• Still an eye injection to halt and stabilise rather than restore lost central vision • Needs regular appointments/check ups

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	• People less able to attend physical appointments for injections may benefit from having to go to fewer • People whose eye sight has deteriorated to point that treatment is ineffective - especially those who might have experienced the deterioration during lockdown when healthcare services have been less accessible
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	

Other issues	
13. Are there any other issues that you would like the committee to consider?	

Key messages

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

- DMO creates high levels of anxiety and fear in people living with diabetes
- Sight loss can turn the lives of people upside down and access to treatments that can delay or mitigate this are extremely welcome
- Given the current treatments available require regular face-to-face appointments and can be uncomfortable, a treatment that is effective but requires fewer appointments and allows for longer intervals between injections will be beneficial for many
- This is particularly important given the disruptions to health care services during the lockdown with an increased risk of complications in people who haven't had routine care and the backlog of appointments increasing pressure on services as they recover
- The availability of new treatments for DMO will also offer more options for clinicians and people living with the condition to choose one that has both the best outcomes and acceptability for their individual circumstance
-
-
-

Thank you for your time.

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

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Brolucizumab for treating diabetic macular oedema [ID3902]

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- Your response should not be longer than 10 pages.

About you	
1.Your name	**Stephen Scowcroft**
2. Name of organisation	Macular Society
3. Job title or position	Director of Services
4a. Brief description of the organisation (including who funds	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

it). How many members does it have?	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 40,000 people, 370,000 website visitors a year and our Advice & Information (A&I) Service responds to over 16,000 queries a year.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant	Alimera Sciences (fluocinolone acetonide intravitreal implant) - NA Allergan (dexamethasone intravitreal implant) - £15,000 (contribution to support activities around information, support and education) Bayer (aflibercept) - £8,100 (contribution to support activities around information, support and education) Novartis Pharmaceuticals (ranibizumab) - £15,000 (contribution to support activities around information, support and education) Organon Pharma (bevacizumab) - NA Pfizer (bevacizumab) - NA

manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	Roche (bevacizumab, faricimab) - £30,000 (contribution to support activities around information, support and education) Sanofi (aflibercept) - NA Thornton & Ross (bevacizumab) - NA Zentiva (bevacizumab) - NA
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients	**DMO patient survey** We carried out a survey and published a report highlighting patient experience of DMO in June 2021. A total of 41 patients with DMO were surveyed about their experiences and their perceptions of the management and support they

and carers to include in your submission?	have received for their diabetes and DMO. This work aimed to understand how the information and support for diabetes compares to that for DMO. **Wet AMD survey** A survey was conducted by the Macular Society in early 2020 to understand the burden that frequent anti-VEGF injections and ophthalmology appointments has on wet AMD patients and their carers or family. A total of 449 responses were received from across the UK. A full report was published August 2020. **Service users** Users of the charities services, such as our Befriending service and Advice and Information service are surveyed every other year. The last survey was completed in April 2020 and had 300 respondents. We also survey our volunteers every other year, most of our volunteers are also affected by macular disease. **Local peer support groups** Our Regional Managers who manage our network of over 400 local groups across the UK feedback regularly. They are our 'frontline', having face to face

	(or phone to phone) interaction every day with people affected by macular disease. We gather case studies which record the experiences of individuals living with macular disease and the impact on their families and carers. We use our social media channels to interact with people with macular disease and provide information and advice. It is also an important way for people to find others with the same condition where they have a rare form of macular disease and to share experiences.
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Diabetic macular oedema (DMO) is a complication of diabetes that can lead to irreversible sight loss. It is a build-up of fluid in the macula due to leaky blood vessels damaged by high blood sugar due to diabetes. It is one of the most common causes of sight loss in the working age group. There are currently around 300,000 people living with the condition in the UK. However, the effects of DMO are still not well known, with recent research from Australia showing only a quarter (26 per cent) of people aged 50-70 are aware of DMO. Less is known about the levels of understanding in the UK. Several treatments are available for DMO. Earlier treatment usually means better outcomes for the patient, including maintaining better sight or stable sight

	for longer. To address early diagnosis and referral for timely treatment, the UK has set up the Diabetic Eye Screening Programme, where those who have been diagnosed with diabetes aged 12 and over are invited to get an eye screen every year. This programme has been very successful in getting patients diagnosed earlier and referring patients to treatment if needed. The lack of information for those newly diagnosed with DMO can lead to higher levels of anxiety, as patients aren't sure of what their diagnosis means for their future. This anxiety can be worsened when patients aren't aware of the support available to help them. Diabetes management is vital for maintaining a healthy life and reducing the risk of developing or accelerating complications such as DMO. However, tasks needed to help manage diabetes, such as reading blood glucose levels and injecting insulin, can become much more difficult after losing central vision. Nearly three-quarters of responders to our survey said they felt anxious about their DMO and the sight loss it might cause, compared to only one person who said they rarely felt anxious. No responders said they never felt anxious about their DMO and possible sight loss

	“It makes me worry what my future may look like. I also would love children and I worry about the impact this would have on my eyes loss.” **“Straight lines look wavy and blurry. It feels very scary and I’m frightened of losing more of my vision in both eyes.”** Loss of central vision through DMO can be very frustrating and can greatly affect everyday life as well as financial impact due to changes in employment and able to drive. Vision loss can make daily tasks more difficult, including tasks needed to monitor and manage diabetes. This can risk further vision loss as poor management of diabetes is a risk factor for DMO progression. This highlights the need for more support and guidance for those newly diagnosed with DMO. Some people with DMO experience visual hallucinations called Charles Bonnet syndrome which adds another level of impact on health and mental well-being. In addition to living with and managing sight loss patients still need to manage their diabetes and the other morbidities and complications related to this. **Family and carers**

	There is a significant burden on family and carers supporting a patient with DMO. A patient with DMO needs to adapt and change to the emotional and practical impacts of the condition and will often rely on family and carers to provide additional support. **"Very difficult to carry out my office work for the small business that I run and also driving issues."** **"Travel to clinic is difficult my daughter has to take time off work for me."** **"Unable to get anyone to take me. I live alone and I am 82 years old."** It can be hard attending appointments, as people with diabetes have to attend multiple check-ups for their condition and other complications. Difficulties might include taking time off work or arranging friends or family to take them to these clinics.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current	**Treatments** Two-thirds of responders (65 per cent) were receiving anti-VEGF injections to treat their DMO. Another 7.5 per cent (those who responded "other") had stable DMO and were under observation, receiving injections when needed. One in

treatments and care available on the NHS?	ten (10 per cent) were receiving steroid injection as treatment and one in eight (12.5 per cent) had laser treatment. One responder was not receiving any treatment due to their sight loss being 'too bad to treat'. Anti-vascular endothelial growth factor (anti-VEGF) injections are the first line of treatment for DMO, and involve injecting these drugs into the eye at repeated intervals. These drugs work to stop the growth and leaking of blood vessels which leads to the damage and vision loss seen in DMO. Some patients do not respond well to these anti-VEGF drugs, or respond better to steroid injections. However, currently there are more restrictions on the use of steroids for DMO due to the increased risk of developing cataracts after steroid use in the eye. Almost four in five participants (78 per cent) feel anxious at least sometimes about their DMO treatment. Often this anxiety is due to having injections, which can be painful. Planning their life around injections can also be stressful, including taking time off work or finding someone to take them to the clinic. **"Regular trips to the hospital for check-ups, having to arrange holidays etc around treatment. Painful treatment."** The remaining 22 per cent do not feel anxious about their treatment, and see injections as a positive step to maintaining their vision.

	“Only positively. It has given me reassurance that my sight is being preserved as well as it can be for as long as possible.” **Care** There is significant pressure on NHS eye care services. Patients regularly feedback personal experiences of cancelled appointments, frustration over communication with clinics, and many hours spent waiting around in clinic. Injections are not available in local health care settings, meaning many patients travel a good distance to attend injection clinics and need a driver to accompany them. There is also a challenge between the management of diabetes and eye condition. Around one in five (22 per cent) responded that they feel like they weren’t managing their eye health well, compared to only one in 20 (5 per cent) who felt they weren’t managing their diabetes well. Overall responders felt less able to manage their eye health and DMO compared to their diabetes. This lack of control may be a reason why responders felt anxious about their eye condition and the sight loss it can cause. It is important that patients feel that they are able to manage their

	condition and have all the necessary information and support. **“I think it’s hard to manage how unpredictable sugar levels can be. Also to calculate the amount of insulin and correction doses are required takes a lot of hard work and concentration.”** **“[It can be hard] keeping it [blood sugar] under control some difficulty reading syringes.”** **“Fear of the unknown is difficult with my eye condition. I have been given great care once it was discovered DMO but there did not appear to be anybody on hand to explain things properly or talk from experience.”** **“Just struggling with understanding it all re HBA1C time in target blood pressure exercise etc.”** More than two in five responders (42.5 per cent) were not given any information about managing their DMO, while only a quarter (24 per cent) were not given any information about managing their diabetes. The importance of managing diabetes is well established, with poor blood sugar management being a major risk factor for developing complications such

	as diabetic macular oedema. Better management of diabetes through lifestyle changes and monitoring blood sugar levels help maintain good vision. **"I was told blood sugar too high and to bring it down quickly. I did bring it down within three months from 116 to 58. Shortly after this I started a range of treatments for retinopathy and DMO."** Only one in four (25 per cent) of those who took the survey felt they were given all the information about DMO that they needed when they were diagnosed. On the other hand, a similar proportion (28 per cent) were given no information at all. It can be difficult for patients to receive a diagnosis of DMO and learn that they could lose their vision. Understanding more about the condition and what treatments are available can be reassuring, and help patients feel more in control of the situation.
8. Is there an unmet need for patients with this condition?	There is no current cure for the condition and treatments can only manage and stabilise the sight loss. There is a need for longer acting treatments to reduce the time between treatment and injections.

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Patients will welcome the need for fewer injections compared to the current anti-VEGF drugs, due to the potential for longer intervals between injections with brolucizumab. Each appointment where there may be an injection can cause anxiety. In our survey of patients with wet AMD, 31% of patients reported always feeling anxious about injection appointments and 24% reported that they were sometimes anxious. When asked to say which of 4 statements on appointments was most important to them, 39% said that 'Keeping the same level of vision with fewer injections' was most important. Some people also experience pain and discomfort following eye injections and a very small minority can suffer serious complications, such as an infection. Fewer eye clinic appointments will mean less disruption to day to day life, particularly where patients need to be accompanied to appointments by family or friends, who may need to take time off work. There will also be less cost to the patient of attending the eye clinic, such as taxi or bus fares and parking fees. In our survey 62% of patients said that they are driven to hospital by family or friends and 28% take public transport.

Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	The disadvantage is that it will be an intravitreal injection which will need to be given regularly, sometimes for years. Appointments at an eye clinic, with all the attendant difficulties of travelling, needing someone to accompany them, costs of transport and hours at the hospital, will still be required, if at a reduced rate. Intraocular inflammation, including retinal vasculitis, and retinal vascular occlusion are adverse drug reactions uncommonly associated with brolucizumab for treatment of wet AMD, which could be an issue for DMO patients as well.
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please	Those who already struggle to attend all their eye clinic appointments, for the reasons given above, will benefit if they have to attend less often. Many patients also suffer from other health conditions associated with diabetes and advancing age, which can leave them unable to maintain their treatment regime. For some just leaving home can be extremely difficult. Only patients who are well enough, have the right transport means and the ability to make arrangements to attend can benefit.

describe them and explain why.	
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Yes, age and disability are issues that need to be considered. As the drugs currently available are not a cure and do not work effectively in everyone, a proportion of patients will still experience significant sight loss such that they will be registered as sight impaired or severely sight impaired. There are also specific groups that may need to be taken into consideration: Pregnancy is a major risk factor for the progression of retinopathy and DMO and is associated with increased prevalence and severity of retinopathy compared to non-pregnant diabetic women. Women with type I diabetes are particularly vulnerable to ocular changes during pregnancy. People with learning disabilities - Type 1 and Type 2 diabetes are more common in people with learning disabilities, this group is likely to have more difficulty managing their diabetes. Reports suggest they are 10 times more likely to experience serious sight loss than other people in the general

	population. There are possible barriers that may affect those with learning disabilities such as a general lack of awareness of the importance of eye screening, problems understanding and processing instructions, fear that the procedures will hurt, memory of previous poor experiences and needing to interact with strangers. Ethnicity is considered a complex risk factor of diabetes. Type 2 diabetes is estimated to be three to four times more common in people of Asian and African–Caribbean origin compared to white Europeans. A UK study found that minority ethnic groups (both South Asians and African/Afro-Caribbeans) had increased odds of having retinopathy compared to their white counterparts. People from lower socio-economic backgrounds tend to have worse DMO outcomes. There is also wider evidence that outcomes are worse in white males who are socio-economically deprived.

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

Key messages

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

- The numbers of people with DMO is increasing and over burdening hospital eye clinics
- The treatment burden on patients and carers is significant and longer acting drugs can alleviate the problem.
- Any measures that reduce the need or frequency of travelling to eye clinics for an invasive, distressing and sometimes painful treatment is a step in the right direction.
- Patients should not have to wait for their vision to deteriorate before they can be treated - the ‘too good to treat’ situation.

- The COVID-19 pandemic has significantly reduced eye clinic capacity due to the infection control measures now required. Any measures that might help to alleviate the pressure on eye clinics, such as longer acting drugs, are therefore even more important.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Brolucizumab for treating diabetic macular oedema [ID3902]

Professional organisation submission

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

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

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

Information on completing this submission

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

About you	
1. Your name	**Luke Nicholson**
2. Name of organisation	**Royal College of Ophthalmologists, United Kingdom**

3. Job title or position	**Consultant Ophthalmologist specialising in Medical Retina**
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☒ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	The Royal College of Ophthalmologists champions excellence in the practice of ophthalmology. We are the only professional membership body for medically qualified ophthalmologists and for those who are undergoing specialist training to become ophthalmologists with over 4,000 members worldwide.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]	• The new RCOphth National Ophthalmology Database Age-Related Macular Degeneration (AMD) Audit is currently funded by the Macular Society, Novartis, Roche and Bayer. • AMD Audit Roche £65,000; AMD Audit Bayer £65,000; and ST1 web-based animated education resource £4,000; AMD Audit Novartis £130,000 https://www.nodaudit.org.uk/news • The RCOphth National Cataract Audit is currently has received funding from Alcon (£90,520) and Bausch + Lomb (£10,000). • Sponsorship for the RCOphth Annual Congress May 2021: Novartis £7950; Bayer £750; Thea £9750; Alcon £6200. **We also work with Bausch and Lomb to equip our surgical skills training centre**

If so, please state the name of manufacturer, amount, and purpose of funding.	
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The primary aim of treatment in this condition, diabetic macular oedema, is to improve vision by reducing or resolving diabetic macular oedema.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by	Improvement in visual acuity by 5 letters or more and/or reduction in central macular oedema to below 320 microns.

x cm, or a reduction in disease activity by a certain amount.)	
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, currently available treatments are effective but a proportion of patients do not respond to this treatment. Furthermore, the demand for monthly injections is a burden to some patients and longer treatment intervals is needed.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	The condition is currently treated with macular laser therapy, intravitreal anti-VEGF treatment (Aflibercept and Lucentis) and/or intravitreal dexamethasone in a subgroup of patients.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Diabetic retinopathy and diabetic macular oedema pathways and management - UK Consensus Working Group (Amoaku, W.M., Ghanchi, F., Bailey, C. et al. Eye 34, 1-51(2020)
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please	The pathway is well defined however, some variations exist between clinicians in regard to considering alternate therapeutic options should there be suboptimal response to the initial treatment of choice. Optimum treatment intervals is also unclear.

state if your experience is from outside England.)	
• What impact would the technology have on the current pathway of care?	Provide an alternate treatment option for patients with this condition which may require less visits as well as an option for patients who are showing signs of suboptimal response to current available treatment options.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes, brolucizumab would be expected to be used in clinical practice in treating diabetic macular oedema specifically in patients with suboptimal response to current available treatment options or as an alternate first-line treatment.
• How does healthcare resource use differ between the technology and current care?	Similar to current care in regard to clinical outcomes but slightly increased treatment intervals may be beneficial for service delivery and compliance.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Should only be prescribed under an ophthalmologist specialising in medical retina in secondary care.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Nil as infrastructure for delivery of treatment and diagnosis and monitoring facilities are already well established.

11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes as it provides an alternative treatment option that may provide a longer interval between treatments as well as an alternative treatment should current available treatments provide suboptimal response. The evidence suggests clinical meaningful benefit for patients with the condition and similar visual outcomes compared to current care.
• Do you expect the technology to increase length of life more than current care?	No
• Do you expect the technology to increase health-related quality of life more than current care?	Possible but evidence is unclear if it is any better than current care in improving quality of life.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Patients who are not responsive to the current treatment options.
The use of the technology	

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Theoretically more difficult as reports in brolucizumab use in age-related macular degeneration and retinal vein occlusion suggests a small risk of intraocular inflammation which will require more detailed clinical assessment for this in each visit along with treatment should this occur. However, the risk of intraocular inflammation in brolucizumab use in diabetic macular oedema in the KITE/KESTREL was not as significant compared with its use in age-related macular degeneration which may reflect the dosing intervals used in KITE/KESTREL.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Should we apply caution following our experience with Brolucizumab use in age-related macular degeneration and retinal vein occlusion, informally, patients with history of uveitis or inflammation are cautioned with commencing brolucizumab and consideration to cease treatment should there be an incidence of intraocular inflammation while on treatment. Treatment intervals should be monitored and not reduced outside protocol due to possible increased risk of intraocular inflammation. It needs to be said that this increase in inflammation was not as significant in KITE/KESTREL when used in diabetic macular oedema which may be a reflection of the dosing intervals used in KITE/KESTREL.

15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Yes but no more than currently available treatments/current care.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	It may provide a meaningful impact on patients who are not responsive to current care. As a first line treatment and comparing with currently available treatment/current care, the impact is unlikely to be different.
• Is the technology a 'step-change' in the management of the condition?	Yes, possibly for patients who are not responsive to current first line treatments.

• Does the use of the technology address any particular unmet need of the patient population?	It provides an alternative effective treatment option for the condition and potentially benefiting patients who are currently not experiencing optimal response with the current care.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The risk of intraocular inflammation can result in added hospital visits and use of added treatment.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes.
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	Vision gains, reduction of macular thickness and incidence of intraocular inflammation which were all measured and reported in the trials.

• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Not applicable
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Risk of intraocular inflammation has been reported in the trials but is more of a concern given our experience outside KITE/KESTREL. A deeper dive into this with a dose interval related response would be beneficial to guide treatment delivery.
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator treatments since the publication of NICE technology appraisal guidance [aflibercept: TA346, ranibizumab: TA274, dexamethasone intravitreal implant: TA349, fluocinolone	Yes but similar vision outcomes from original studies.

intravitreal implant: TA301 and TA613]?	
21. How do data on real-world experience compare with the trial data?	Not aware of any real-world data on brolucizumab in diabetic macular oedema but a more relaxed dosing regimen (longer intervals) used in KITE/KESTREL may provide comparable outcomes as compliance will be improved.
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
22b. Consider whether these issues are different from issues with current care and why.	N/A
Key messages	

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

- Brolucizumab provides an effective treatment option for patients with diabetic macular oedema in improving vision and resolving macular oedema
- The slightly longer intervals between treatments/dose would also be useful in clinical practice for service delivery and patient compliance
- Risk of intraocular inflammation needs to be considered – effect on patient, increased monitoring, treatment
- May be an attractive second line option should first line treatment prove suboptimal
-

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NICE National Institute for Health and Care Excellence

Clinical expert statement

Brolucizumab for treating diabetic macular oedema [ID3902]

Thank you for agreeing to comment on the evidence review group (ERG) report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please 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. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

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

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Deadline for comments by **5pm** on **Monday 25 April**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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

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

NICE National Institute for Health and Care Excellence

Part 1: Treating diabetic macular oedema and current treatment options

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

1. Your name	Winfried Amoaku
2. Name of organisation	
3. Job title or position	Assoc Professor/Reader And Hon Consultant Ophthalmologist
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with diabetic macular oedema? ☐ A specialist in the clinical evidence base for this condition or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	No
8. What is the main aim of treatment for diabetic macular oedema ? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	The aim of DMO treatment is to reduce the macular oedema, and stop progression of visual loss in DMO.

9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	A clinically significant treatment response in DMO is the maintenance of vision (visual acuity [VA] change +/- 5 letters and achieving resolution or reduction of macular oedema, as defined by Amoaku et al, 2020. Full response will result in complete resolution of DMO and/or VA gain of >5 letters. Partial response is considered as (VA change of <5 letter gain and/or >20% reduction in central retina thickness). A poor or 'non-response' to treatment is defined as VA loss of 5 letters and/or <20% reduction in central retina thickness.
10. In your view, is there an unmet need for patients and healthcare professionals in diabetic macular oedema?	There is a significant unmet need in the treatment of DMO. Currently, patients will normally be started on ranibizumab or aflibercept. Approximately 25% these patients are poor responders (Protocol I, VIVID/VISTA 100 weeks). It is known that approximately 40% of eyes still have evident macular oedema at 12-24 months after commencing treatment, despite optimum treatment. If a poor response is demonstrated (<5 letter gain and/or <20% reduction in central retina thickness) then they will be switched to the other anti-VEGF, if deemed appropriate by the treating consultant ophthalmologist. If they continue to show a poor response to the second anti-VEGF then dexamethasone implant will be considered. In the DRCR.net Protocol T, 29% of eyes treated with aflibercept, 59% of bevacizumab, 35% ranibizumab eyes had central foveal thickness of >250 microns at 24 months despite monthly treatment. Visual acuity (VA) improvement from baseline levels were found to be lower in eyes that had chronic persistent macular oedema compared to eyes without persistent oedema. There is therefore need for anti-VEGF agents that will dry up the macular more efficiently, reduce treatment frequency or monitoring visits without compromising visual improvement. Brolucizumab seems to offer that unmet need as it has a more efficient drying effect, and intervals are longer.
11. How is diabetic macular oedema currently treated in the NHS?	Laser photocoagulation- laser is still recommended in eyes with non-centre involving leakage. However, where laser photocoagulation is considered

• Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	detrimental or not beneficial (leakage too close to the fovea, centre involving, or too diffuse), alternative therapies are indicated. Ranibizumab as per NICE TA 274, and aflibercept (NICE TA 346), are recommended by NICE specifically to treating DMO but excludes eyes with foveal thickness <400 microns on OCT, whilst Fluocinolone implant (NICE TA 301) is recommended in eyes with DMO that are pseudophakic, and where ranibizumab or aflibercept are not indicated, or after other therapies have failed, or are not indicated. There is no reference to chronicity in this guidance. The treatment regimens for the anti-VEGF agents are: i) ranibizumab, 3 monthly initiating doses followed by a prn/Treat & Extend regime; ii) aflibercept, 5 monthly initiating doses followed by 2 monthly treatments. In year 2 onwards this treatment interval can be extended. Ranibizumab and aflibercept are the only agents currently recommended for the treatment of phakic patients with centre-involving DMO. However, anti-VEGF drugs are not the best treatment option in some patients. These include pregnant women, recent cardiovascular events, or where patient does not like frequent injections, or cannot attend at monthly intervals (as required with anti-VEGF therapies) resulting in suboptimal treatment.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	The RCOphth DMO Guidelines (2012), available @ https://www.rcophth.ac.uk/resources-listing/diabetic-retinopathy-guidelines/) currency has been updated by the UK Consensus document. (Amoaku WM et al. Diabetic retinopathy and DMO pathways and management: UK Consensus Working Group. Eye 34, 1–51 (2020). https://doi.org/10.1038/s41433-020-0961-6* Eye (2020) 34:1–51 and Corrigendum https://doi.org/10.1038/s41433-020-1087-6. Other guidelines exist elsewhere, e.g. EURETINA: Schmidt-Erfurth U et al. Guidelines for the management of DME. Ophthalmologica 2017; 237:185–222. Figueira J et al. Guidelines for the management of center-involving DME. Clin Ophthalmol 2021;15:3221-3230. The NICE Clinical Guidelines for Diabetic Retinopathy [GID-NG10256] is now in development, with anticipated publication date of 03 Apr 2024. (The scope was published on March 29 2022.

13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	No. Brolicizumab has a better drying effect, i.e. it reduces the macular oedema more efficiently, and has a longer duration of activity compared to the currently available treatments. It also provides good improvement in visual acuity. Overall, it has a favourable benefit profile. It should therefore contribute to improving quality of life more than existing technologies.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The technology will especially benefit DMO patients who require frequent injections currently or are unresponsive to existing therapies.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	Capacity sparing: Use of intravitreal brolucizumab results in a reduced burden of injections when compared to currently available intravitreal anti-VEGF injections and, therefore, capacity sparing. It is expected that patients treated with the technology will attend fewer appointments due to longer injection intervals resulting in reduction in clinic visits. This is even more important during current COVID pandemic. Adoption of the expanded technology indication can further "free-up" clinic slots and staff resources which can potentially be made available for other conditions and services.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Treatment will be indicated in eyes with DMO
17. Do you consider that the use of the technology will result in any substantial health-related benefits that	Yes. This should be supported by health economic assessments.

are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	Yes, the technology is innovative, and represents a step-change in DMO management. The particular unmet need is longer duration of drying effect: less frequent injections, and better reduction in the macular oedema, and improved visual acuity. The RCOphth guidance on Management of Ophthalmology Services during the COVID pandemic recommends that treatment changes that can reduce the frequency of required attendances for the next few months e.g. changes in intravitreal treatment regime or longer-acting drug or procedure that would result in a lower number of hospital visits (RCOphth 2020, COVID-19 Clinical Guidance and National Information. RCOphth Management of Ophthalmology Services during the Covid pandemic dated 28th March 2020. https://www.rcophth.ac.uk/about/rcophth-covid-19-response/on 3rd August 2020). • During this unprecedented time of COVID-19, there is a stronger need for a therapy in phakic DMO with a predictable, extended treatment duration that would result in fewer hospital visits versus Anti-VEGF thus minimizing the risk of exposure to COVID for both the patients and healthcare worker. • Diabetes is strongly associated with COVID-19 mortality. A nationwide analysis in England demonstrated that a ⅓ of all in-hospital deaths with COVID-19 in England occurred in people with diabetes (Barron E et al. Lancet Diabetes Endocrinol 2020; 8:813-822).

19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Intraocular inflammation (IOI), particularly retinal vasculitis and retinal vascular occlusions are newly recognised serious adverse events of anti-VEGFs, and brolucizumab, in particular. IOI occurred in 3.7% with brolucizumab 6mg vrs 0.5% aflibercept in KESTREL, and 1.7% brolucizumab vrs 1.7% aflibercept treated eyes. Retinal vascular occlusions seems to have a less frequent occurrence in DMO eyes compared to neovascular AMD (nAMD), although IOI occurrence is similar in nAMD and DMO. In the KESTREL and KITE 52-week (results from 2 Phase III trials), the overall incidence of serious ocular adverse events was 3.7% for brolucizumab c.f. 2.1% aflbercept (in KESTREL) and 2.2% vrs 1.7% respectively for brolucizumab and aflibercept respectively (in KITE). Brown DM, Emanuelli A, Bandello F et al. KESTREL and KITE: 52-week results from two Phase III pivotal trials of brolucizumab for diabetic macular edema. Am J Ophthalmol. 2022 Jan 13:S0002-9394(22)00006-X. doi: 10.1016/j.ajo.2022.01.004. Online ahead of print. PMID: 35038415. Retinal vasculitis was observed in 0.5% of brolucizumab 6mg treated eyes c.f. none with aflibercept, and none with brolucizumab 6mg or aflibercept in KITE. Retinal vascular occlusions occurred in 0.5% brolucizumab and 0% aflibercept treated eyes in KESTREL, and 0.6% each in aflibercept and brolucizumab eyes in KITE. Endophthalmitis was observed in 0.6% of aflibercept and brolucizumab eyes in KITE, and 0.5% of aflibercept, 1.1% of 3mg , and 0% in 6mg brolucizumab. Vision loss (of $\geq$15L) was related to the IOI in a few cases. Non-ocular SAEs are similar for brolucizumab and aflibercept treated arms.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials?	Brolucizumab is not currently in use as treatment for DMO in the UK, although several UK centres participated in the KESTREL trial. It is expected that clinical use will reflect the clinical trial outcomes. Over 50% of eyes treated with brolucizumab received and were maintained ion 12 weekly

• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	dosing. Eyes treated with brolucizumab werte likely to have significantly less intraretinal or subretinal fluid c.f. aflibercept treated eyes. In naïve eyes with DMO, Intravitreal brolucizumab it is expected will be given at 6 weekly intervals x 5 doses followed by extension to 12-weekly, extending further to 16 weeks as necessary and practical. In some eyes previously treated, (inadequate response to other anti-VEGFS) a single dose of brolucizumab may be adequate in drying up the macular oedema and allowing earlier extension of treatment intervals. (Chakraborty et al, 2021; Murray et al, 2021). *(Chakraborty D, et al. Off-label intravitreal brolucizumab for recalcitrant diabetic macular edema: A real-world case series. Am J Ophthalmol Case Rep. 2021).* Similarly, in a larger series of 110 eyes intravtreal brolucizumab resulted in significant improvement in macular oedema in eyes that were unresponsive to other anti-VEGF treatments, without serious adverse events. *(Murray JE, Gold AS, Latiff A, Murray TG. Brolucizumab: Evaluation of Compassionate Use of a Complex Anti-VEGF Therapy. Clin Ophthalmol 2021 Dec 18;15:4731-4738. doi: 10.2147/OPTH.S339393.)* Reduction in macular oedema and visual acuity improvement. Not currently. It is anticipated that all adverse events have been picked up in clinical trial. It is noteworthy that retinal vasculitis was not detected in the original HAWK & HARRIER (brolucizumab in nAMD) studies. These were detected post-hoc by unmasked investigators, with an incidence of IOI of 4.6%
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	

22. Are you aware of any new evidence for the comparator treatments aflibercept and ranibizumab since the publication of NICE technology appraisal guidance TA346 and TA274?	Yes. There is a comparator trial with aflibercept (Brown et al, 2022). No comparator trials with ranibizumab available to date.
23. How do data on real-world experience compare with the trial data?	There is currently no real-world data from the UK experiences with DMO, although nAMD treated case series exist. There are a few real-world data from the USA (cited above).
24. NICE considers whether there are any equalities issues at each stage of an appraisal. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this appraisal could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people.	No

Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

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Part 2: Key messages

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

There is an unmet need for longer acting anti-VEGF drugs in the treatment of DMO.
Such longer acting anti-VEGF therapies will increase treatment intervals and burden on both patients and physicians, and allow the NHS Trusts to cope better with service delivery.
Brolucizumab will provide that unmet need, with a good benefit-risk profile, and will be valuable in managing DMO eyes.

Click or tap here to enter text.

Click or tap here to enter text.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Patient expert statement

Brolucizumab for treating diabetic macular oedema [ID3902]

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

Your comments and feedback on the key issues below are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources. The evidence review group (ERG) report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking you about living with diabetic macular oedema or caring for a patient with this condition. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

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

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

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We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

Deadline for comments by **5pm** on **Monday 25 April**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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

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

NICE National Institute for Health and Care Excellence

Part 1: Living with this condition or caring for a patient with diabetic macular oedema

Table 1 About you, diabetic macular oedema, current treatments and equality

1. Your name	Stephen Scowcroft
2. Are you (please tick all that apply)	☐ A patient with diabetic macular oedema? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with diabetic macular oedema? ☒ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Macular Society
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☒ I agree with it and **do not wish to** complete a patient expert statement ☒ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☐ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☐ I am drawing from personal experience ☒ I have other relevant knowledge or experience (for example, **I am drawing on others' experiences**). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the

	expert engagement teleconference ☒ I have not completed part 2 of the statement
6. What is your experience of living with diabetic macular oedema? **If you are a carer (for someone with this condition) please share your experience of caring for them**	
7a. What do you think of the current treatments and care available for diabetic macular oedema on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	
8. If there are disadvantages for patients of current NHS treatments for diabetic macular oedema (for example, how treatment is given or taken, side effects of treatment, and any others) please describe these	
9a. If there are advantages of brolucizumab over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does brolucizumab help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	
10. If there are disadvantages of brolucizumab over current treatments on the NHS please describe these.	

For example, are there any risks with brolucizumab? If you are concerned about any potential side effects you have heard about, please describe them and explain why	
11. Are there any groups of patients who might benefit more from brolucizumab or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	
12. Are there any potential equality issues that should be taken into account when considering diabetic macular oedema and brolucizumab? Please explain if you think any groups of people with this condition are particularly disadvantaged Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	

NICE National Institute for Health and Care Excellence

Part 2: Key messages

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

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

Thank you for your time.

Your privacy

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NICE National Institute for Health and Care Excellence

Patient expert statement

Brolucizumab for treating diabetic macular oedema [ID3902]

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NICE National Institute for Health and Care Excellence

Part 1: Living with this condition or caring for a patient with diabetic macular oedema

Table 1 About you, diabetic macular oedema, current treatments and equality

1. Your name	Bernadette Warren
2. Are you (please tick all that apply)	☒ A patient with diabetic macular oedema? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with diabetic macular oedema? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Macular Society
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☒ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: My other experience comes from conversations that have been had on a one to one basis or with groups of others with DMO through the facebook group 'Diabetic retinopathy uk support group' as well as the Macular Society DMO

	support group which met on line in September, October and November 2021. these people reside all across the UK. ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☒ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with diabetic macular oedema? **If you are a carer (for someone with this condition) please share your experience of caring for them**	I was diagnosed with DMO (CSMO) in 2011 at the time I was in my early 40's working as a teacher in a primary school I am married and at the time of diagnosis my children were aged 12 and 14. Little did I know the severe impact that this condition would have not only on myself but on my family and friends too. Below I describe the treatment I have had for DMO and the impact the condition has had on myself and my family. **Treatment** Once I had been diagnosed treatment started promptly with injections in both eyes but it soon became apparent that my left eye which was my best seeing eye then was not responding. A Fluorescein angiogram was performed in 2015 and it was found I had ischemia in that eye and so all treatment for that eye stopped. My vision in that eye at the start of treatment was 6/9 it is now 1/60 (snellen). We were able to carry on treatment with my right eye and to date I have had over 90 injections in that eye. My vision at the start of treatment was 6/12 and it is now 6/24-30 Unfortunately with the injections I developed cataracts that then caused ocular hypertension for which I had bilateral iridotomies in

	2016. My injections have generally caused no short term issues however in September 2021 and November of the same year I developed corneal abrasions after my injections these were extremely painful and far worse than the injection itself. On examination I was found to have very dry eyes and now take Clinitas 4 times a day as well as Carbomer eye gel at night. At a recent appointment I was told the dry eye syndrome could well be a complication of diabetes as well as having the injections. Not many clinicians I have seen know of many (if any) patients that have had so many injections. We have tried all 3 drugs available, unfortunately I could not try any steroid implants as I have been found to be a steroid responder (someone who experiences raised intraocular pressure while taking steroid medication). This means the only drug available to me are VEG-F drugs. **Impact** The impact on DMO has been huge not only on my physical life but at times my mental health too. As already stated when diagnosed I was starting middle age and was working as well as driving and very much enjoying life. Within 14 months of diagnosis I lost my beloved job and the following year my driving license. The loss was so quick and sudden it took me 6 months to regain any feeling of self worth. Feelings of guilt and shame overwhelmed me and I honestly did not know what I would do with my life whilst trying to set a good example to my children and supporting my husband financially as well as with all the practical issues bringing up children bring. My eldest daughter started to blame herself because at that time it was thought my

	diabetes had been gestational. It has been a really hard few years. I have attended appointments every month for DMO since 2011. I have great difficulty with my sight and was registered sight impaired in 2016. Difficulties include recognising peoples faces, colours, reading of text and contrast. As someone with poor sight I have missed out on clearly seeing some of the things I would normally see without issue such as the recent graduation of both my daughters, and last year the funerals of my father and father in law. Everyday life is a challenge with many forgetting or not realising I have a sight issue, though more often than not I do use a long cane now which helps. On a day to day basis life with DMO has been a struggle, not being able to drive has left me dependent on public transport or family or friends giving me a lift. My husband has recently been away for six weeks and so the onus has been on my daughter to take me and collect me from places I want to go and to be honest the embarrassment of asking for a lift or the effort to go by public transport is sometimes too much to bear and I stay at home. When going out socially with my husband he can never enjoy a drink because he will always be the driver and that has made me feel guilty. Recently my hospital appointments for diabetes have changed to a hospital I cannot get to by public transport and it has made me feel annoyed that my needs have not been met especially as my appointments used to be at a hospital just down the road from me. it was only when I pointed this out and

	said I might need to change hospitals that they gave me an appointment more easily accessible. Things I used to enjoy doing are now difficult and my hobbies and interests have had to adapt. I have however tried to remain positive and concentrate on things I can do not things I can't but I miss the things I so enjoyed doing such as driving to garden centres and walking around on my own for a couple of hours having some 'me' time or being able to nip down to supermarket to get the items I have run out of. I now struggle to recognise friends as I go about my business I just don't see them and unless they say 'Hello' I just don't know who they are. As mentioned earlier people often forget I have sight loss and because they can see well they forget I cannot. I often end up confused and left out of conversations because I can't see what others are referring too, this is particularly the case when watching television.
7a. What do you think of the current treatments and care available for diabetic macular oedema on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	7a. At the moment the main treatment option is injection therapy. Those with diabetes not just myself are told many a time that diabetes can sometimes complicate the way we respond to treatments whether that be for the eyes or any other part of the body. Many for example are given 5 loading injections for DMO instead of the usual 3 as 'Diabetics sometimes take longer to respond to treatment' I am an active Facebook user and often see posts on 'Diabetic retinopathy UK support group' page and it does seem to be a difference in care and treatment for DMO around the country which can lead to confusion and

	misunderstanding. I also found this when taking part and helping to lead the Macular Society DMO support group. One example of this involves after care. Once an injection has been administrated some are given chloramphenicol antibiotic eye drops to be taken for 4 days after an injection some are not. When I questioned why these were not given at a hospital I was told that they did not want someone to build up an immunity to it in case it was really needed for an actual infection yet my hospital give them to me each month and it leads me to wonder should I take them or not. Another example is that some hospitals have a 'One stop shop' appointment system but some do not. A friend of mine has to attend one appointment for the assessment and another for the injection this not only takes up a lot of time but also costs twice as much to attend by public transport. Lastly I have felt myself that at times we with DMO are being left behind as far as drugs and research go and that those with AMD are given priority over us. It is only in the last two months that I have heard of any research for DMO. Through conversations I found I am not the only one who has felt this way. The role out of ranibizumab helped to fuel this thought as it was offered for AMD many months before it was offered to myself. I had to sit next to patients receiving the very drug I and my opthalmologist were desperate for me to try.

	7b. The views that I have are very similar to those of the others that I have responded with for example when I asked about research not one person with DMO knew that any research primarily for DMO takes place, only that of AMD. In the DMO support group patients described their treatments and it was surprising to find how different their experiences were which led to some confusion and some feelings of insecurity over the way their treatment was manged. This was particularly in the case of the antibacterial eye drops which were given to some patients and not others.
8. If there are disadvantages for patients of current NHS treatments for diabetic macular oedema (for example, how treatment is given or taken, side effects of treatment, and any others) please describe these	There are some disadvantages of the current treatments for DMO some of these are relevant to me some to others I have communicated with over the years. he disadvantages are listed below **Time** - some even take the day off work not just themselves but a career too so that they can attend an appointment without using public transport. One employer insisted that a patient took time off for treatment as part of her annual leave. **Complications** - Like me the injections can lead to other complications such as *cataracts* then ocular hypertension. I have cataracts (posterior subcapsular as well as nuclear) in my right eye which is the one having injection therapy. It is my best seeing eye and causes many issues with contrast and glare. short term complications such as *corneal abrasions* are very painful and *dry eyes* need careful and time consuming management. Many I have heard directly from have a *reaction to the iodine* administrated this can be very painful leading to anxiety for following appointments. Many have eyes washed out afterwards which can help but takes extra time and can be stressful. *Infection* is also a risk though I have never had this happen to me

	Aftercare -The taking of antibiotics for some can be an issue these need to be kept in the fridge but if taking them 4 times a day if away from home this can be problematic. After an injection vision can remain blurred for many hours for me I have to get 2 buses home and my sight is very blurred this is even more difficult if appointments are in the afternoon when it can get dark quickly in the winter.
9a. If there are advantages of brolucizumab over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does brolucizumab help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	9a. Brolucizumab is a drug that will be used every 8 weeks this has advantages over those drugs that need to be given more regularly. This will have a positive impact on patients who work and have other responsibilities Another advantage involves aftercare I for example am given a bottle of antibiotic eye dops after each injection 4 times a day for 4 days this is to prevent infection these have to be kept refrigerated which can be an issue if away from home or a fridge. Another advantage is that patients are often advised not to wash their hair for a week after an injection for some this is an issue and so reducing this to only 1 week in eight will be a great benefit over the 1 in 4 scenerio. Another advantage is that if it is given every 8 weeks it will lessen the risk of complications such as infection to the injected eye Much discussion that I have heard recently also involves contact lens wearers if a person wears these the advice is that they avoid wearing them for a period of time after an injection this would obviously only affect a few days within a 8 week time frame if they had brolucizumab. 9b. Reducing the risk of complications to the injected eye would bring the most benefit in my case for example I am injected into my best seeing eye and if this then had a complication then it might cause even greater sigh loss.

	9c. If a patient only has to attend only every 8 weeks then this would be advantageous as it would reduce the amount of time away from work or other commitments.
10. If there are disadvantages of brolucizumab over current treatments on the NHS please describe these. For example, are there any risks with brolucizumab? If you are concerned about any potential side effects you have heard about, please describe them and explain why	Having read much about brolucizumab I have found that the drug itself does carry some risks that I as a diabetic patient would need to look into further if it were offered to me. For example there is a risk for those that have had either a stroke, myocardial infarction or a history of transient ischemic attack these are medical episodes that those with diabetes are already a risk of having. Those with an eye pressure above 30 mmHg or above cannot have this treatment and common or very common side affects include Cataracts and other eye disorders which are a risk factor for other anti-vegf treatment. At the beginning of treatment there is more of a risk of adverse side affects such as retinal vasculitis which is not mentioned as a risk in the anti veg f drug I am currently on. Another disadvantage maybe that since the appointments would be every 8 weeks eye issues that have no side affects such as an increased ocular pressure may not be noticed until the next appointment which may cause further issues to the eyes
11. Are there any groups of patients who might benefit more from brolucizumab or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	In order to receive this treatment you need to be fit and able without having had any of the conditions mentioned above this will mean that its benefits will only be experienced by those who are fit and well. I myself has to miss an injection due to being an inpatient with Covid in March 2022 because I missed one injection my sight went from 6/30 in my best seeing eye to 6/60 I only retuned to 6/30 after my injection in April. This treatment also needs to be given in hospital and therefore only those with means of transport will be able to have it.

	The antibiotic eye drop bottle can be difficult to open and the bottle can be hard to squeeze to release the eye drop this might be an issue for some with dexterity issues.
12. Are there any potential equality issues that should be taken into account when considering diabetic macular oedema and brolucizumab? 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.	Information gathered states that those that are female of Japanese origin are at a great risk of adverse reactions if taking this drug (MHRA/CHM advice) Also women of child bearing age should remain on contraception while using this drug. This could be problematic if there is no end date for treatment.
13. Are there any other issues that you would like the committee to consider?	DMO in its very nature combines 2 chronic conditions. I have found during the last ten years that my diabetes team know very little about DMO and what causes it. **I** believe that better communication is needed between diabetes experts/consultants and opthalmologists so that each can learn from each other about the challenges of both diabetes and DMO and in particular what causes DMO.

Part 2: Key messages

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

- DMO can have a huge negative impact on a persons life leading to job loss and the ability to drive
- DMO can lead to further eye complications such as dry eye syndrome and cataracts which can cause further sight loss
- DMO treatment and after care is not the same across the UK
- Brolucizumab needs to be used at 8 week intervals and should not be administered within this time frame.
- Brolucizumab is not suitable for those that have had certain health complications and not be used at all in one particular group of people namely females of Japanese origin

Thank you for your time.

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Brolucizumab for treating diabetic macular oedema

Cost Comparison Evaluation

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Contribution of authors:

Steve Edwards	Critical appraisal of the company's submission; provided feedback on all versions of the report. Guarantor of the report
Victoria Wakefield	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; cross checking of company's search strategies; and drafted the summary and clinical results sections
Nicole Downes	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; cross checking of company's search strategies; and assisted with drafting the clinical results sections
Conor Hickey	Critical appraisal of the company's submission; critical appraisal of the economic model; cross checking of company's search strategies; critical appraisal of the economic evidence; carried out the economic analyses; and drafted the economic sections
Tracey Jhita	Critical appraisal of the company's submission; critical appraisal of the economic evidence; and provided feedback on the economic sections

All authors read and commented on draft versions of the EAG report.

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List of Abbreviations

AE	Adverse event
AESI	Adverse event of special interest
BCVA	Best-corrected visual acuity
CI	Confidence interval
CrI	Credible interval
CRT	Central retinal thickness
CS	Company submission
CSFT	Central subfield thickness
DAA	Disease activity assessment
DIC	Deviance information criterion
DMO	Diabetic macular oedema
DRSS	Diabetic Retinopathy Severity Scale
EAG	Evidence Assessment Group
ETDRS	Early Treatment Diabetic Retinopathy Scale
EURETINA	The European Society of Retinal Specialists
FAS	Full analysis set
FFA	Fundus fluorescein angiography
HbA_{1c}	Glycated haemoglobin
HRQoL	Health-related quality-of-life
ILM	Internal limiting membrane
IRF	Intra-retinal fluid
IVT	Intravitreal treatment
KM	Kaplan-Meier
LOCF	Last observation carried forward
LSM	Least squares mean
NEI VFQ-25	National Eye Institute Visual Functioning Questionnaire-25
NHS	National Health Service
NICE	The National Institute for Health and Care Excellence
NMA	Network meta-analysis
OCT	Optical coherence tomography
ONS	Office for National Statistics
PAS	Patient access scheme
PPS	Per protocol set
PRN	Pro re nata
qXw	Every X weeks
RAN	Ranibizumab
RCT	Randomised controlled trial
RWE	Real-world evidence
SAE	Serious adverse event

SAF	Safety set
SD-OCT	Spectral domain optical coherence tomography
SE	Standard error
SLR	Systematic literature reivew
SoC	Standard of care
SPC	Summary of product characteristics
SRF	Subretinal fluid
SS-OCT	Swept-source optical coherence tomography
SUCRA	Surface under the cumulative ranking curve
TREX	Treat-and-extend
UK	United Kingdom
VEGF	Vascular endothelial growth factor
wAMD	Wet age-related macular degeneration

1 Summary of EAG's view of the company's CCE case

This section provides a summary of the Evidence Assessment Group's (EAG's) view on whether the topic meets the criteria for a cost-comparison, with key issues that may deter the National Institute for Health and Care Excellence (NICE) from proceeding with the cost-comparison and what drives these concerns listed under clinical and economic subheadings with an overall summary of the EAG's view provided. Further details are provided in Section 5 of the report.

Clinical

- The final scope issued by NICE specifies the population of interest to be people with visual impairment due to diabetic macular oedema (DMO) but the company has submitted for a narrower indication that restricts the population to only those with a central retinal thickness (CRT) of ≥400 µm. The EAG considers the narrower population addressed by the company submission (CS) to be reasonable given the company's decision to submit a cost-comparison versus aflibercept and ranibizumab. However, the EAG notes that the focus of the clinical data from KESTREL and KITE (the key studies of brolucizumab), and from the company network meta-analyses (NMAs) presented in the CS relate to a broader DMO population. The EAG also notes that the company assumes central subfield thickness (CSFT) is equivalent to CRT and that CRT was not captured in KITE and KESTREL.
- Outcomes reported in KESTREL and KITE trials cover those included in comparator models for aflibercept[1] and ranibizumab,[2] with the exception of EQ-5D. However, the EAG notes that results for Visual Function Questionnaire-25 (VFQ-25), a health-related quality of life measure, were reported in KESTREL and KITE.
- There were also a number of [redacted], which the EAG's clinical experts reported may be clinically important and influence the results. Nevertheless, the primary outcome for KESTREL and KITE was mean change from baseline in BCVA at 52 weeks, and both trials demonstrated non-inferiority of brolucizumab 6 mg compared to aflibercept 2 mg in the overall DMO population. Additionally, [redacted]

- The EAG is concerned about the robustness of the ≥400 µm CSFT subgroup analyses from KITE and KESTREL, and considers that it may not be appropriate to conclude that the [redacted]. However, the EAG notes that the results [redacted], although they were *post-hoc* analyses and [redacted]
- [redacted], concerns were raised by the EAG's clinical experts about intraocular inflammation with brolucizumab due to events that have occurred during the post-marketing surveillance of brolucizumab for use in wet age-related macular degeneration (wAMD). [redacted] Intraocular inflammation is also flagged for brolucizumab in the Summary of Product Characteristics for Beovu®.
- The EAG's clinical experts also reported that due to potential safety concerns, in terms of intraocular inflammation with brolucizumab, it may be used as a second-line treatment with preference for aflibercept or ranibizumab as first-line therapy. However, the company reported that their panel of six clinicians considered the primary positioning of brolucizumab would be as a first-line treatment and highlighted an absence of clinical trial data for brolucizumab use at second-line.
- [redacted]

Economic

- A major area of uncertainty is the positioning of brolucizumab as a first-line treatment option for adult patients with visual impairment caused by DMO. The EAG's clinical experts

noted that, due to safety concerns regarding potentially higher intraocular inflammation rates, brolucizumab may be used as second-line treatment following aflibercept or ranibizumab. Due to a lack of clinical trial data for brolucizumab use at second-line, the company were unable to provide a requested scenario analysis considering relevant second-line comparators. The EAG considers dexamethasone to be a relevant second-line comparator for pseudophakic DMO patients who have failed on a first-line anti-vascular endothelial growth factor (anti-VEGF; i.e. had an insufficient response to non-corticosteroid treatments). However, this comparison has not been explored.

- The EAG is concerned that the company's base case analysis incorporates an indirect treatment effect as this is inconsistent with the cost-comparison modelling approach. The model structure allows for fellow eye DMO incidence to occur only in patients remaining on anti-VEGF treatment but patients discontinue brolucizumab, aflibercept and ranibizumab at different rates. Hence the patient cohort in each arm has an unequal risk of developing bilateral DMO over the time horizon. The company explored scenario analyses applying the same discontinuation rate to all treatment arms, this adjustment suitably equalised the risk of developing bilateral DMO across all treatment arms but is not incorporated in the company's base case.
- The company's deterministic base case results utilised patient access scheme (PAS) discounts, known to the company, for brolucizumab and ranibizumab. The list price is used for aflibercept. These results show that brolucizumab is cost saving versus aflibercept and ranibizumab. This is primarily due to the [redacted] and injection frequency, applied in the company's base case. Results with an additional commercial in confidence (CIC) aflibercept PAS are provided by the EAG in the CIC Appendix.
- The company's application of pooled brolucizumab injection frequency estimates in year 2 from the KITE and KESTREL studies concerned the EAG as patients in KITE could have their treatment interval extended to 16 weeks at Week 72, whereas the anticipated license only specifies extension to 12 weeks in the maintenance phase of treatment. As such to avoid underestimating brolucizumab injection frequency, the EAG's preference was for unpooled KESTREL injection frequency data. The EAG were also concerned by the company's use of injection frequency estimates derived from a United Kingdom (UK) real world evidence study as opposed to the aflibercept arm of the KESTREL trial. Although this data may be more accurate to the use of aflibercept in current clinical practice, the EAG preferred the like with like comparison of injection frequency provided by the KESTREL trial. Under this paradigm,

brolucizumab became more cost saving as the aflibercept injection frequency in the KESTREL trial was higher than observed by the UK real world evidence study.

- The EAG are generally satisfied that the unit costs applied in the model are appropriate. However, the EAG's clinical experts noted that wide field fundus examinations are conducted at monitoring visits, but were not included in the company base case.
- Although the company assumed additional cost benefits derived from lower brolucizumab monitoring frequency, the EAG's clinical experts noted that due to a potentially higher risk of intraocular inflammation in patients treated with brolucizumab, brolucizumab patients would receive closer monitoring in the first six months of treatment compared with patients. An EAG produced scenario analysis, demonstrated that the cost of this additional monitoring was not large enough to overcome the cost savings from lower brolucizumab injection frequency.

Overall summary

- The EAG considered there to be sufficient evidence of equivalent efficacy to support the cost-comparison of brolucizumab and aflibercept. However, due to the lack of a direct comparison of brolucizumab and ranibizumab and limitations to the company's network meta-analyses, the EAG did not consider there to be sufficient justification for the brolucizumab versus ranibizumab cost-comparison.
- The EAG also considered the narrower population of DMO patients with visual impairment and a CRT ≥400 µm addressed by the CS to be reasonable given the company's decision to submit a cost-comparison versus aflibercept and ranibizumab. However, the EAG notes that the focus of the clinical data from KESTREL and KITE (the key studies of brolucizumab), and from the company NMAs presented in the CS relate to a broader DMO population.
- The EAG's clinical experts reported potential safety concerns in terms of intraocular inflammation with brolucizumab and that brolucizumab may be used as a second-line treatment with preference for aflibercept or ranibizumab as first-line therapy although the company reports there are no clinical data for second-line use of brolucizumab in DMO.

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

The company provided a summary of the final scope issued by the National Institute for Health and Care Excellence (NICE),[3] together with their rationale for any deviation from the final scope (Table 1). The company highlights that the submission differs from the final scope primarily in terms of the population of interest to the decision problem. The key differences between the decision problem addressed in the company submission (CS) and the scope are discussed in greater detail in the sections that follow but the Evidence Assessment Group (EAG) notes that the population in the CS is narrower than that specified by NICE.

Table 1. Summary of decision problem as outlined in the company submission (Adapted from CS, Table 1)

	Final scope issued by NICE	Decision problem addressed in the submission	Company rationale if different from the scope	EAG comment
Population	People with visual impairment due to DMO	People with visual impairment due to DMO and a CRT of ≥400 µm	This is the optimised population recommended by NICE for both aflibercept[1] and ranibizumab[2] and is addressed in line with the NICE methods guide for cost-comparison[4]	The EAG considers the narrower population addressed by the CS to be reasonable given the company's decision to submit for cost-comparison versus aflibercept and ranibizumab. However, the EAG notes that the focus of the clinical data from KITE and KESTREL (the key studies of brolucizumab), and from the company NMAs presented in the CS all relate to the broader population. During the clarification stage, the EAG therefore requested additional data from the clinical studies and NMAs for the CRT of ≥400 µm population in which the company is positioning brolucizumab but the EAG notes that the subgroup data from KITE and KESTREL are for patients with baseline CSFT ≥400 µm, and the company consider CSFT to be equivalent to CRT. The results for this subgroup are discussed in Section 3.3.5. The EAG's clinical experts also consider the company's proposed target population for brolucizumab to be reasonable given the existing NICE guidance for aflibercept[1] and ranibizumab[2].

Intervention	Brolucizumab	As per scope	N/A	The EAG notes that the posology for brolucizumab will allow the treating physician to individualise treatment intervals based on disease activity as assessed by visual acuity and/or anatomical parameters after the initial 5 loading doses: • In patients without disease activity, treatment every 12 weeks (3 months) should be considered; • In patients with disease activity, treatment every 8 weeks (2 months) should be considered. The EAG notes that in KITE the maintenance treatment could be extended up to 16 weekly dosing after Week 72 and the company presented results for the proportion of patients who remained on the different maintenance treatment regimens in KESTREL and KITE.
Comparator(s)	• Laser photocoagulation alone The following technologies alone or in combination with laser photocoagulation: • Aflibercept • Bevacizumab (does not currently have a marketing authorisation in the UK for this indication) • Dexamethasone intravitreal implant • Faricimab (subject to NICE appraisal) • Fluocinolone acetonide intravitreal implant	• Aflibercept • Ranibizumab	The following comparators are not considered, for the reasons provided below. **Bevacizumab** • Bevacizumab is not currently licensed for this indication and has not been appraised by NICE. It was listed in the final NICE scope for brolucizumab for the treatment of wAMD, but the appraisal committee agreed that because it has not been appraised by NICE, it could not be considered a comparator in the FTA process [5]. **Laser photocoagulation** • UK consensus guidelines on DMO recommend laser photocoagulation (if appropriate) for eyes not meeting NICE criteria (CRT ≥400 µm) [6]. Laser photocoagulation is only recommended for use in non-centre involving DMO, thus it occupies a different	The EAG and its clinical experts agree with the company that the most relevant comparators (given the company's proposed positioning of brolucizumab in the treatment pathway for DMO) are aflibercept and ranibizumab. The EAG notes that the key clinical trials for brolucizumab, KESTREL and KITE, both compare brolucizumab versus aflibercept. The EAG also notes that indirect treatment comparisons have been conducted by the company to enable a comparison

	• Ranibizumab		position in the pathway of care to the anticipated position of brolucizumab. • Use of laser photocoagulation in clinical practice is low. In TA346, clinical experts advised that in recent years, the use of laser photocoagulation has declined due to retinal scarring associated with the procedure and the uptake of new treatments (anti-VEGF therapies and corticosteroids) [7]. **Dexamethasone intravitreal implant and fluocinolone acetonide intravitreal implant** • The corticosteroids fluocinolone and dexamethasone are recommended by NICE in different positions in the clinical pathway of care to the anticipated position of brolucizumab (CS, Figure 1) [8, 9]. • Clinical experts in TA346 confirmed that these are only given as second-line therapies for patients whose disease has not adequately responded to first-line anti-VEGF treatment [7]. **Faricimab (subject to NICE appraisal)** • Faricimab is currently undergoing appraisal by NICE for the treatment of DMO, however NICE guidance will not be published before this submission (publication of faricimab guidance is not expected until the 22nd of June 2022). Therefore, faricimab cannot be considered part of established NHS practice in England and is not a relevant comparator based on Section 6.2.2. of the new NICE methods guide [4]. In TA672 for brolucizumab for the treatment of wAMD, the committee slides confirmed that a cost-comparison only requires comparison against one NICE-recommended comparator [10], therefore a comparison versus faricimab should not be considered necessary.	with ranibizumab and these are discussed further in Section 3.4.
Outcomes	• BCVA (the affected eye) • BCVA (both eyes) • central foveal subfield thickness • central retinal thickness • contrast sensitivity • disease severity	As per scope, except for: BCVA (both eyes), contrast sensitivity, need for cataract surgery	The outcomes not addressed in this submission were not captured in the clinical trial programme (the Phase 3 studies KITE and KESTREL).	The EAG and its clinical experts consider the results for the key outcomes of clinical relevance have been reported by the company (in the CS, CS appendices and company response to clarification) from the KITE and KESTREL clinical trials. The

	• intraretinal and subretinal fluid • mortality • need for cataract surgery • adverse effects of treatment • health-related quality of life (HRQoL)			EAG notes that the company has assumed central subfield thickness (CSFT) is equivalent to central retinal thickness (CRT) and that CRT data were not captured in KITE and KESTREL. The EAG notes that HRQoL data from KESTREL and KITE were measured using the VFQ-25 questionnaire which is a vision-targeted HRQoL tool.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost-comparison may be carried out. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.	A cost comparison analysis of brolucizumab versus aflibercept and ranibizumab will be presented.	A cost comparison analysis will be presented, as brolucizumab is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication [11]. There are two phase 3 head-to-head trials (KITE and KESTREL) comparing brolucizumab with aflibercept in adult patients with visual impairment due to DMO (CS, Section B.3). In both studies, non-inferiority of brolucizumab 6 mg was demonstrated versus aflibercept 2 mg with respect to the mean CFB in BCVA at Week 52, despite fewer intravitreal treatment injections in the brolucizumab arm, as a result of an extended dosing schedule for patients treated with brolucizumab [12-15] (CS, Section B.3.7.1). Post-hoc subgroup analysis (CS, Section B.3.8) demonstrated that the relative efficacy of brolucizumab versus aflibercept for patients with DMO and CRT ≥400 µm was consistent between the subgroup and the full KITE and KESTREL study populations. Data aligned to the expected brolucizumab marketing authorisation (and KITE and KESTREL full study populations) are used in the cost-comparison since they provide more robust head-to-head evidence whereas the	The EAG notes that the results from the full trial populations of KESTREL and KITE studies are used to inform the economic model rather than results from the CRT ≥400 µm subgroup but the EAG also acknowledges there are limitations in the data. Aflibercept and ranibizumab are both included as comparators in the company's cost-comparison model but the EAG is concerned about the robustness of the NMAs for concluding similar clinical efficacy between ranibizumab and brolucizumab.

	Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability of any managed access arrangement for the intervention will be taken into account. Cost effectiveness analysis should include consideration of the benefit in the best and worst seeing eye.		CRT ≥400 µm subgroup data are more limited and uncertain. In the absence of head-to-head data vs. ranibizumab, an NMA was performed (CS, Section B.3.9). The primary analysis covered the wider population of patients with DMO due to data limitations for patients with CRT ≥400 µm. An exploratory (frequentist) analysis in the subgroup is presented in CS, Appendix D. In the primary analysis of all enrolled patients included in the studies, brolucizumab is ranked amongst the best treatments for several outcomes including change in BCVA, improvement in DRSS and decrease in retinal thickness while maintaining a comparable adverse event profile. The comparative benefit of brolucizumab versus aflibercept and ranibizumab in the exploratory analysis (CS, Appendix D) were comparable with the results of the more robust wider network. Therefore, the wider network and FAS population results from the KITE and KESTREL studies can be used as proxies for NICE decision making.	
Subgroups to be considered	If the evidence allows the following subgroups will be considered. These include: • type of DMO (focal or diffuse, central involvement, ischaemic or non-ischaemic maculopathy) • duration of DMO • baseline visual acuity • baseline central retinal thickness • previous treatment history (including people who have received no prior treatment, and those who have received and/or	Post-hoc subgroup analysis of patients with CRT ≥400 µm, in line with the aflibercept and ranibizumab NICE recommendations	Novartis do not propose to include the subgroups described in the draft scope in the model as brolucizumab is expected to be cost-saving in the optimised population being targeted, aligned to the comparator NICE recommendations. For type of DMO (central involvement, ischaemic or non-ischaemic maculopathy), previous treatment history, and prior cataract surgery, subgroup analyses cannot be performed as data are not available. Clinical subgroup analyses for type of DMO (focal or diffuse), duration of DMO, baseline BCVA, baseline central subfield thickness (considered to be equivalent to central retinal thickness [16]), baseline HbA_{1c}, age, sex and diabetes type all showed	The EAG notes that none of the subgroup analyses reported in the scope were provided in the CS but results from the *post-hoc* subgroup analysis of patients with CSFT ≥400 µm is provided from KITE and KESTREL.

	whose disease is refractory to laser photocoagulation, ranibizumab or bevacizumab) • prior cataract surgery		[redacted] [12, 13].	

Abbreviations: BCVA, best-corrected visual acuity; CFB, change from baseline; CS, company submission; CSFT, central subfield thickness; DMO, diabetic macular oedema; FTA, fast track appraisal; DRSS, diabetic retinopathy severity scale; N/A; not applicable; NHS, National Health Service; NICE, the National Institute for Health and Care Excellence; NMA, network meta-analysis; UK, United Kingdom; VEGF, vascular endothelial growth factor; wAMD, wet age-related macular degeneration.

2.1 Population

Clinical effectiveness data in the submission are derived from KESTREL and KITE, key trials designed to evaluate the efficacy and safety of brolucizumab. Patients eligible for inclusion in KESTREL and KITE were adults with DMO involving the centre of the macula and central subfield retinal thickness (CSFT) of ≥320µm on SD-OCT (spectral domain optical coherence tomography) at screening (further details in Section 3.2).

The final scope issued by NICE specifies the population of interest to be people with visual impairment due to DMO but the company has submitted for a narrower indication that restricts the population to only those with a central retinal thickness (CRT) of ≥400 µm. The EAG considers the narrower population addressed by the CS to be reasonable given the company's decision to submit a cost-comparison versus aflibercept and ranibizumab. However, the EAG notes that the focus of the clinical data from KESTREL and KITE (the key studies of brolucizumab), and from the company network meta-analyses (NMAs) presented in the CS relate to a broader DMO population. During the clarification stage, the EAG therefore requested additional data from the clinical studies and NMAs for the CRT of ≥400 µm population in which the company is positioning brolucizumab. The EAG notes that KITE and KESTREL report only data for CSFT and not CRT, although the company reported that they could be considered to be equivalent and referenced a paper by Waheed *et al.*2013[16] where it is reported that CSFT and CRT are closely correlated. However, the EAG's clinical experts reported that this is not always the case and some patients may have different measurements for CSFT and CRT. The EAG's clinical experts also highlighted that the definition typically used for CSFT is the average retinal thickness in the central 1mm, whereas there is less consensus on the definition of CRT and therefore it is difficult to assess how well the patients in the KITE and KESTREL trials (CSFT of ≥320µm) align with the anticipated population in England of DMO patients with a CRT of ≥400 µm. The EAG therefore considers that the full trial populations of KITE and KESTREL may have patients with a lower CRT than expected to be treated with brolucizumab in clinical practice (CRT of ≥400 µm) as they included patients with a CSFT of ≥320µm. The results for the CSFT of ≥400 µm subgroups from KITE and KESTREL are discussed in Section 3.3.5.

The EAG's clinical experts reported that aside from the CRT issue, the populations in KESTREL and KITE possibly comprise of patients with a slightly lower HbA_{1c} and a lower proportion of females compared to expected in clinical practice in England. Further discussion around the external validity of KESTREL and KITE is provided in Section 3.2.2, but in general, the EAG considers the population in the KESTREL and KITE trials to be broadly representative of patients in England who are likely to be

eligible for brolucizumab. However, the EAG has concerns around the population with the KITE study demonstrating some differences in baseline characteristics, in particular for mean best-corrected visual acuity (BCVA) and [redacted]. The EAG therefore considers KESTREL to potentially be more suitable for drawing conclusions on the efficacy of brolucizumab versus aflibercept than KITE.

In summary, the EAG's clinical experts consider the company's proposed positioning and target population for brolucizumab to be reasonable given the existing NICE guidance for aflibercept and ranibizumab, and that the data from KITE and KESTREL are likely to be relevant for patients in England.

2.2 Intervention

Brolucizumab (BEOVU®) is an anti-vascular endothelial growth factor (anti-VEGF) that is currently authorised for use in adults for the treatment of neovascular (wet) age-related macular degeneration. In addition, brolucizumab is licensed for treating visual impairment due to diabetic macular oedema. Brolucizumab received a CHMP positive opinion for use in this indication in February 2022 [17], with marketing authorisation granted by the European Commission and MHRA in April 2022.

Brolucizumab is administered via intravitreal treatment (IVT) injection, and the recommended dose is 6 mg brolucizumab (0.05 mL solution) administered every 6 weeks for the first five doses. Thereafter, the maintenance treatment intervals can be individualised based on disease activity:

- In patients without disease activity, treatment every 12 weeks (q12w [3 months]) should be considered; and
- In patients with disease activity, treatment every 8 weeks (q8w [2 months]) should be considered.

The EAG notes that the treatment schedules in KESTREL were generally consistent with the licensed posology for brolucizumab. However, the EAG notes that in the KITE trial there was the option for patients to extend their treatment interval by 4 weeks during the second year from q8w to q12w or q12w to q16w (every 16 weeks) and that the 16-week treatment interval is not included in the posology in the Summary of Product Characteristics (SmPC). The treatment regimens in KITE and KESTREL are discussed further in Section 3.2.

2.3 Comparators

As discussed in Table 1, the company has focused their submission on patients with visual impairment due to DMO and with a CRT of ≥400 µm and as a result they have narrowed down the comparators in the cost comparison to just aflibercept and ranibizumab. The EAG's clinical experts agree with the company that the most relevant comparators for the use of brolucizumab in this population are aflibercept and ranibizumab. However, the EAG's clinical experts also reported that due to potential safety concerns in terms of intraocular inflammation with brolucizumab it may be used as a second-line treatment with preference for aflibercept or ranibizumab as first-line therapy. The EAG notes that in wet age-related macular degeneration (wAMD) safety concerns around intraocular inflammation emerged only during the post-marketing surveillance of brolucizumab and that it has been captured as an adverse event of special interest in KITE and KESTREL. However, the EAG considers that KITE and KESTREL [redacted]

The EAG sought clarification on the treatment pathway from the company and the company reported that their panel of six clinicians considered the primary positioning of brolucizumab would be as a first-line treatment and highlighted an absence of clinical trial data for brolucizumab use at second-line.

The EAG notes that the key clinical trials for brolucizumab, KESTREL and KITE, both compare brolucizumab versus aflibercept, although they do not exclusively comprise of patients with a baseline CRT ≥400 µm. The EAG also notes that indirect treatment comparisons have been conducted by the company to enable a comparison with ranibizumab but the EAG is concerned about the robustness of the NMAs. This is because the primary analysis is in a wider DMO population than those with a CRT ≥400 µm, and the study used to inform ranibizumab in the NMA for the DMO subgroup with a CRT of ≥400 µm uses a lower dose of ranibizumab compared to in clinical practice in England. The EAG thus considers the comparison of the efficacy and safety of brolucizumab with ranibizumab to be uncertain.

The results of the company's NMAs are discussed further in Section 3.4.

In summary, the EAG considers the key comparators have been included in the company submission but the conclusions for the comparison of brolucizumab versus ranibizumab in the correct population are uncertain due to a lack of data for ranibizumab.

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

3.1 Critique of the methods review

The company conducted a systematic literature review (SLR) to identify randomised controlled trial (RCT) data for adults (≥18 years) with a confirmed diagnosis of diabetic macular oedema (DMO) to compare evidence on the efficacy and safety of brolucizumab with aflibercept and ranibizumab. Full methods and results of the SLR are reported in Appendix D of the company submission (CS).

A total of 44 studies (from 140 publications) were included in the SLR (detailed in Table 6 of Appendix D of the CS), evaluating either the use of brolucizumab or a comparator of relevance (or both) in adults with DMO as set out in the National Institute for Health and Care Excellence (NICE) scope. Of the studies matching the broad inclusion criteria of the NICE scope, two RCTs (from four publications) directly comparing outcomes for brolucizumab with aflibercept (KESTREL and KITE studies) were identified.

In addition, of the 44 studies originally identified, 14 studies (from 72 publications, including KESTREL and KITE) were selected to be included in the network meta-analysis (NMA) by narrowing the inclusion of comparators to those that the company considered to be the most relevant, which were the anti-vascular endothelial growth factors (anti-VEGFs) aflibercept (2 mg) and ranibizumab (0.5 mg). The purpose of this NMA was to enable a comparison between brolucizumab and ranibizumab given the lack of RCTs comparing these two drugs head-to-head in the DMO population. Details of the 30 studies (from 72 publications) identified as meeting the broad inclusion criteria in the NICE scope (but not included in the NMA), including their quality assessment, were provided by the company (CS Appendix D, Table 23). However, the Evidence Assessment Group (EAG) notes that clinical data from these studies has not been analysed further in the CS.

The final list of the 14 studies used in the CS in terms of clinical evidence is provided in Appendix D of the CS (Table 8 of Appendix D).

An overview of the methods used by the company for the SLR, together with the EAG's critique of the appropriateness of these methods, is presented in Section 3.1. In brief, the EAG considers the methods applied by the company to be robust and likely to have identified all clinical evidence of relevance to the decision problem.

Table 2. Summary of the EAG's critique of the methods implemented by the company to identify evidence relevant to the decision problem

Systematic review step	Section of CS in which methods are reported	EAG assessment of robustness of methods
Data sources	Appendix D, section D1.1.	**The EAG considers the sources and dates searched to be appropriate.** Databases searched: Embase, MEDLINE (Daily, In-Process and Other Non-indexed citations, and e-pub ahead of print), Cochrane Library (Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews) via Ovid. Searches conducted on 6th December 2021 and no restrictions were placed on the date of the published studies (search performed from date of database inception to date search performed). Additional sources searched: conference proceedings of relevant conferences between 2019 and 2021, clinical trial registries (clinicaltrials.gov and WHO ICTRP), previous HTA submissions, reference lists of relevant studies and other grey literature sources recommended by NICE.
Search strategies	Appendix D, section D1.2	**The EAG is satisfied that searches have identified all evidence relevant to the decision problem.** Search strategies for the literature review combined comprehensive terms for the population, interventions and study designs, using free-text and medical subject headings. The search focused on RCTs, with specific search filters used to distinguish between study designs
Inclusion criteria	Appendix D, section D1.3	**The EAG considers it likely that no relevant evidence was excluded based on the eligibility criteria used.** Initial inclusion criteria were in line with the NICE scope; however, some of these studies were not used further in the CS, with only those meeting stricter criteria included in the NMA (section D1.8 in Appendix D of CS, Table 8). Further exclusion criteria not specified in the NICE scope were applied, such as studies with an assessment period of <44 weeks and/or sample size of <30 patients, but these were considered by the EAG to be reasonable given a time-period of at least 52 weeks was focused on in TA346 for aflibercept[1] and TA274 for ranibizumab[2] and that much smaller studies could introduce more uncertainty into the NMA model. Full reference details of all studies meeting the broader NICE scope are available in Appendix D of the CS (section D1.7.1, Table 6), as well as for studies excluded at full-text appraisal (section D1.7.2, Table 7). It was not explicitly stated that the review was limited to English-language publications but 'language' was used as a reason for one study being excluded, so it is likely that English language was an inclusion criterion.
Screening and data extraction	Appendix D, section D1.4	**The EAG considers the methods for screening and data extraction likely to be robust.**

		Two reviewers independently screened titles and abstracts, and studies selected for full text appraisal, against predefined criteria, with a third and more senior reviewer consulted when consensus could not be reached. Results of the literature screening processes were summarised in a PRISMA diagram. Data extraction was carried out by one reviewer into a standardised, piloted data extraction table in Excel. Extractions were checked and validated by conducting an internal data check, though it was unclear whether this validation stage was conducted by an independent and/or more senior reviewer.
Tool for quality assessment of included study or studies	B.3.6 & Appendix D, sections D1.5, D1.14 and D3	**The EAG agrees with the company's choice of quality assessment tool.** The company used the standard NICE checklist for RCTs for quality assessment of all included studies, including key trials KESTREL and KITE, additional studies in the NMA and the 30 studies said to be included but not used as part of the CS. The company also assessed RoB using the Jadad scale and provided Jadad scores for each study, which were not considered to be relevant by the EAG as this scale is less detailed than the NICE standard checklist for RCTs. Quality assessment was performed by two independent reviewers and clear justification for the risk of bias assigned to each domain has been provided. See Appendix 8.2 for EAG validation of the quality assessments for key trials focused on in the CS (KESTEL and KITE) and Table 3 for EAG assessment of design, conduct and internal validity.

Abbreviations: CS, company submission; EAG, Evidence Assessment Group; HTA, health technology appraisal; NICE, National Institute for Health and Care Excellence; NIHR, National Institute for Health Research; NMA, network meta-analysis; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT, randomised controlled trial; SLR, systematic literature review; WHO ICTRP, World Health Organization International Clinical Trials Registry Platform.

3.2 Critique of trials of the technology of interest, the company's analysis and interpretation

In subsequent sections, the EAG focuses on aspects of trial design, conduct and external validity of KESTREL and KITE studies, the main studies focused on in the CS.

3.2.1 Internal validity of KESTREL and KITE

The EAG's assessment of the design, conduct and internal validity of the KESTREL and KITE studies is summarised in Table 3. The EAG considers that for most domains assessed (See Appendix 8.2), KESTREL and KITE are at low risk of bias for analysis of the primary outcomes, based on the full trial population. However, the EAG highlights that there are a number of issues that could represent a risk of bias for both studies, including some differences between trial arms in variables at baseline, investigators administering injections not being masked to treatment and the use of the last

observation carried forward (LOCF) method of imputation for missing or censored data (see Appendix 8.2).

In terms of differences between trial arms in baseline measurements, the biggest concern for the EAG and the EAG's clinical experts was the [redacted] One of the EAG's clinical experts noted that there may be differences in the performance of anti-VEGFs based on baseline BCVA. At the clarification stage the company stated that due to a ceiling effect, change from baseline scores in BCVA are generally higher in those with lower baseline scores suggesting that the results could favour the aflibercept group; however, although the EAG note this as a possibility, the literature provided by the company to support this also notes that gains in those with particularly poor baseline visual acuity can also be limited.[18] The EAG is therefore unsure about the direction of any potential bias in the KITE study but notes that there was heterogeneity between the KITE and KESTREL studies for multiple outcomes, with results more favourable for brolucizumab in the KITE study.

The issue of investigators administering injections not being masked to treatment was highlighted as a potential source of risk of bias by the EAG; however, given they were not involved in outcome assessment other than safety events occurring immediately post-injection, the risk of bias this issue poses for most reported outcomes is likely to be low.

The use of the LOCF method of imputation for missing or censored data in KESTREL and KITE was a concern for the EAG as the assumption that the condition does not deteriorate further over time without treatment may not be appropriate in DMO. Although the study discontinuation rates [redacted]. The EAG notes that the LOCF method of imputation was also used in the key trials included in the aflibercept (VIVID and VISTA) and ranibizumab (RESTORE and Diabetic Retinopathy Clinical Research Network Protocol I) NICE TA 346[1] and TA 274,[2] respectively.

The EAG also notes that the rate of dropouts in terms of treatment discontinuation could only be assessed and compared between groups [redacted].

KESTREL and KITE are both 2-year, phase III, multicentre RCTs designed to assess the efficacy and safety of brolucizumab (6 mg/0.05 ml) compared to aflibercept (2 mg/0.05 ml) in patients with visual impairment due to DMO. The EAG notes that the trial design, end-points and patient eligibility criteria are similar or identical between the two trials (Table 4 of CS); however there are some differences, including KITE having the option to extend the dosing schedule by 4 weeks at week 72 and timing of disease activity assessment (DAA) visits (which were used to inform whether dosing intervals should be 8 or 12/16 weeks for each patient) differing between trials after 72 weeks (every 4 weeks in KITE and every 12 weeks in KESTREL). KESTREL also included a 3 mg brolucizumab arm and although the company included the results in the CS, they are not discussed by the EAG as the licensed dose is 6 mg. The primary endpoint was identical between the studies but secondary endpoints differed slightly. Despite similarities between the two studies, formal pooling of the results of the two trials was not performed and results for each of the studies were reported separately in the CS. The EAG sought clarification from the company on their decision not to pool the trial results in the CS and considers the company rationale unclear (company response to clarification question A10); although the EAG do not think that the rationale provided would preclude meta-analyses being presented, it is acknowledged that pooled results are unlikely to change the conclusions, [redacted] and that the company has not provided any rationale for these potential differences.

The EAG notes that the company has provided data separately for the subgroup with a central subfield thickness (CSFT) of ≥400 µm in each of these trials, to reflect the population in which the company is positioning brolucizumab (see Section 2.1). [redacted]

[redacted] Further discussion of the subgroup and its results in comparison to the overall population is provided in Section 3.3.5.

Table 3. Summary of the design and conduct of KESTREL and KITE trials, which were the key trials focused on in the CS

Aspect of trial design or conduct	Section of CS providing details on trial characteristic	Summary of KESTREL	Summary of KITE
Trial conduct			
Randomisation	B.3.3.1, Appendix D (Table 23) of CS and CSR (section 9.4.3 for KESTREL and KITE)	**Appropriate** Randomised design with parallel assignment of participants in 1:1:1 ratio to brolucizumab 6 mg, brolucizumab 3 mg or aflibercept 2 mg. Dosing was 5 doses (once every 6 weeks) loading followed by doses every 8 or 12 weeks depending on DAA visits for brolucizumab, and 5 doses (once every 4 weeks) loading followed by doses every 8 weeks for aflibercept. Randomisation was performed using IRT and [redacted]	**Appropriate** Randomised design with parallel assignment of participants in 1:1 ratio to brolucizumab 6 mg or aflibercept 2 mg. Dosing was 5 doses (once every 6 weeks) loading followed by doses every 8 or 12 weeks depending on DAA visits for brolucizumab, and 5 doses (once every 4 weeks) loading followed by doses every 8 weeks for aflibercept. For the brolucizumab group, after week 72 dosing intervals could be increased by 4 weeks based on DAA (increasing to 12 weeks if dosing was every 8 weeks or to 16 if dosing was every 12 weeks at time of assessment). This was a difference in protocol compared to the KESTREL study. Randomisation was performed using IRT and [redacted]
Concealment of treatment allocation	Appendix D (Table 23) of CS	**Appropriate** Treatment allocation concealed through use of IRT, an automated system.	
Eligibility criteria	B.3.3.2	**Appropriate** Adults (≥18 years) with type 1 or 2 diabetes and HbA_{1c} of ≤10% at screening, with visual impairment due to DMO in the study eye: BCVA score 78-23 letters using ETDRS visual acuity testing charts at distance of 4 m at screening and baseline; DMO involving centre of macula, with CSFT ≥320 µm on SD-OCT at screening. Detailed inclusion and exclusion criteria are provided in Table 5 of the CS.	

		The EAG's clinical experts advised that the eligibility criteria employed were appropriate overall, although it was noted that in clinical practice some people will have higher HbA_{1c} values than included in the study.	
Baseline characteristics	B3.4 and Appendix D (Table 23) of CS	Most baseline characteristics were well balanced between the brolucizumab 6 mg and aflibercept 2 mg groups. The EAG notes there was a difference between groups for the [redacted] and the proportion with HbA_{1c} levels ≥7.5% (59.6% vs. 42.8%). However, one of the EAG's clinical experts advised that HbA_{1c} levels should not have a large impact on treatment efficacy. Full baseline characteristics are available in Appendix 8.1.	Most baseline characteristics were well balanced between the brolucizumab 6 mg and aflibercept 2 mg groups. The EAG considers that there was a difference between groups for the [redacted] and there was a [redacted] Full baseline characteristics are available in Appendix 8.1.
Masking appropriate	B.3.3.4, Appendix D (Table 23) of CS and respective CSRs (section 9.4.4 for KESTREL and KITE)	Double-blind study. Patients in all arms received sham or active injections at each visit to establish an identical treatment schedule to ensure masking (with the exception of weeks where no treatment was scheduled). [redacted] Investigators, patients and biostatisticians all reported to be masked.	
No difference between groups in treatments given, other than intervention versus control	B.3.3.4.5 and respective CSRs for KESTREL and KITE	From week 36, if DMO worsened (loss of ≥10 letters at two consecutive visits or ≥15 letters at one visit compared with previous best measurement, with BCVA not better than baseline), rescue treatment (laser photocoagulation) in addition to study treatment was permitted in study eyes of both treatment arms where they were identified as needing 8-weekly dosing at a previous DAA visit. Although said to be prohibited prior to week 36, if it was used before this time-point continuation of study treatment was at the investigator's discretion. [redacted] In fellow (non-study) eyes, standard of care/other treatments were permitted at any time for DMO and other diseases.	

		[redacted]	
		The EAG notes that details of the proportion receiving each of these specific rescue or concomitant treatments during the study period is not reported; [redacted]	The EAG notes that details of the proportion receiving each of these specific rescue or concomitant treatments during the study period is not reported; [redacted]
Dropouts (high dropout and any unexpected imbalance between groups)	Appendix D2 (Figures 3 and 4) and Appendix D1.8.1	Proportion discontinuing study treatment up to week 52 was similar but slightly higher in the brolucizumab 6 mg group compared to aflibercept 2 mg group (13.2% vs 9.6%). The proportion in each group discontinuing treatment for each specific reason (for example adverse events) was generally similar across groups. For study discontinuation at 52 weeks, the rate was also slightly higher in the brolucizumab group at 52 weeks (9.5% vs 8.0% in brolucizumab vs aflibercept). [redacted]	Proportion discontinuing study treatment up to week 52 was similar but slightly higher in the brolucizumab 6 mg group compared to aflibercept 2 mg group (10.6% vs 8.3%). The proportion in each group discontinuing treatment for each specific reason (for example adverse events) was generally similar across groups. For study discontinuation at 52 weeks, the rate was also slightly higher in the brolucizumab group at 52 weeks (9.5% vs 6.6% in brolucizumab vs. aflibercept). [redacted]

Outcomes assessed	B.3.3.5	The EAG considers that the outcomes reported in KESTREL and KITE cover most of those listed in the NICE final scope. No evidence to suggest that additional outcomes of relevance were assessed and not reported. The primary outcome was change from baseline in BCVA at 52 weeks. See Tables 7 (KESTREL) and Tables 7 and 8 (KITE) in the CS for detailed description of all secondary outcomes included.
ITT analysis carried out	B.3.5 and Appendix D (Table 23) of CS	**Yes - modified ITT** Main analysis reported was in the FAS population, described as all patients that were randomised and received at least one IVT injection of the study treatment. This represents a modified ITT analysis. Analysed according to treatment assigned at randomisation, with the LOCF method employed for imputation of missing/censored data. The EAG is concerned about the use of LOCF as although missing data [redacted]. Reasons for drop-out include those related to the study (for example adverse events) and discontinuing treatment may lead to deterioration in outcome rather than maintenance of effect from previous measurement. However, the EAG also noted that this may apply for both brolucizumab and aflibercept arms and the risk of bias may depend on the differences in proportions of missing data between arms. Assuming efficacy is maintained once discontinued may therefore benefit the [redacted]
Subgroup analyses	B.3.8, Appendix D5 of CS and respective CSRs (section 9.4.3 for KESTREL and section 9.7.2.1 for KITE)	The company provided results for a *post-hoc* subgroup of those with CSFT ≥400 µm to reflect the CRT ≥400 µm population that aflibercept and ranibizumab are recommended for by NICE in DMO (TA346 for aflibercept[1] and TA274 for ranibizumab[2]).
Statistical analysis plan		
Sample size	B.3.5.2	The company reported that based on sample size calculations, 160 patients per group were required to be randomised 1:1:1 (KESTREL) or 1:1 (KITE) to allow the demonstration of non-inferiority between brolucizumab 6 mg or 3 mg vs aflibercept 2 mg groups in the primary outcome. A non-inferiority margin of 4 ETDRS letters was used. A drop-out rate of 10% was considered when considering how many patients should be randomised in the study.

		[redacted]	
Power	B.3.5.2	The company reported that, with a sample size of 160 patients per arm, the study would have 90% power at a one-sided alpha level of 0.025 for demonstrating non-inferiority in relation to the primary outcome (change from baseline in BCVA at week 52), assuming equal means and a common SD of 11 letters. It was also reported that a power ≥90% could be expected for non-inferiority when average change from baseline in BCVA across four time points was used as the outcome, assuming that averaging over the four time-points would not lead to an increase in the SD.	
		N=534 patients (n=178 per arm, three arms) were planned to be randomised, with actual numbers randomised being slightly higher than this.	N=356 patients (n=178 per arm, two arms) were planned to be randomised, with actual numbers randomised being slightly higher than this.
Analysis sets	B.3.5.1	The primary analysis for most primary and secondary outcomes was within the FAS set, representing a modified ITT analysis of all of those that were randomised and received at least one IVT injection of study treatment. The exception was safety outcomes (adverse events), which were analysed according to the safety (SAF) population (all patients receiving at least one study drug IVT injection, analysed according to treatment arm in which they received most treatment up to and including week 48). The EAG notes that it is unclear whether the FAS and SAF analysis sets differ in terms of those included in each group, but numbers for FAS and SAF analyses are identical, with no mention of switching between drugs being allowed in the protocol. Additional analysis sets described in the trial are described in section B.3.5.1 of the CS.	

Abbreviations: BCVA, best-corrected visual acuity; CRT, central retinal thickness; CS, company submission; CSFT, central subfield thickness; CSR, clinical study report; DAA, disease activity assessment; DMO; diabetic macular oedema; EAG, Evidence Assessment Group; ETDRS, Early Treatment Diabetic Retinopathy Scale; FAS, full analysis set; HbA_{1c}, glycated haemoglobin; IRT, Interactive Response Technology; ITT, intention to treat; IVT, intravitreal treatment; LOCF, last observation carried forward; NICE, National Institute for Health and Care Excellence; SAF, safety analysis set; SD, standard deviation; SD-OCT, spectral domain optical coherence tomography; VEGF, vascular endothelial growth factor.

3.2.2 *External validity of KESTREL and KITE*

The EAG's clinical experts consider the characteristics of the populations in the KESTREL and KITE trials to be broadly similar to those eligible for anti-VEGF treatments for DMO in England.

However, certain characteristics that made the trials less representative of the population seen in clinical practice in the United Kingdom (UK) were identified. Clinical experts noted that they would expect the proportion of males and females in practice to be more of an even split, rather than ~60% being male. It was also highlighted that the proportion of people that were Black, African American or Asian would be higher in UK clinical practice; however, it was also noted that this may differ across different local regions of the UK and the proportions seen in the trial may be representative for some regions. The EAG note that although [redacted] For characteristics related to DMO, mean HbA_{1c} levels, which indicate the level of diabetes control being achieved, were considered by the EAG's clinical experts to be better than would be seen in clinical practice overall. Both KESTREL and KITE studies restricted inclusion to people with HbA_{1c} levels ≤10%, whereas the EAG's clinical experts reported that in clinical practice people with levels >10% are also seen and may be eligible for brolucizumab. It was estimated by one clinical expert that people with levels >10% could represent up to 20% of all patients but that this likely varies between regions and that it should not have a large impact on clinical efficacy of anti-VEGFs. In addition, the EAG's clinical experts reported that in clinical practice, usually only those with central retinal thickness (CRT) values ≥400 µm would be treated with anti-VEGFs, and the inclusion criterion of central subfield thickness (CSFT) ≥320 µm in KESTREL and KITE may potentially represent a broader population than would usually be treated with anti-VEGFs in DMO. The EAG notes that the company reported that CRT and CSFT could be considered to be equivalent and referenced a paper by Waheed *et al*. 2013[16] where it is reported that CSFT and CRT are closely correlated. However, the EAG's clinical experts also reported that CSFT does not necessarily equal CRT, and so it is difficult to draw conclusions for the CRT ≥400 µm population based on the CSFT subgroup. The EAG also notes that [redacted].

The EAG's clinical experts were also unsure as to how a small proportion of patients in both trials were reported to have 'absent' intra-retinal fluid (IRF), as macular oedema refers to fluid in the

retina and 100% would therefore be expected to have IRF. However, it was noted that the proportion is very small and may be based on specific definitions used in the trials which were not provided.

Despite some differences between the trial populations and those seen in UK clinical practice, overall the EAG considers that the populations in the trials were broadly representative of the UK population.

3.3 Clinical effectiveness results of KESTREL and KITE

The results of KESTREL and KITE for change from baseline in BCVA, change from baseline in CSFT and change from baseline in Visual Functioning Questionnaire-25 (VFQ-25) overall score for the full trial populations and the baseline CSFT≥400 µm subgroup are summarised in Table 4 and discussed in detail in the subsections below. Additionally, the outcomes used in comparator health economic models are discussed below (Section 3.3.3) and results for additional outcomes of relevance to the decision problem are summarised in Appendix 8.3.

Table 4. Summary of clinical effectiveness results from KITE and KESTREL

Study	KITE		KESTREL	
Treatments	Brolucizumab 6 mg vs aflibercept 2 mg		Brolucizumab 6 mg vs aflibercept 2 mg	
Population	Full trial population (N=360)	Baseline CSFT ≥400 µm subgroup* [redacted]	Full trial population (N=376)	Baseline CSFT ≥400 µm subgroup* [redacted]
ANOVA results for change from baseline in BCVA (letters read) for the study eye (FAS – LOCF) [A non-inferiority margin of 4 ETDRS letters was used][1]				
Week 52 LSM difference (95% CI for treatment difference)	1.2 (–0.6 to 3.1; p-value for non-inferiority (1-sided) <0.001)	[redacted]	–1.3 (–2.9 to 0.3; p-value for non-inferiority (1-sided) <0.001)	[redacted]
Week 100 LSM difference (95% CI for treatment difference)	NR	[redacted]	NR	[redacted]
ANOVA results for change from baseline in CSFT (µm) at Week 52 and Week 100 for the study eye (baseline CSFT≥400 µm subgroup – LOCF)[2]				
N in analysis at week 52	[redacted]	[redacted]	[redacted]	[redacted]
Week 52 LSM difference (95% CI for treatment difference)	[redacted]	[redacted]	[redacted]	[redacted]

N in analysis at week 100				
Week 100 LSM difference (95% CI for treatment difference)				
ANCOVA results for change from baseline in VFQ-25 overall score by visit (baseline CSFT ≥400 µm subgroup – Observed)[3]				
N in analysis at week 52				
Week 52 LSM difference (95% CI for treatment difference)				
N in analysis at week 100				
Week 100 LSM difference (95% CI for treatment difference)				

n=the number of patients with data used in the model.

* Patients with baseline CSFT <400 are excluded from this analysis.

[1] Analysed using the ANOVA model with baseline BCVA categories (≤65, >65 letters), age categories (<65, ≥65 years) and treatment as fixed effect factors. BCVA assessment after the start of alternative DMO treatment in the study eye are censored and replaced by the last value prior to the start of the alternative treatment.

[2] Analysed using ANOVA model with baseline CSFT categories (<450, ≥450–<650, ≥650 µm), age categories (<65, ≥65 years) and treatment as fixed effect factors. CSFT assessments after start of alternative DMO treatment in the study eye are censored and replaced by the last value prior to start of this alternative treatment.

[3] Analysed using the ANCOVA model with treatment as a fixed effect factor and corresponding baseline value of the endpoint as a covariate. Data after start of alternative DMO treatment in the study eye are censored and are not included in this analysis.

Abbreviations: ANOVA, analysis of variance; ANCOVA, analysis of covariance; BCVA, best-corrected visual acuity; CI, confidence interval; CRT, central retinal thickness; CSFT, central subfield thickness; FAS, full analysis set; LOCF, last observation carried forward; LSM, least squares mean; SE, standard error; VFQ-25, visual functioning questionnaire-25.

3.3.1 BCVA change from baseline

The primary objective in the KESTREL and KITE studies was to demonstrate that brolucizumab is non-inferior to aflibercept in terms of change from baseline in BCVA in the study eye at week 52.

Both studies confirmed non-inferiority of 6 mg brolucizumab vs 2 mg aflibercept at week 52, with non-inferiority defined as the lower limit of the 95% confidence interval (CI) for the corresponding treatment difference (brolucizumab – aflibercept) being > –4 letters. In KESTREL, least squares mean (LSM) treatment difference at week 52 was –1.3 (95% CI: –2.9 to 0.3), while in KITE the LSM treatment difference was 1.2 (95% CI: –0.6 to 3.1) (Table 4).

The company also provided a narrative summary (section K1.1 of Appendix K) and graph (Figures 1 and 2 of Appendix K) of LSM change from baseline in BCVA score at each post-baseline visit up to week 100 which suggest that

[redacted]

3.3.2 CSFT change from baseline

CSFT is defined as the average thickness of the macula in a 1 mm circular area around the fovea and is assessed by spectral domain optical coherence tomography (SD-OCT). An increase in this measurement in DMO is a measure of abnormal fluid accumulation and oedema, and may result in reduced vision. For both studies, the company describes

[redacted] These trends for KITE and KESTREL generally continued across the study period but there were some time-points where this was not the case, which the company explain may be due to [redacted]; for example, [redacted] The EAG also notes that up to week 52 [redacted] The company notes that in [redacted]

Results for brolucizumab 6 mg vs aflibercept 2 mg as LSM treatment difference at weeks 52 indicate [redacted]; however, there is [redacted]

3.3.3 Health-related quality of life (VFQ-25) at weeks 52 and 100

VFQ-25 is a validated instrument used to measure health-related quality of life (HRQoL) specific to vision in patients with chronic eye conditions. Overall scores are an average of eleven subscales, with each subscale ranging from 0 to 100 and higher scores representing better functioning.

At week 52, [redacted] in VFQ-25 overall score (composite) were present for brolucizumab 6 mg and aflibercept 2 mg groups [redacted] for the brolucizumab group compared to aflibercept [redacted]

[redacted] in VFQ-25 overall score (composite) were observed at week 100, [redacted] (CS, Table 24), although the EAG notes that for KITE, the difference between groups [redacted] while for KESTREL the treatment difference [redacted] (Table 4).

3.3.4 Outcomes used in comparator health economic models for aflibercept and ranibizumab appraisals

This section discusses efficacy results from KESTREL and KITE that were key to health economic models of the appraisals for aflibercept[1] and ranibizumab,[2] which were the proportion of patients experiencing a change of ≥15 and/or ≥10 letters on the BCVA (Table 5). The EAG notes that the comparator models also included EQ-5D, but this was not reported in the KESTREL and KITE studies; however, a discussion of results for Visual Function Questionnaire-25 (VFQ-25), a health-related quality of life measure reported in KESTREL and KITE, is provided in Section 3.3.3. Adverse events were also included in comparator health economic models but these are discussed separately in Section 3.3.6 below.

Results for treatment difference were determined using a logistic regression model adjusting for baseline BCVA categories (≤65 letters vs >65 letters), age categories (<65 years vs ≥65 years) and treatment as fixed effect factors. Results are for the full analysis set (FAS) analysis set, with LOCF used for missing or censored data. The associated p-values were not provided. The EAG notes that proportions reported for each group often do not align with mean differences reported between treatments as the mean differences were calculated using regression analysis.

Table 5. Other secondary endpoints related to BCVA (FAS – LOCF) (Adapted from CS, Table 21)

Trial name		KITE	KESTREL
Secondary endpoint	Week	Treatment difference, (brolucizumab 6 mg vs aflibercept*), % (95% CI†)	Treatment difference, brolucizumab 6 mg vs aflibercept*, % (95% CI†)
BCVA gain of ≥10 or ≥15 letters (or BCVA of ≥84 letters)			
≥10 letters gain from baseline or BCVA of ≥84 letters	52	[redacted]	[redacted]
	100	[redacted]	[redacted]
≥15 letters gain from baseline or BCVA of ≥84 letters	52	[redacted]	[redacted]
	100	[redacted]	[redacted]
BCVA loss of ≥10 or ≥15 letters			
≥10 letters loss from baseline	52	[redacted]	[redacted]
	100	[redacted]	[redacted]
≥15 letters loss from baseline	52	[redacted]	[redacted]
	100	[redacted]	[redacted]

BCVA assessments after start of alternative DMO treatment in the study eye are censored and replaced by the last value prior to start of this alternative treatment.
*Estimate of treatment difference from statistical model using logistic regression adjusting for baseline BCVA categories (≤65, >65 letters), age categories (<65, ≥65 years) and treatment as fixed effect factors.
†95% CI for the treatment difference estimated using bootstrap method.
Abbreviations: BCVA, best-corrected visual acuity; CI, confidence interval; DMO, diabetic macular oedema; FAS, full analysis set; LOCF, last observation carried forward.

3.3.4.1 Proportion with gain or loss of ≥10 BCVA letters from baseline, or BCVA of ≥84 letters, at 52 and 100 weeks

Gain of ≥10 BCVA letters from baseline or BCVA of ≥84 letters

At 52 weeks in KESTREL, [redacted] in the brolucizumab 6 mg group [redacted] gained ≥10 letters on the BCVA from baseline or had a BCVA of ≥84 letters compared to the aflibercept 2 mg group [redacted], with a treatment difference of [redacted]. The [redacted] was

observed for KITE, as there was a [redacted] in the brolucizumab 6 mg group [redacted] who gained ≥10 letters on the BCVA from baseline or had a BCVA of ≥84 letters compared to the aflibercept 2 mg group [redacted], with a treatment difference of [redacted].

[redacted]

At 100 weeks, the

[redacted] 5[redacted]

Loss of ≥10 BCVA letters from baseline

At 52 weeks,

[redacted] (Table 5). At 100 weeks, the [redacted]. For KESTREL, the proportion with a loss of ≥10 BCVA letters from baseline was [redacted] in the brolucizumab 6 mg group compared to aflibercept 2 mg [redacted], with a treatment difference of [redacted] KITE there was [redacted].

[redacted]

3.3.4.2 Proportion with gain or loss of ≥15 BCVA letters from baseline, or BCVA of ≥84 letters, at 52 and 100 weeks

Gain of ≥15 BCVA letters from baseline or BCVA of ≥84 letters

Results from KESTREL and KITE for gain of ≥15 BCVA letters from baseline or BCVA of ≥84 letters at both 52 weeks and 100 weeks

[redacted]

[redacted] (Table 5). In KESTREL, [redacted] in the brolucizumab 6 mg group gained ≥15 letters on the BCVA from baseline or had a BCVA of ≥84 letters compared to the aflibercept 2 mg group

[redacted] was observed for KITE, and at 100 weeks the

[redacted]

Loss of ≥15 BCVA letters from baseline

Results from KESTREL and KITE for loss of ≥15 BCVA letters from baseline at both 52 weeks and 100 weeks [redacted] (Table 5). At 52 weeks, [redacted] in the brolucizumab 6 mg group [redacted] lost ≥15 letters on the BCVA compared to baseline compared to the aflibercept 2 mg group.

[redacted]

At 100 weeks, a [redacted] in the brolucizumab 6 mg group compared to aflibercept 2 mg had a loss of ≥15 letters in BCVA compared to baseline in KESTREL. For KITE, the [redacted] at 52 weeks had

[redacted]

3.3.5 Subgroup analyses

As discussed in Section 2, the company provided results from *post hoc* subgroup analyses of people with a CSFT ≥400 µm and <400 µm,

[redacted] At the clarification stage the company provided results for other outcomes in the ≥400 µm subgroup, as requested by the EAG because it is the population in which the company is proposing the use of brolucizumab in.

The results for the primary outcome indicate [redacted] 4[redacted], the EAG notes that point estimates suggest results for the [redacted], the EAG also notes that 95% [redacted] however, it may not be [redacted] Additionally, the EAG notes that formal testing of non-inferiority for the primary outcome was not possible for the subgroup analysis as the studies were not powered for this.

[redacted]

The EAG also notes that there are [redacted], although the EAG also notes that the [redacted] The EAG therefore notes that there are [redacted]

3.3.6 Adverse effects

The Summary of Product Characteristics for brolucizumab (Beovu®) reports various common and uncommon adverse events (AEs) associated with the drug (Table 1 of Appendix C of the CS). Those specifically mentioned under precautions for use include endophthalmitis, intraocular inflammation, intraocular pressure increase, traumatic cataract, retinal detachment, retinal tear, retinal vasculitis, and/or retinal vascular occlusion. Intraocular inflammation events were of particular concern to the EAG's clinical experts, as discussed further in section 3.3.6.1.2 below. The Summary of Product Characteristics reports evidence that after dosing with brolucizumab for 52 weeks in DMO, treatment-emergent anti-brolucizumab antibodies were detected in 12-18% of patients; of these patients, a higher number of intraocular inflammation adverse reactions were observed and after investigation these events were found to be immune-mediated adverse events related to brolucizumab exposure.

An overview of the adverse event profiles from KESTREL and KITE is provided below, which includes those specifically mentioned in the NICE final scope (mortality and adverse effects of treatment), though need for cataract surgery in the scope is not reported for these trials. Discontinuations are also mentioned here given they were considered in the health economic assessment of this appraisal. Analyses for adverse events are reported within the safety (SAF) population (see Table 3 above for the definition of this analysis set).

Across the different adverse event groupings discussed below, the EAG note that there are [redacted]

3.3.6.1 Ocular adverse events

3.3.6.1.1 Any severity

The overall rate of ocular AEs was comparable between brolucizumab 6 mg and aflibercept 2 mg groups at week 52 (29.6% vs 28.7% in KITE and 40.2% vs 39.0% in KESTREL) [redacted] in both studies.

Of those occurring in at least 2% of patients in either arm of either study up to 52 weeks (Table 2 of Appendix F of the CS), a ≥2% higher rate was observed for the brolucizumab 6 mg group compared to aflibercept 2 mg for conjunctivitis (2.8% vs 0.6% in KITE), eye pruritus (2.2% vs 0.0% in KITE), vitreous floaters (5.3% vs 2.1% in KESTREL), vitreous detachment (4.2% vs 0.5% in KESTREL) and increased intraocular pressure (3.2% vs 0.0% in KESTREL), with a ≥2% lower rate observed in the brolucizumab group for conjunctival haemorrhage (7.4% vs 9.6%), reduced visual acuity (1.1% vs 3.2%) and corneal abrasion (0.0% vs2.1%) in the KESTREL trial.

At 100 weeks, of events where at least 2% in either study arm of either study experienced them, ≥2% higher rates in the brolucizumab 6 mg group were observed for [redacted] Events where there was a ≥2% lower rate for the brolucizumab 6m group were [redacted]

3.3.6.1.2 Serious events

Up to week 100, event rates were [redacted] for serious ocular AEs suspected of being related to the study treatment [redacted] and serious ocular AEs suspected of being related to the intravitreal treatment (IVT) injection procedure [redacted]

Ocular AEs of special interest (AESI) were also reported ([redacted] in KITE and [redacted] in KESTREL for brolucizumab 6 mg vs aflibercept 2 mg groups), which includes [redacted]; the EAG's clinical experts noted that there is concern about intraocular inflammation associated with brolucizumab, which emerged during the post-marketing surveillance of brolucizumab for use in wet age-related macular degeneration (wAMD), and the same concern about this adverse event was not noted for

aflibercept and ranibizumab. Given that the concern about brolucizumab in wAMD was only identified after entering routine use, the EAG is concerned that the same may occur for DMO and would not expect large signals to be identified from regulatory trials.

[redacted] (Table 31 of CS).

[redacted]

Intraocular inflammation related to brolucizumab treatment is also flagged under special warnings and precautions for use in the Summary of Product Characteristics, with evidence in DMO reporting treatment-emergent anti-brolucizumab antibodies were detected in 12-18% of patients and a higher number of intraocular inflammation events occurring in those that developed antibodies, which were found to be immune-mediated adverse events related to Beovu® exposure (Appendix C of the CS). At the clarification stage, the company stated that the safety of brolucizumab, including in the DMO population, is being monitored and that the data from KITE and KESTREL studies are in line with what is known about the safety profile of brolucizumab in wAMD. They noted that data from KITE and KESTREL shows no evidence that underlying diabetes has a negative impact on the brolucizumab-related incidence of intraocular inflammation (company response to clarification question A14).

3.3.6.2 Non-ocular adverse events

3.3.6.2.1 Any severity

The overall rate of non-ocular AEs was comparable between brolucizumab 6 mg and aflibercept 2 mg groups at week 52 for the KESTREL study (67.7% vs 65.2%) but was lower in the brolucizumab group for KITE (60.3% vs 70.2%).

[redacted].

Of non-ocular AEs occurring in at least 2% of patients in either arm of either study up to 52 weeks (Table 3 of Appendix F of the CS), there were a number where there was a ≥2% higher or lower rate

in the brolucizumab 6 mg group compared to aflibercept 2 mg, though the differences were generally only just >2% and/or the same differences were not observed across both trials. [redacted] (Table 30 of the CS).

3.3.6.2.2 Serious events

Event rates up to week 100 for serious non-ocular AEs suspected of being related to study treatment were [redacted] in KITE and [redacted] in KESTREL; see Table 31 of the CS).

3.3.6.3 Discontinuations

Treatment discontinuations were said to have been considered in the health economic analysis for this appraisal (section B.4.2.2.3 of the CS) with reference to values from the NMA; however, it is noted in Appendix D of the CS (section D4.2) that an NMA was not done for treatment discontinuation and was only performed for study discontinuation. The company reported that this was because very few studies reported treatment discontinuation, so an NMA was not possible for this outcome. Therefore, the results below refer to study discontinuation rather than treatment discontinuation. The EAG notes that treatment discontinuation may provide a better insight into how acceptable or effective treatments were, as study discontinuation does not capture those that discontinued study treatment but remained in the study in terms of outcome assessment.

Study discontinuations at 52 weeks were reported in Figures 3 and 4 of Appendix D of the CS, with 9.5% vs 8.0% in brolucizumab 6 mg vs aflibercept 2 mg groups for KESTREL and 9.5% vs 6.6% for KITE. Data for 100 weeks (KESTREL) or 104 weeks (KITE) [redacted].

Study discontinuation due to adverse events are also reported in Figures 3 and 4 of Appendix D of the CS for 52 weeks, with similar event rates between brolucizumab 6 mg and aflibercept 2 mg arms in both studies (1.1% vs 2.7% in KESTREL and 2.2% vs 1.7% in KITE). Data was also available for 104 weeks in both studies (Table 13 of Appendix D of the CS), with [redacted]

[redacted]

3.3.6.4 Mortality

Up to week 100, deaths were [redacted] See Table 31 in the CS. [redacted]

3.4 Critique of the indirect comparison and/or multiple treatment comparison

The company presented two network meta-analyses (NMAs) in the company submission:

- The primary analysis which covered the wider population of patients with DMO; and
- An exploratory analysis in the subgroup of patients with CSFT ≥400 µm at baseline.

The company reported that due to limited data and lack of stratification in the studies identified for inclusion in the NMAs, the wider DMO population was used as the primary analysis because it was deemed to be more robust. The EAG is concerned that the primary NMA does not reflect the people with visual impairment due to DMO and a CRT of ≥400 µm population in which brolucizumab is being positioned. The EAG is also concerned about the inclusion of KITE in the analysis due to the imbalance in baseline characteristics discussed in Section 3.2.1. In particular, the EAG was concerned that [redacted] Additionally, the mean baseline BCVA in the study eye was 2.3 letters higher in the brolucizumab arm (66.0 letters) compared with the aflibercept arm (63.7 letters) at baseline in KITE. During clarification, the EAG requested the company conduct additional exploratory NMAs removing KITE, pooling the different treatment regimens for each of the drugs in the network (i.e. aflibercept and ranibizumab) and using a single treatment regimen in the network for each drug. The EAG notes that the company considers the exclusion of KITE from the NMAs not to be appropriate as it omits valid evidence from a pivotal trial;

however, the EAG considers the results from KESTREL to be more reliable. The EAG discusses the results of the company NMA with KITE and KESTREL alongside the equivalent NMA excluding KITE below. The EAG considers that the exploratory NMAs combining treatment regimens and for single treatment regimens are broadly consistent with the primary analysis including each treatment regimen as a separate node, and therefore the EAG focuses on the company's primary NMA and the equivalent NMA excluding KITE.

With regards the company's exploratory NMA in the subgroup of patients with CSFT ≥400 µm at baseline, the EAG is concerned that the PROTOCOL T trial included to inform the efficacy of ranibizumab uses a lower dose of ranibizumab (0.3 mg) compared to that typically used in clinical practice in England (0.5 mg). No evidence was submitted by the company to demonstrate how the efficacy of the different doses of ranibizumab compare and therefore the EAG considers the results of the CSFT ≥400 µm at baseline NMA subgroup analysis to be unreliable. The EAG notes that the company used different trials to inform the efficacy of ranibizumab in the primary NMA for the wider DMO population that used the 0.5 mg ranibizumab dose and therefore the EAG focuses only on the NMAs in the wider DMO population and does not discuss the CSFT ≥400 µm at baseline subgroup analysis further.

3.4.1 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

The trials included in the primary NMA (Table 6) were identified via the SLR detailed in Section 3.1 and Figure 1 shows the network diagram for the company's primary analysis.

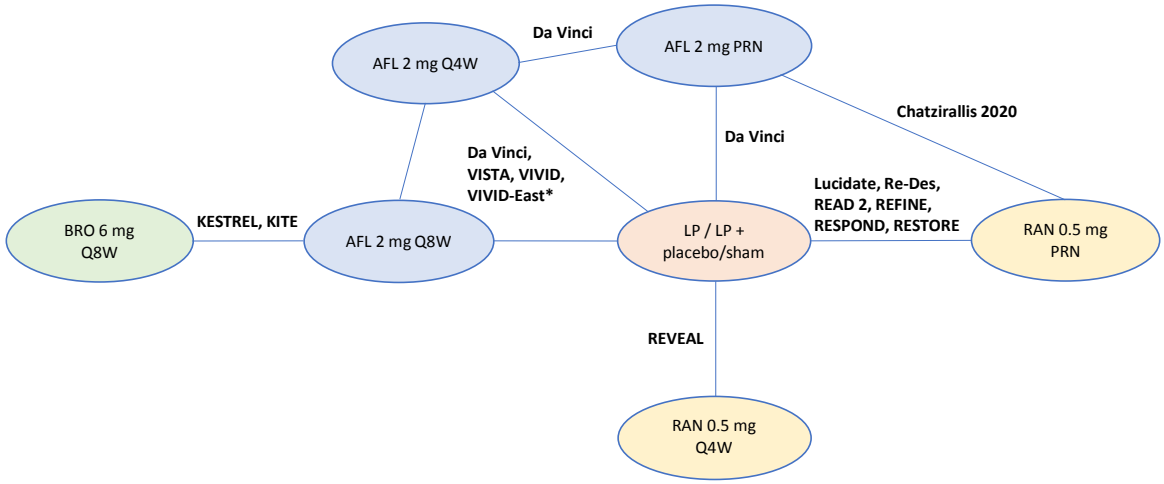
Table 6. Summary of the trials used to carry out the primary NMA (Reproduced from CS, Table 27)

Trial	BEO 6 mg Q8W	AFL 2 mg Q4W	AFL 2 mg Q8W	AFL 2 mg PRN	RAN 0.5 mg Q4W	RAN 0.5 mg PRN	LP/LP+ placebo/sham
Chatzirallis				✓		✓	
Da Vinci		✓	✓	✓			✓
KESTREL	✓		✓				
KITE	✓		✓				
Lucidate						✓	✓
READ-2						✓	✓
Re-Des						✓	✓
REFINE						✓	✓
RESPOND						✓	✓
RESTORE						✓	✓
REVEAL					✓		✓
VISTA		✓	✓				✓
VIVID		✓	✓				✓
VIVID-East		✓	✓				✓

Abbreviations: AFL, aflibercept; BEO, brolucizumab; LP, laser photocoagulation; PRN, pro re nata; RAN, ranibizumab.

The company separated studies reporting every 4 weeks (q4w), every 8 weeks (q8w) and pro re nata (PRN) treatment regimens in the primary NMA but reported that pooling by treatment was also considered as a scenario for inclusion in the cost-comparison model.

Figure 1. Network diagram (Reproduced from CS, Figure 16)



Abbreviations: AFL, aflibercept; BRO, brolucizumab; LP, laser photocoagulation; PRN, pro re nata (as needed) qXw, every X weeks; RAN, ranibizumab.

3.4.1.1 Methods

The company reported that the NMA methods they used followed the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 2 guidelines, and were implemented using publicly available WinBUGS code.[19]

The company presented results for pairwise meta-analysis for each outcome to assess heterogeneity across studies reporting the same treatment comparisons in addition to the NMA results. The NMA results were provided for both random effects models and fixed effect models. In terms of the NMA outcomes, for count outcomes, the Mantel-Haenszel method was used for fixed effects and for continuous outcomes, τ^2 was estimated using the inverse variance for fixed effects. For both count and continuous outcomes the DerSimonian and Laird method was used for random effects.

The company reported that for many of the meta-analyses and NMA outcomes there were only a small number of studies per treatment link in the network, and so it was challenging to estimate the between-studies heterogeneity parameter. Nevertheless, the company explored both fixed and random effect models for each outcome and decisions on the best fitting model were made on the basis of the deviance information criterion (DIC) (approximate difference of DIC ≥3 in favour of one model over another), as well as a comparison of the total residual deviance with the number of datapoints, and findings from the direct pairwise analyses.

3.4.1.2 Results

3.4.1.2.1 BCVA

The random effects model was selected as the best fit for change from baseline in BCVA at 1 year, whether including or excluding KITE from the analysis (Company response to CQ A1, Table 1).

The NMA results for 1-year change from baseline in BCVA suggest that aflibercept, brolucizumab and ranibizumab are broadly comparable, although in the NMA where KITE is removed the mean mean differences are less favourable for brolucizumab. Brolucizumab was favoured over ranibizumab 0.5 mg q4w with a higher gain in Early Treatment Diabetic Retinopathy Scale (ETDRS) letters over the course of 1 year of follow-up with brolucizumab ([redacted] in the company NMA (KITE and KESTREL), whereas when KITE is removed from the NMA the result no longer reaches statistical significance ([redacted]). No data on ranibizumab were available for 2-year change from baseline in BCVA in the wider DMO population.

The company also provided results for the outcomes of ≥10 letter improvement from baseline in BCVA and ≥15 letter improvement from baseline in BCVA at 1 year follow-up when including and excluding KITE. The EAG notes that these results

[redacted]

[redacted] (Company response to CQ A1, Table 6 and Table 10).

Table 7. Change from baseline in BCVA at 1 year, BRO 6 mg q12w/q8w vs comparator (both BRO trials and excluding KITE) (Adapted from Company response to CQ A1, Table 2)

Intervention	Comparator	KITE and KESTREL		Excluding KITE	
		Random effects		Random effects	
		Median mean difference (95% CrI)	Mean mean difference (SD)	Median mean difference (95% CrI)	Mean mean difference (SD)
BRO 6 mg q12w/q8w	LP	[redacted]	[redacted]	[redacted]	[redacted]
BRO 6 mg q12w/q8w	AFL 2 mg q4w	[redacted]	[redacted]	[redacted]	[redacted]
BRO 6 mg q12w/q8w	AFL 2 mg q8w	[redacted]	[redacted]	[redacted]	[redacted]
BRO 6 mg q12w/q8w	AFL 2 mg PRN	[redacted]	[redacted]	[redacted]	[redacted]
BRO 6 mg q12w/q8w	RAN 0.5 mg q4w	[redacted]	[redacted]	[redacted]	[redacted]
BRO 6 mg q12w/q8w	RAN 0.5 mg PRN	[redacted]	[redacted]	[redacted]	[redacted]

Font in bold and italics indicates one treatment is favoured over another.
Abbreviations: AFL, aflibercept; BCVA, best corrected visual acuity; BRO, brolucizumab; CrI, credible interval; LP, laser photocoagulation; PRN, pro re nata; qXw, every X weeks; RAN, ranibizumab; SD, standard deviation.

3.4.1.2.2 Study discontinuation (all cause)

For all cause discontinuations, the fixed effects model was considered the best fit compared with the random effects model. All cause discontinuation across treatments was similar, except for ranibizumab 0.5 mg q4w, which showed fewer overall discontinuations when compared with all other treatments. The EAG notes that brolucizumab was generally associated with numerically higher mean all cause discontinuations compared with the other treatments but the mean hazard ratio (HR) was not statistically significant with the exception of the comparison with ranibizumab 0.5 mg q4w. The EAG also notes that the exclusion of KITE from the analyses did not change the conclusions, although it generally resulted in more similar discontinuations between brolucizumab and the other treatments.

Table 8. All cause discontinuations, BRO 6 mg q12w/q8w vs comparator (both BRO trials and excluding KITE) (Adapted from Company response to CQ A1, Table 14)

Intervention	Comparator	KITE and KESTREL		Excluding KITE	
		Fixed effects		Fixed effects	
		Median HR (95% CrI)	Mean HR (SD)	Median HR (95% CrI)	Mean HR (SD)
BRO 6 mg q12w/q8w	LP	[redacted]	[redacted]	[redacted]	[redacted]
BRO 6 mg q12w/q8w	AFL 2 mg q4w	[redacted]	[redacted]	[redacted]	[redacted]
BRO 6 mg q12w/q8w	AFL 2 mg q8w	[redacted]	[redacted]	[redacted]	[redacted]
BRO 6 mg q12w/q8w	AFL 2 mg PRN	[redacted]	[redacted]	[redacted]	[redacted]
BRO 6 mg q12w/q8w	RAN 0.5 mg q4w	[redacted]	[redacted]	[redacted]	[redacted]
BRO 6 mg q12w/q8w	RAN 0.5 mg PRN	[redacted]	[redacted]	[redacted]	[redacted]

Font in bold and italics indicates one treatment is favoured over another.

Abbreviations: AFL, aflibercept; BRO, brolucizumab; CrI, credible interval; HR, hazard ratio; LP, laser photocoagulation; PRN, pro re nata; qXw, every X weeks; RAN, ranibizumab; SD, standard deviation.

3.5 Conclusions of the clinical effectiveness section

- The company's proposed positioning of brolucizumab is in people with visual impairment due to DMO and a CRT of ≥400 µm. The EAG considers the narrower population addressed by the CS compared to that specified in the final scope issued by NICE to be reasonable given the company's decision to submit a cost-comparison versus aflibercept and ranibizumab. However, the EAG notes that the focus of the clinical data from KESTREL and KITE (the key studies of brolucizumab), and from the company NMAs presented in the CS relate to a broader DMO population.
- KITE and KESTREL provide RCT data for the comparison of brolucizumab with aflibercept and the company submitted NMAs to enable a comparison of brolucizumab with ranibizumab.
- Overall, the EAG considered the methods used by the company for the literature search were robust and likely to have identified all clinical evidence relevant to the decision problem and

the EAG agreed that for most domains, the KESTREL and KITE studies are at low risk of bias for analysis of the primary outcomes based on the full trial population.

- The EAG considers there to be a [redacted] The EAG therefore considers KESTREL to be a more robust source of efficacy data for brolucizumab.
- In terms of external validity, although the EAG's clinical experts noted some potential differences, it was agreed that the characteristics of those included in KESTREL and KITE were broadly similar to those eligible for anti-VEGF treatments for DMO in clinical practice in England.
- The primary outcome for KESTREL and KITE was mean change from baseline in BCVA at 52 weeks, and both trials demonstrated non-inferiority of brolucizumab 6 mg compared to aflibercept 2 mg in the overall DMO population.
- [redacted]
- Subgroup results suggest [redacted] the EAG has some concerns about the robustness of the evidence from the subgroup and how appropriate it is to conclude that [redacted] given that it is a *post-hoc* analysis and that there are [redacted] .
- In terms of AEs, the EAG's clinical experts considered the AE of most concern was intraocular inflammation,

[redacted]

- Study discontinuations

  [redacted]

- [redacted]

- The NMA results for 1-year change from baseline in BCVA suggest that aflibercept, brolucizumab and ranibizumab are

  [redacted]

3.5.1 Clinical issues

- The EAG's clinical experts noted that mean HbA_{1c} levels, indicating level of diabetes control, in the two trials may be better than would be seen in clinical practice and the trials exclude people with levels >10% and who would be treated in clinical practice. However, it was not expected to have a large impact on the clinical efficacy of anti-VEGFs. The EAG also noted that the trials include those with CSFT values ≥320 µm, while the positioning of brolucizumab in clinical practice is for only those with CRT ≥400 µm.

- [redacted], which the EAG's clinical experts reported may be clinically important and influence the results. The EAG considered this to be important particularly as the

[redacted]. Analysis for [redacted] did adjust for baseline scores but not all other outcomes were adjusted for baseline [redacted].

- [redacted]

- For most outcomes, missing or censored data was imputed using the LOCF method. The EAG is concerned that the use of the LOCF method in DMO may be inappropriate as it assumes maintenance of effect from the previous measurement once treatment is discontinued. Additionally, the EAG notes that study discontinuation rates [redacted]

- There was a lack of formal non-inferiority testing for most secondary outcomes, and p-values for significance were also not reported for all outcomes (non-inferiority testing and p-values were reported as per the multiple testing strategy and statistical analysis plan); however, treatment differences with 95% confidence intervals were generally sufficient to indicate whether or not large differences were present and whether there was uncertainty in the direction of the treatment difference

- [redacted]The EAG is concerned about the robustness of the subgroup analyses from KITE and KESTREL based on CRT measurement at baseline, and considers that it may not be appropriate to conclude that the [redacted], although they were *post-hoc* analyses and [redacted]

- Concerns were raised by the EAG's clinical experts about increased intraocular inflammation with brolucizumab, [redacted].

- [redacted]

4 Summary of the EAG's critique of submitted cost effectiveness evidence

The company's deterministic base case results are given in Table 9. These results utilised patient access scheme (PAS) discounts, known to the company, for brolucizumab and ranibizumab. The list price is used for aflibercept. These results show that brolucizumab is cost saving versus aflibercept and ranibizumab. Several parameters and assumptions have been varied by the Company and Evidence Assessment Group (EAG) in scenario analyses, brolucizumab continues to be cost saving in each instance. An additional PAS discount available for aflibercept is not considered by these results but is reflected in the results presented in the EAG's confidential appendix.

Table 9. Company's base case results

Interventions	Total Costs (£)	Incremental costs (£)
Brolucizumab	[redacted]	-
Aflibercept	£34,332	[redacted]
Ranibizumab	[redacted]	[redacted]

Note: negative incremental costs indicate brolucizumab is cost saving.

4.1 EAG comment on the company's review of cost effectiveness evidence

The company performed a systematic literature review (SLR) to identify published studies reporting cost and resource use data that could inform the cost-comparison evaluation of brolucizumab for adult patients with visual impairment caused by DMO, with a central retinal thickness (CRT) of 400 µm or greater at the start of treatment. The company did not conduct SLRs to identify cost-effectiveness evidence or health-related quality of life evidence as these are not prerequisites for a cost-comparison evaluation. The cost and resource use SLR identified studies and prior economic evaluations which reported; estimates/assumptions of resource use, direct healthcare costs including the costs of hospitalisation, health state costs, indirect and societal costs, cost of carer and productivity losses.

Database searches were run on 25 October 2021 and were restricted to studies published after 2011. Only English-language publications were included. A summary of the EAG's assessment of the company's economic SLR is presented in Table 10 below.

Table 10. Systematic literature review summary

Systematic review step	Section of CS in which methods are reported			EAG assessment of robustness of methods
	Cost effectiveness evidence	HRQoL evidence	Resource use and costs evidence	
Search Strategy	No HRQoL or Cost effectiveness evidence search conducted – not required for cost comparison evaluations.		Appendix G	Appropriate sources were searched using Ovid. Databases included: MEDLINE, Embase®, CRD DARE, HTAD & NHS EED, and EconLit®. Grey literature searches included conference proceedings from: AAO, EURETINA, ARVO, WOC, RCO, ASRS, EVER, ESO, and Submission documents from the following HTA agencies were reviewed also searched for relevant data: ISPOR. NICE, SMC, CADTH, PBAC, HAS, IQWiG, and G-BA. EconPapers (RePEc), INAHTA HTA Database and the Cost Effectiveness Analysis Registry were also hand searched. Search strings were provided in Appendix G and were peer-reviewed by an Information specialist at the ScHAAR, Sheffield University using the PRESS checklist.
Inclusion/exclusion criteria			Table 6 of Appendix G	Studies considering adults with confirmed diagnosis of DMO were included irrespective of gender or race. No exclusions were made based on interventions or comparators, which the EAG considers to be inclusion. The 2011 date restriction is considered appropriate by the EAG as up-to-date cost data will be captured. Publications before this would likely reflect outdated practice; in the UK anti-VEGF were first approved for use in DMO in 2013. Non-English language publications were also excluded.
Screening			Figure 1 of Appendix G	Appropriate, PRISMA flow diagram provided.
Data extraction			Table 7 of Appendix G	Appropriate.
Quality assessment of included studies			Appendix G	Appropriate, no quality assessment conducted, not needed for resource use and cost studies.

Abbreviations: CS, company submission; EAG, Evidence Assessment Group; HRQoL, health-related quality of life; NHS, national health service; NICE, National Institute for Health and Care Excellence; SMC, Scottish Medicines Consortium; CADTH, Canadian Agency for Drugs and Technologies in Health; HAS, Haute Autorité de Santé; IQWiG, German Institute for Quality and Efficiency in Health Care; G-BA, Gemeinsamer Bundesausschuss; CRD DARE, HTAD & NHS EED, Centre

for Reviews and Dissemination Database of Abstracts of Reviews of Effects, Health Technology Assessment Database & National Health Service Economic Evaluation Database; RePEc, Research Papers in Economics; INAHTA, International Network of Agencies for Health Technology Assessment; AAO, American Academy of Ophthalmology; EURETINA, The European Sociaty of Retina Specialists; ARVO, The Association for Vision and Ophthalmology; WOC, World Ophthalmology Congress; RCO, Royal College of Ophthalmologists; ASRS, The American Society of Retina Specialists; EVER, European Association for Vision and Eye Research; ESO, European Society of Ophthalmology; ISPOR, International Society of Pharmacoeconomics and Outcomes Research; ScHAAR, School of Health and Related Research; PRESS, Peer Review, of Electronic Search Strategies.

Of the 106 studies included in the cost and resource use SLR based on the predefined inclusion criteria, 10 publications reported UK-specific data for 9 studies and were considered relevant to the decision problem. All 10 publications reported costs for either patients with DMO or with diabetic forms of macular oedema; however, none reported costs or resource use related to brolucizumab. Further details of these studies are provided in Section 2.1 of Appendix G of the company submission.

The EAG considered the company's review of cost and resource use evidence to be generally reasonable, though none of cost and resource use data identified was used to parameterise the company's cost-comparison model. Instead the cost and resource use data used in the model were sourced from the company's clinical experts, the British National Formulary, NHS Reference Costs 2019-2020,[20] previous NICE technology appraisals (TAs) and guidelines, and the Peto *et al*. 2021[21] real world evidence study (which was published after the company's database searches and hence not identified by the SLR). Specific issues pertaining to the application of identified data sources in the model are discussed in the following sections.

4.2 Summary and critique of company's submitted economic evaluation by the EAG

4.2.1 NICE reference case checklist

Table 11 summarises the EAG's appraisal of the company's economic evaluation against the requirements set out in the NICE reference case checklist for the base-case analysis, with reference to the NICE final scope outlined in Section 2.

Table 11. NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	The company submitted a cost-comparison analysis, supported by evidence demonstrating non-inferiority of treatment effect between brolucizumab, aflibercept

		and ranibizumab. As such direct health effects were not captured by the model. The company's base case analysis does, however, incorporate indirect health benefits through avoidance of bilateral DMO. This is not consistent with the cost-comparison approach.
Perspective on costs	NHS and PSS	All relevant costs have been included and are based on the NHS and PSS perspective
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	The company undertook a cost-comparison analysis to compare brolucizumab to aflibercept and ranibizumab.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Lifetime horizon (36.9 years)
Synthesis of evidence on health effects	Based on systematic review	A systematic review was carried out and the company conducted two NMAs which did not identify any significant difference in treatment effect between brolucizumab, aflibercept and ranibizumab. The results supported the use of a cost-comparison model.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Direct health effects were not considered by the cost-comparison analysis. The company's base case analysis incorporates indirect health benefits through avoidance of bilateral DMO. This is not in line with the cost-comparison approach.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	In line with the cost-comparison approach, health-related quality of life was not considered by the model.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be	All relevant costs have been included and are based on the NHS and PSS perspective.

	valued using the prices relevant to the NHS and PSS	
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Costs have been discounted in line with the NICE reference case (3.5% per annum).

Abbreviations: EAG, evidence review group; NHS, national health service; PSS, personal social services; QALY, quality adjusted life year; NMA, network meta-analysis; DMO, diabetic macular oedema.

4.2.2 Population

The modelled population considered by the company for this Cost Comparison Evaluation (CCE) is adult patients with visual impairment caused by DMO, with a CRT of 400 µm or greater at the start of treatment. This population is also narrower than that of both the anticipated marketing authorisation and the NICE final scope, neither of which restrict the use of brolucizumab based on central retinal thickness. The company elected to restrict the modelled population to patients with CRT ≥ 400 µm in line with the optimised population recommended by NICE for both aflibercept and ranibizumab.

4.2.2.1 EAG Critique

Baseline characteristics of the modelled population reflect the pooled FAS populations of KITE and KESTREL, which are the key trials for brolucizumab as first-line treatment for visual impairment caused by DMO. The EAG notes that the FAS populations of KITE and KESTREL do not reflect patients with CRT ≥ 400 µm. However, CRT ≥ 400 µm subgroup analyses were conducted by the company and the baseline characteristics of this subgroup were similar to the pooled FAS populations. Furthermore, the EAG's clinical experts considered the baseline characteristics of the pooled FAS populations broadly similar to the DMO patient population in UK clinical practice. As such, the results are considered generalisable to the UK patient population. The only noted difference was that the sex split in UK DMO patients was expected to be closer to 50% female as opposed to [redacted]%. As discussed in Section 2.1, the EAG had some concerns with differences in baseline characteristics between treatment arms in the KITE study particularly with regards to mean BCVA and the proportion of patients with ≤65 EDTRS letters at baseline. However, these concerns were exclusively pertinent to drawing conclusions on the efficacy of brolucizumab versus aflibercept rather than whether the population characteristics used in model reflect a UK patient population. Although the KESTREL trial was considered more suitable for drawing brolucizumab versus aflibercept comparative efficacy conclusions, with regards to the baseline characteristics used in the cost-

comparison model (mean age and percentage female), there was negligible difference between the pooled KITE and KESTREL population and the KESTREL only population. Given the similarity in baseline characteristics between the FAS population and the CRT ≥ 400 µm subgroup, the EAG considers the modelled population appropriate and relevant to the decision problem.

4.2.3 Interventions and comparators

The intervention considered for the cost-comparison analysis is brolucizumab. Brolucizumab, which is a 6mg IVT injection, is administered 6-weekly for the first 5 doses and either 8- or 12-weekly thereafter for patients with or without disease activity, respectively. As discussed in Section 2.2, this posology (outlined in the marketing authorisation) aligns with dosing in the KESTREL trial but not KITE, which allowed further extension of the treatment interval to 16 weeks. This, among other reasons discussed in Section 3.2.1, limited the generalisability of the KITE study results. The EAG considered the KESTREL trial results to better reflect the efficacy of brolucizumab under the dosing outlined in the anticipated marketing authorisation.

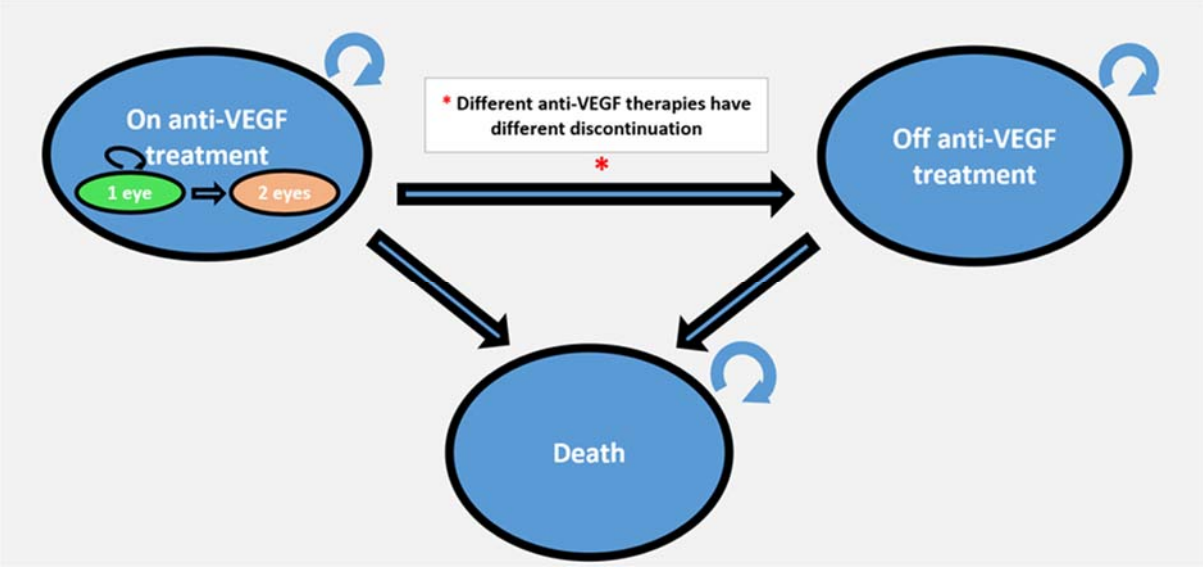
The primary comparator included in the cost-comparison analysis is aflibercept, as the KITE and KESTREL studies provided direct comparisons with brolucizumab. The company have also included ranibizumab as a comparator. As discussed in Section 2.3 the EAG's clinical experts considered aflibercept and ranibizumab to be the most relevant first-line comparators. However, the EAG's clinical experts noted that, due to safety concerns regarding potentially higher intraocular inflammation rates, brolucizumab may be used as second-line treatment following aflibercept or ranibizumab. Due to a lack of clinical trial data for brolucizumab use at second-line the company were unable to provide a requested scenario analysis considering relevant second-line comparators. The company considered aflibercept and ranibizumab to be appropriate comparators for second-line brolucizumab as well as first-line as the company's clinical experts expected that DMO patients with insufficient response to a first anti-VEGF would be switched to another anti-VEGF treatment. However, clinical expert opinion provided to the EAG considers that aflibercept is more effective than ranibizumab and, as such, is the preferred anti-VEGF at first-line. It seems clinically implausible to the EAG that in current clinical practice if patients do not have an adequate response to aflibercept they would be switched to what is considered a less effective treatment. More plausibly, the EAG notes that dexamethasone is currently available for use in pseudophakic DMO patients who are unsuitable for, or who did not respond to, non-corticosteroid (anti-VEGF) treatment. As such, the

EAG consider dexamethasone to be a relevant second-line comparator for pseudophakic DMO patients.

4.2.4 *Modelling approach and model structure*

A *de novo* cost-comparison model was developed in Microsoft© Excel, using a Markov cohort approach, to assess the costs of brolucizumab compared with aflibercept and ranibizumab as first-line anti-VEGF treatment for adult patients with visual impairment caused by DMO.

Figure 2. Model structure (Reproduced from CS, Figure 6)



The model structure (Figure 2) developed by the company aims to estimate the costs associated with DMO while on anti-VEGF treatment but also to capture the disease pathway by incorporating progression from unilateral to bilateral disease. Once patients develop bilateral DMO they cannot revert to unilateral. Three mutually exclusive health states are defined; on anti-VEGF treatment, off anti-VEGF treatment, and death. Patients can progress from unilateral to bilateral DMO within the on anti-VEGF treatment state and incur additional associated costs treating a second eye. Once patients discontinue from treatment and enter the off anti-VEGF treatment state, no further progression from unilateral to bilateral DMO occurs. Patients may transition from either the on or off anti-VEGF treatment states to death. For further detail on state transitions in the model, please refer to Section 4.2.5.

The company assumed a model cycle length of one year with half cycle correction applied. The model time horizon was set to 36.9 years (lifetime), as the mean age of the pooled FAS populations of KITE and KESTREL at baseline was 63.1 years. The NHS and Personal Social Services perspective was adopted, with costs discounted at 3.5% per annum, in line with the NICE reference case.

4.2.4.1 EAG Critique

As discussed in Section 3, the EAG considers the KESTREL non-inferiority trial FAS population and CRT≥400 µm subgroup results to demonstrate that brolucizumab and aflibercept have similar efficacy in adult patients with visual impairment caused by DMO, with a central retinal thickness (CRT) of 400 µm or greater at the start of treatment. The EAG consider this sufficient evidence to motivate the present cost-comparison evaluation. However, due to the lack of a direct comparison of brolucizumab and ranibizumab and limitations to the company's network meta-analyses discussed in Section 3.4, the EAG do not consider there to be sufficient justification for the brolucizumab versus ranibizumab cost-comparison. However, this comparison remains informative as a scenario analysis.

The time horizon used in the company base case in notably longer than that used in TA274 for ranibizumab treatment of DMO, which adopted a 10-year time horizon, while a lifetime time horizon was adopted for TA346 for aflibercept treatment of DMO. The EAG's clinical experts estimated that DMO patients receive anti-VEGF treatments for between 5 and 10 years. Although the EAG agrees with the company that a lifetime time horizon is sufficiently long to reflect any differences in costs between the technologies being compared, a shorter time horizon would also do so while limiting the uncertainty associated with assuming a constant treatment discontinuation rate over a 37-year timeframe. The EAG requested, and the company provided, scenario analyses which reduced the time horizon to 5, 10, and 15 years. These scenarios reduced the incremental costs versus aflibercept from [redacted] to [redacted], [redacted], and [redacted], respectively. The EAG considered a 10-year time horizon most appropriate as this was in line with TA274 and the upper end of EAG's clinical experts estimates of anti-VEGF treatment duration. As such, a 10-year time horizon has been applied in the EAG's preferred base case.

4.2.5 Model transitions

4.2.5.1 Incidence of bilateral DMO

KITE and KESTREL did not report the number of patients with bilateral DMO at baseline. The company therefore used an average ([redacted] %) of estimates provided by the company's clinical experts. Scenario analyses were provided by the company which explored two alternative values for the proportion of patients with bilateral DMO at baseline, 12.7% from the VISTA and VIVID trials,[22] and 46.5% from TA346 (derived from another UK clinicians survey).[23]

As mentioned in Section 4.2.4 patients with unilateral DMO are at risk of developing bilateral disease. The company applied annual probabilities DMO diagnosis in the fellow eye sourced from the VISTA and VIVID trials,[22] assuming that probability is constant from year 2 onwards. These probabilities are provided in Table 12 below. All patients who have existing bilateral disease at baseline, or those who develop bilateral disease thereafter are assumed to receive bilateral treatment.

Table 12. Annual probability of developing DMO in fellow eye (Table 34 of company submission)

Year	Value	Source
1	37.6%*	Dhoot et al. 2020[24] (VISTA and VIVID)
2+	13.5%^	

* 48-week probability of developing fellow eye DMO (266 of 755 patients) converted to annual probability.

^ 66 out of 489 patients developed fellow eye DMO between weeks 48 and 100. This rate is assumed to be constant for all subsequent years.

4.2.5.2 Treatment discontinuation

Treatment discontinuation is captured in the model through transitions from the on anti-VEGF state to the off anti-VEGF state. In the company base case the discontinuation rate applied to the aflibercept arm was calculated from the pooled aflibercept arms of the KITE and KESTREL studies. Hazard ratios estimated from the company's primary fixed effects NMA were applied to the aflibercept rate to estimate brolucizumab and ranibizumab rates (further details on the company's NMA are provided in Appendix D of the company submission). Scenario analyses were also provided by the company wherein a variety of equivalence assumptions were investigated. The discontinuation rates applied in each scenario are provided in Table 13 below.

Table 13. Discontinuation rates (Table 39 of company submission)

Scenario	Annual probability of discontinuation			Scenario Assumptions
	Brolucizumab	Aflibercept	Ranibizumab	
Base case	[redacted]	[redacted]	[redacted]	NMA hazard ratios applied to KITE and KESTREL aflibercept discontinuation probability to estimate brolucizumab and ranibizumab probabilities.
Scenario 1	[redacted]	[redacted]	[redacted]	Brolucizumab and aflibercept discontinuation probabilities estimated from the respective treatment arms of the pooled KITE and KESTREL studies. Ranibizumab discontinuation assumed equal to pooled KITE and KESTREL aflibercept probability.
Scenario 2	[redacted]	[redacted]	[redacted]	Brolucizumab discontinuation probability from pooled KITE and KESTREL studies used for all comparators.
Scenario 3	15.03%	15.03%	15.03%	Anti-VEGF discontinuation probability estimated from Peto *et al*. 2021[21] real world evidence study used for all comparators.

4.2.5.3 Mortality

Patients in both the on and off anti-VEGF treatment states experience an age- and gender-matched mortality rate based on the Office for National statistics 2018-2020 national life tables for England and Wales.[25]

4.2.5.4 EAG Critique

The EAG identified several issues in the company's base case model. Namely, how fellow eye DMO incidence, anti-VEGF treatment discontinuation and mortality are captured. These issues are discussed in the following subsections.

Fellow eye DMO incidence

The EAG noted that the model structure allows for fellow eye DMO incidence to occur only in patients remaining on anti-VEGF treatment. As a result, treatment effectiveness has been indirectly introduced into the cost-comparison model because patients discontinue brolucizumab, aflibercept, and ranibizumab at different rates, and hence the patient cohort in each treatment arm have unequal risk of developing bilateral DMO. As the discontinuation rate for patients treated with

brolucizumab is higher in the company base case, patients in the brolucizumab arm are exposed to risk of developing bilateral DMO for a shorter period of time. As such, a greater proportion of patients in the brolucizumab arm avoid the additional costs associated with bilateral DMO compared to the aflibercept or ranibizumab arms.

At the clarification stage the EAG noted that the inclusion of indirect treatment effect was inconsistent with the cost-comparison approach and requested the company to adapt the model such that the same rate of DMO incidence was applied to the on and off anti-VEGF treatment model states. This adjustment would ensure indirect treatment effect was not captured in the cost-comparison model and was in line with feedback obtained from the EAG's clinical experts which suggested that the risk of developing fellow eye DMO would be similar whether patients were on or off anti-VEGF treatment. The company agreed that DMO incidence would continue after patients discontinue an anti-VEGF treatment but noted that patients with incident bilateral DMO would not receive fellow eye treatment with the same treatment that had been discontinued for their other eye and that there wasn't sufficient data to inform a treatment sequencing model. The company did not provide the requested model adjustments or make changes to the base case analysis. The EAG, therefore, do not consider the company's base case analysis to be a true cost comparison analysis. However, the company did provide two scenario analyses wherein equal discontinuation rates were applied to all anti-VEGF treatments (results provided in Section 4.3.1), thereby avoiding differential risks of developing bilateral DMO between treatment arms. The EAG considers this a pragmatic solution, although note that the estimated absolute costs will have been underestimated in all treatment arms as no costs are included for incident fellow eye DMO following discontinuation of 1st line anti-VEGF treatment in the patients first DMO affected eye. The incremental costs between treatment arms should be minimally affected by the exclusion of subsequent treatment costs provided there is no large price discrepancy between anti-VEGF treatments.

Treatment discontinuation

Due to the abovementioned issues with the application of different discontinuation rates to each treatment arm, the EAG does not consider the discontinuation rates applied in the company base case or in Scenario 1 of Table 13 appropriate. The EAG also notes that differences in discontinuation observed in the brolucizumab and aflibercept arms of the KITE and KESTREL trials were not statistically significant. Furthermore, the EAG's clinical experts expected discontinuation from brolucizumab to be similar to aflibercept and ranibizumab. One expert noted that discontinuation

may be slightly higher for brolucizumab due to a higher proportion of patients experiencing intraocular inflammation, while another expert noted that brolucizumab discontinuation may actually be lower than other anti-VEGF treatments due to the extended period between injections. Of the two scenarios supplied by the company which applied equal discontinuation to all treatment arms, the EAG consider Scenario 2, which used the brolucizumab discontinuation from the pooled KITE and KESTREL trials, most appropriate for the following reasons:

- Although the Peto *et al*. 2021[21] real world evidence study considered a UK patient population, both of the EAG's clinical experts considered the discontinuation rates observed in the KITE and KESTREL studies more reflective of current UK clinical practice.
- In Peto *et al.* 2021[21] patients who had not received an anti-VEGF injection for at least 180 days were classified as discontinued with the time to discontinuation defined as the time from treatment initiation to the day after the final injection. Given that the decision to discontinue anti-VEGF treatment is unlikely to have been made immediately following the final administration, rather in the following weeks or months the mean time to discontinuation is likely underestimated, and the resulting discontinuation rate overestimated.

The EAG also notes, that given that no significant difference in discontinuation was observed between the brolucizumab and aflibercept arms of the KITE and KESTREL studies, a pooled discontinuation rate would have been preferable to the company's scenario which applied the brolucizumab discontinuation rate to all treatment arms. Given the limitations of KITE study discussed in Section 3.2.1, the EAG has provided an additional scenario analysis in Section 6.2 wherein an average (weighted by the patient numbers in each treatment arm) of the brolucizumab and aflibercept discontinuation rates from the KESTREL trial was applied reducing the incremental costs versus aflibercept from [redacted] to [redacted]. This assumption is also adopted for the EAG preferred base case.

The EAG's clinical experts agreed that the company's estimated proportion of patients with bilateral DMO at treatment initiation aligned with their experience of UK clinical practice. In the absence of fellow eye incidence data from the KITE and KESTREL studies, the EAG considered the use of data from the VISTA and VIVID studies appropriate, although the EAG noted that a smaller proportion of patients (12.7%) had bilateral disease at baseline compared with the company's estimate for UK clinical practice. One of the EAG's clinical experts noted that the probability of developing fellow eye

DMO in year 1 of the VISTA and VIVID studies was higher than what would be expected in UK clinical practice. The lower proportion of patients entering the VISTA and VIVID studies with bilateral DMO may have resulted in a higher risk of developing fellow eye DMO in year one of treatment compared with current practice as patients in UK clinical practice are already further along the disease pathway. Furthermore, the EAG's clinical experts disagreed on whether the annual probability of developing DMO in fellow eyes would increase or decrease from year 2 onwards. The company's assumption that this would remain constant is therefore considered reasonable by the EAG. Although the EAG considers the year 1 fellow eye DMO risk estimates uncertain, no alternative estimates were identified by the EAG and the VISTA and VIVID[24] data was considered the best available. The EAG produced a scenario analysis wherein the year one probability of bilateral DMO is reduced by half to test the model sensitivity to this parameter. This reduced the incremental costs versus aflibercept from [redacted] to [redacted].

Mortality

The EAG has concerns that general population mortality was applied in the company base case without adjustment for additional mortality risk experienced by a diabetic patient population. Previous NICE technology appraisals for DMO treatments (TA346,[23] TA349,[26] and TA613[27]) applied a relative risk of mortality for individuals with diabetes (1.95), sourced from Preis *et al.* 2009[28], to adjust the general population curves. The EAG's clinical experts agreed that the patient population in question would experience mortality risk exceeding that of the general population and aligned with the diabetes patients. The EAG requested, and the company provided, a scenario analysis wherein the Preis *et al.* 2009[28] relative risk estimate was applied which reduced the incremental costs versus aflibercept from [redacted] to [redacted]. This is also applied in the EAG preferred base case.

4.2.6 Resource use and costs

The costs included in the economic model consist of drug acquisition costs, administration costs and disease monitoring costs. The details of each are given in the following subsections. Unit costs used in the model were inflated to 2020 prices using the Office for National Statistics inflation indices.

4.2.6.1 *Drug acquisition costs*

Brolucizumab is administered by intravitreal injection using a pre-filled, single use syringe. The list price per 6 mg dose (120 mg/mL solution) is £816.00. The company sourced this cost from the British National Formulary (BNF). There is currently a patient access scheme (PAS) discount in place for brolucizumab. As such, the net cost per 6 mg dose of brolucizumab is [redacted] For the proportion of patients estimated to receive bilateral treatment, the cost of two 6 mg doses of brolucizumab (one per eye) was applied per administration.

The administration frequency of brolucizumab was based on annual pooled injection frequency data from years one and two of the KITE and KESTREL studies. This was in line with the anticipated marketing authorisation of 6-weekly injections during a 5-dose loading phase followed by 8-weekly or 12-weekly dosing in the maintenance phase. Patients in the KITE and KESTREL studies were initially scheduled to receive 12-weekly doses and if more frequent maintenance dosing was deemed necessary following disease activity assessment patients were moved to 8-weekly dosing for the remainder of the study.

Aflibercept and ranibizumab injection frequencies for years one and two were assumed equal to a blend of anti-VEGF dosing regimens used in the UK, sourced from the Peto *et al*. 2021[21] UK real world evidence study. The list prices for aflibercept and ranibizumab (provided in Table 14 below) were sourced from the BNF and a ranibizumab PAS price, known to the company, was applied in the company base case. As the company did not have access to an available aflibercept PAS, this is only reflected in the results provided in the confidential appendix.

Table 14. List price and injection frequencies in years 1 and 2 (adapted from tables 36 & 37 of company submission)

Comparator	List price (PAS price)	Injection frequency		Sources
		Year 1	Year 2	
Brolucizumab	£816.00 ([redacted])	6.91	4.11	Pooled KITE and KESTREL
Aflibercept	£816.00	7.70	5.60	Peto *et al*. 2021[21] UK real world evidence study
Ranibizumab	£551.00 ([redacted])	7.70	5.60	

Note: an additional PAS is available for aflibercept, this has been applied in a set of commercial in confidence results provided by the EAG in the confidential appendix. Further details of the aflibercept PAS are also provided in the confidential appendix.

Given that treatment is expected to continue past the 2 years follow up of the KITE and KESTREL studies, the company applied injection frequency estimates sourced from TA346[23] to all comparators. The injection frequencies applied are provided in Table 15 below.

Table 15: Injection frequency in years 3+ (adapted from Table 38 of company submission)

Year	Injection frequency
3	2.30
4	1.20
5+	1.00
Note: injection frequencies in all treatment arms assumed equal to that accepted by committee for TA346.	

4.2.6.2 Administration costs

Unit administration costs for each anti-VEGF treatment were based on the outpatient attendances, consultant led, ophthalmology cost code (service code 130) from the NHS Reference costs 2019-2020,[20] which is £110.34. Based on feedback from the company's clinical experts, the company assumed that all anti-VEGF administrations would be consultant led in an outpatient setting but also provided model functionality to adjust the proportion led by consultants and non-consultants (the latter was costed based on the outpatient attendances, non-consultant led, ophthalmology cost code from the NHS Reference costs 2019-2020,[20] which was £95.07). This model parameter had minimal impact on the incremental costs. The unit administration cost was applied per administration appointment for brolucizumab, aflibercept or ranibizumab treatment. For unilateral treatment the annual number of administration appointments in each treatment arm was informed by the injection frequency estimates provided in Table 14 and Table 15.

For patients with bilateral DMO, the company assumed anti-VEGF injections would be administered in both eyes in a single appointment on 50% of occasions, whereas for the remaining 50%, separate appointments would be needed for each eye. This assumption was based on the approach adopted in NICE TA672[29] and NG82[30]. An administration cost multiplier of 1.5 is therefore applied to the proportion of patients with bilateral disease who remain on anti-VEGF treatment.

4.2.6.3 Disease monitoring and diagnostic test costs

The company has also included the costs associated with regular monitoring of patients. The frequency of monitoring in the first two years of brolucizumab treatment was assumed to be equal to the injection frequency observed in the KITE and KESTREL studies, though no additional monitoring costs were applied for patients with bilateral DMO compared to those with unilateral

DMO. For the aflibercept and ranibizumab arms, monitoring frequencies in years one and two of treatment were derived from the Peto *et al*. 2021[21] UK real world evidence study. Annual monitoring frequency beyond year two was assumed equal for all anti-VEGF treatments and was sourced from TA346[23] and are provided, alongside the year one and two data, in Table 16 below. A unit cost of £124.94 for optical coherence tomography (OCT) testing was applied at each monitoring visit.

Table 16. Annual monitoring frequencies applied in the company base case (adapted from Tables 43 & 44 of the company base case).

Comparator	Monitoring frequency					Sources
	Year 1	Year 2	Year3	Year 4	Year 5+	
Brolucizumab	6.91	4.11	4	4	2	Assumed equal to injection frequency for years 1 & 2, NICE TA346[23] for years 3+.
Aflibercept	14.2	13.4	4	4	2	UK RWE study for years 1 & 2, NICE TA346[23] for years 3+.
Ranibizumab	14.2	13.4	4	4	2	

Abbreviations: RWE, real world evidence; NICE, National Institute for Health and Care Excellence; TA, technology appraisal.

A one-off diagnostic cost of £130.74 for a fundus fluorescein angiography examination was also included for each affected eye in year 1 or at diagnosis of bilateral disease.

4.2.6.4 Adverse event costs

In line with the assumption of no appreciable difference in treatment effect, underlying the cost-comparison approach adopted by the company, adverse event costs are not included in the base case analysis. The company did, however, provide a scenario analysis wherein the adverse event rates from the pooled aflibercept arm of KITE and KESTREL were applied, with NMA derived hazard ratios used to adjust these aflibercept rates from the brolucizumab and ranibizumab arms (further details are provided in Appendix D of the company submission). Adverse event costs for this scenario were derived from the NHS Reference costs 2019-2020[20] and from NICE NG82[30] (inflated to 2020 prices).

4.2.6.5 EAG Critique

The EAG considered the company's approach to estimating unit costs to be generally appropriate except for treatment monitoring, for which the EAG's clinical experts identified several monitoring tests which were not costed in the company base case. Additionally, a number of concerns were

identified with regards to the injection and monitoring frequency estimates used in the company base case. These areas of uncertainty are explored in the following subsections.

Injection frequency

As discussed in Section 3.2.1, patients in KITE could extend the treatment interval to 16 weeks in their second year of brolucizumab treatment. However, the marketing authorisation only specifies extension to 12-weekly dosing for patients without disease activity. The EAG is concerned that the year 2 injection frequency data from KITE, and hence the pooled year 2 KITE and KESTREL data, underestimates the injection frequency for patients treated in line with the license. In addition, the EAG considers the KESTREL trial results to be more robust given the previously noted imbalances in baseline patient characteristics in KITE (discussed in Section 3.2). The company provided model functionality wherein the unpooled KESTREL trial data could be used to inform injection frequency in the first two years of the model and discontinuation throughout. The EAG considers the unpooled KESTREL trial data to be the preferred source of brolucizumab injection frequency and discontinuation data and this has been applied in the EAG preferred base case.

The EAG are concerned that the company's use of anti-VEGF injection frequency estimates from the Peto *et al.* 2021[21] real world evidence study for the aflibercept arm, while utilising pooled KITE and KESTREL data to inform brolucizumab injection frequency, is potentially biased by the different dosing regimens adopted in clinical practice compared with the more structured clinical trial setting. The company's clinical experts suggested that a majority (approximately 79%) of patients treated with anti-VEGFs in current clinical practice follow flexible PRN or TREX regimens as opposed to the fixed aflibercept dosing regimen used in the KITE and KESTREL trials (a loading phase of five 4-weekly doses, following by 8-weekly doses). As such the company considered the real-world evidence data to be a more accurate reflection of UK clinical practice. Furthermore, the company noted that the number of aflibercept doses received KITE and KESTREL was higher than reported by the Peto *et al.* 2021[21] real world evidence study and therefore the adoption of the RWE was a conservative assumption. The EAG acknowledge this, however, it remains uncertain whether similar deviations from the fixed brolucizumab dosing regimen would also occur in clinical practice. As such the EAG's preference is for the like-for-like comparison offered by the KESTREL trial. The company provided a scenario analysis, wherein unpooled injection frequency and discontinuation data from the KESTREL trial was used for all treatment arms, with ranibizumab injection frequency and discontinuation assumed equal to aflibercept. The incremental costs versus aflibercept were reduced from [redacted] to

[redacted]. This data has been applied in the EAG preferred base case, although the EAG applied a weighted average discontinuation rate from the brolucizumab and aflibercept arms to all treatment arms for the reasons described in Section 4.2.5.4.

Administration costs

The EAG's clinical experts estimated that in current UK clinical practice, between 80% and 90% of bilateral DMO patients treated with aflibercept or ranibizumab would have both eyes treated in a single appointment. The company's estimate was based on the approach adopted in NICE NG82[30] and accepted for TA672;[29] the more recent estimates provided by the EAG's clinical experts indicate that the 50% estimate reflect outdated clinical practice. The EAG requested, and the company provided a scenario analysis wherein a bilateral DMO administration cost multiplier of 1.15 was applied to the aflibercept and ranibizumab arms based on the assumption that 85% of bilateral DMO patients would have both eyes treated in a single appointment. This scenario reduced the incremental costs versus aflibercept from [redacted] to [redacted] For brolucizumab the EAG's clinical experts noted that due to the increased risk of intraocular inflammation relative to the other two anti-VEGF treatments, patients would not have both eyes treated in a single appointment. The company also provided a scenario analysis under this assumption by applying an administration cost multiplier of 2 for the brolucizumab arm which reduced the incremental costs versus aflibercept from [redacted] to [redacted]. This multiplier has been applied to the brolucizumab arm in the EAG's preferred base case, while the abovementioned 1.15 administration cost multiplier is applied to the aflibercept and ranibizumab arms.

Disease monitoring

In addition to forgoing single appointment bilateral treatment, the EAG's clinical experts advised that due to the increased risk of intraocular inflammation, patients treated with brolucizumab would require monthly monitoring visits for the first six months of treatment. On request from the EAG at the clarification stage the company provided a scenario analysis wherein the cost of six ophthalmologist visits were applied in the first six months of brolucizumab treatment. However, the company did not consider it necessary to include additional ophthalmologist costs for monitoring visits in the base case because monitoring would coincide with injection visits. The EAG notes, however, that during the first six months of treatment only five injection visits would occur as 6-weekly dosing applies for the first five brolucizumab loading doses. The EAG conducted an additional

scenario analysis where one additional monitoring visit was applied to the first six months of brolucizumab treatment, this reduced the incremental costs versus aflibercept from [redacted] to [redacted].

The EAG's clinical experts also noted that in addition to the OCT test considered in the company base case, each anti-VEGF monitoring visit would consist of wide field fundus photography and an eye examination with an ophthalmologist at a slit lamp. Another scenario analysis was provided by the company wherein the cost of wide field fundus photography was applied to all monitoring visits based on the 2019-2020 NHS reference cost for outpatient digital retinal photography (£137.43). This increased the incremental costs versus aflibercept from [redacted] to [redacted]. A slit lamp examination was assumed to be included in each ophthalmologist visit and so no extra cost was applied. This assumption was also applied in the EAG preferred base case.

Finally, the EAG's clinical experts, did not consider the monitoring frequency estimates, applied in the company's base case for the first two years of aflibercept or ranibizumab, reflective of current UK clinical practice. Although the Peto *et al.* 2021[21] real world evidence estimates were roughly twice the injection frequencies in years 1 and 2, the EAG's clinical experts noted that for the most part, monitoring was conducted at injection appointments. This was also the assumption accepted by committee for TA346. The EAG are concerned that the company's base case assumption that monitoring would occur only during injection appointments for the brolucizumab arm, while additional monitoring visits are assumed for the aflibercept and ranibizumab arms, does not reflect current UK clinical practice and biases the cost-comparison results in favour of brolucizumab. At the request of the EAG, the company provided a scenario analysis wherein the annual monitoring frequency for aflibercept or ranibizumab treatment were assumed equal to the aflibercept injection frequency in years 1 and 2. Incremental costs versus aflibercept decreased from [redacted] to [redacted]. This assumption is applied in the EAG preferred base case.

The EAG was satisfied with the company's injection and monitoring frequency assumptions from year 3 onwards as these were consistent with TA346 and no preferred assumptions were identified. The EAG was also satisfied with the unit administration cost applied per anti-VEGF injection. Although a higher per injection costs of £137.00 was applied in TA283 and TA346 (excluding OCT monitoring costs) based on an outpatient cost for "Vitreous Retinal Procedures – category 1", this cost is not present in updated 2019-2020 NHS reference costs and the EAG considered the "outpatient attendances, consultant led, ophthalmology" cost code to be an appropriate alternative.

The company's exclusion of AE-related costs from the base case was also considered appropriate as including these costs would have indicated a meaningful difference in treatment effect, inconsistent with cost-comparison modelling.

4.3 Company's cost effectiveness results

As noted in Section 4.2.6.1, a patient access scheme (PAS) discount is available for brolucizumab. The results included in this section are based on this PAS price. A ranibizumab PAS was also know to the company and is reflected in the results. A further set of results incorporating the aflibercept PAS discount are provided by the EAG in the confidential appendix. No probabilistic sensitivity analysis was conducted by the company, as such only deterministic results were produced by the cost-comparison model. The company's base case results are provided in Table 17. One-way sensitivity analyses were also provided by the company and presented in Figures .

Table 17. Company's base case results

Interventions	Total Costs (£)	Incremental costs (£)
Brolucizumab	[redacted]	-
Aflibercept	£34,332	[redacted]
Ranibizumab	[redacted]	[redacted]

Note: negative incremental costs indicate brolucizumab is cost saving.

*Caution is advised when interpreting brolucizumab versus ranibizumab results as the EAG did not consider there to be sufficient justification for the brolucizumab versus ranibizumab cost-comparison.

Figure 3. Tornado plot - brolucizumab versus aflibercept (Figure 18 of the CS)

Figure 4. Tornado plot - brolucizumab versus ranibizumab (Figure 19 of the CS)

4.3.1 Company's scenario analyses

The company undertook a series of scenario analyses to assess the impact of applying alternative assumptions to key model parameters including several analyses requested by the EAG at the clarification stage. These scenarios are presented in Table 18. Brolucizumab remained cost saving across all scenarios tested. Results incorporating an available aflibercept PAS are provided by the EAG in the CIC Appendix.

The largest change in incremental costs occurred when a discontinuation rate estimated from the Peto et al. 2021[21] real world evidence study was applied to all treatment arms, the incremental costs versus aflibercept dropped to [redacted] however for the reasons outlined in Section 4.2.5.4 the EAG did not consider this to be the optimal discontinuation rate. Other incremental cost drivers identified by the company's scenario analyses included; time horizon, injection frequency, monitoring frequency, and monitoring visit costs.

Table 18. Company's scenario analyses results

Model assumption	Base case	Scenario	Incremental cost versus	
			aflibercept	Ranibizumab*
Base case	-	-	[redacted]	[redacted]

Original company submission scenarios (adapted from Table 48 of the company submission)				
Discount rate	3.5% per annum	0% per annum	[redacted]	[redacted]
% of patient cohort with bilateral disease at baseline	27.9% (clinicians estimate)	46.5% (NICE TA346)	[redacted]	[redacted]
		12.7% (VISTA and VIVID)	[redacted]	[redacted]
Injection frequency – years 3+	NICE TA346	Company's clinical expert estimates (3 per year)	[redacted]	[redacted]
Discontinuation rate	Pooled KITE and KESTREL aflibercept rate applied, NMA estimates hazard ratios applied for brolucizumab and ranibizumab arms.	Brolucizumab and aflibercept estimates from respective arms of pooled KITE and KESTREL trials, ranibizumab assumed equal to aflibercept.	[redacted]	[redacted]
		Aflibercept and ranibizumab assumed equal to pooled brolucizumab KITE and KESTREL rate.	[redacted]	[redacted]
		Peto *et al*. 2021[21] real world evidence study estimate used for all arms	[redacted]	[redacted]
Administration cost	Consultant lead outpatient ophthalmology attendance	Nurse lead outpatient ophthalmology attendance	[redacted]	[redacted]
Monitoring frequency in years 3+	NICE TA346 estimates used	Glassman *et al*. 2020[31] – Protocol T extension study	[redacted]	[redacted]
Adverse event costs	Excluded	Included	[redacted]	[redacted]
Clarification response scenarios				
Time horizon	Lifetime (36.9 years)	5 years	[redacted]	[redacted]
		10 years	[redacted]	[redacted]
		15 years	[redacted]	[redacted]
Mortality	General population mortality	Relative risk of mortality (1.95) associated with diabetes patients applied	[redacted]	[redacted]
Injection frequency – years 1 & 2	Pooled brolucizumab KITE and KESTREL frequencies for brolucizumab arm, Peto *et al*. 2021[21] real world evidence study frequencies used for aflibercept and ranibizumab arms.	Unpooled brolucizumab and aflibercept KESTREL data, ranibizumab assumed equal to aflibercept.	[redacted]	[redacted]
		Unpooled brolucizumab and aflibercept KITE data, ranibizumab assumed equal to aflibercept.	[redacted]	[redacted]
		Pooled aflibercept KITE and KESTREL data used, ranibizumab assumed equal to aflibercept.	[redacted]	[redacted]

Monitoring frequency years 1&2	Peto *et al*. 2021[21] real world evidence data used for aflibercept and ranibizumab arms, brolucizumab monitoring frequency assumed equal to injection frequency	Aflibercept and ranibizumab monitoring frequency assumed equal to aflibercept injection frequency	[redacted]	[redacted]
Discontinuation rate, injection & monitoring frequencies – years 1 & 2.	Injection frequency taken from pooled KITE and KESTREL studies for brolucizumab, and Peto *et al*. 2021[21] real world evidence for aflibercept and ranibizumab. Discontinuation rate for aflibercept taken from pooled KITE and KESTREL, NMA hazard ratios applied for brolucizumab and ranibizumab. Aflibercept and ranibizumab monitoring frequency taken from Peto *et al*. 2021[21], brolucizumab monitoring frequency assumed equal to injection frequency.	Aflibercept and ranibizumab injection frequency and discontinuation rate from KESTREL aflibercept data. Monitoring frequency assumed equal to injection frequency.	[redacted]	[redacted]
		Aflibercept and ranibizumab injection frequency and discontinuation rate from KITE aflibercept data. Monitoring frequency assumed equal to injection frequency.	[redacted]	[redacted]
		Aflibercept and ranibizumab injection frequency and discontinuation rate from pooled KITE & KESTREL aflibercept data. Monitoring frequency assumed equal to injection frequency.	[redacted]	[redacted]
Monitoring visit cost	Optical coherence tomography test cost applied for each monitoring visit	Additional cost of wide field fundus photography applied at each monitoring visit.	[redacted]	[redacted]
Brolucizumab monitoring frequency	No additional monitoring-specific ophthalmologist visits costed as monitoring assumed to occur	Six additional ophthalmologist visits costed for monthly monitoring during the first six months of brolucizumab treatment.	[redacted]	[redacted]

	during injection visits.			
Bilateral DMO – additional administration costs	Bilateral DMO administration cost multiplier of 1.5 applied for all treatment arms (50% of fellow DMO eye's treated in separate appointment)	Bilateral DMO administration cost multiplier of 1.15 applied for aflibercept and ranibizumab arms.	[redacted]	[redacted]
		Bilateral DMO administration cost multiplier of 2 applied for brolucizumab arm.	[redacted]	[redacted]

Note: negative incremental costs indicate brolucizumab is cost saving.

Abbreviations: NICE, National Institute for Heath and Care Excellence; TA, technology appraisal; DMO, diabetic macular oedema.

*Caution is advised when interpreting brolucizumab versus ranibizumab results as the EAG did not consider there to be sufficient justification for the brolucizumab versus ranibizumab cost-comparison.

4.3.2 *Model validation and face validity check*

The company did not report any quality control checks performed by the model developers, or external parties, to ensure calculations were correct and consistent with the model specification. No external validation of the model structure or overall health economics approach was reported. The company conducted a clinical elicitation exercise in which 8 clinical experts from throughout England and Wales were asked questions related to the DMO treatment pathway and model parameter estimates. Details are provided in Appendix J or the company submission.

The EAG conducted model validation and face validity checks and aside from the issues discussed in Sections 4.2.4.1, 4.2.5.4 and 4.2.6.5, the EAG consider the company's model to be functionally sound. No errors in the model were identified by the EAG. As discussed in Section 4.2.3, the EAG reiterate that a major remaining area of uncertainty is whether brolucizumab will be used as a first-line treatment option for adult patients with visual impairment caused by DMO, or due to safety concerns regarding potentially higher intraocular inflammation rates, if brolucizumab will be used as second-line treatment following aflibercept or ranibizumab. The company were unable to provide an analysis comparing brolucizumab to relevant second-line comparators.

5 EAG commentary of the robustness of the evidence submitted by the company

Clinical

The final scope issued by National Institute for Health and Care Excellence (NICE) specifies the population of interest to be people with visual impairment due to diabetic macular oedema (DMO) but the company has submitted for a narrower indication that restricts the population to only those with a central retinal thickness (CRT) of ≥400 µm. The Evidence Assessment Group (EAG) considers the narrower population addressed by the company submission (CS) to be reasonable given the company's decision to submit a cost-comparison versus aflibercept and ranibizumab. However, the EAG notes that the focus of the clinical data from KESTREL and KITE (the key studies of brolucizumab), and from the company network meta-analyses (NMAs) presented in the CS relate to a broader DMO population and only data on central subfield thickness (CSFT) are available from KITE and KESTREL, rather than CRT. The EAG notes that CSFT and CRT are reported by Waheed *et al.*2013[16] to be closely correlated and so potentially KITE and KESTREL may have patients with a lower CRT than those expected to be treated with brolucizumab in clinical practice as the trials included patients with a CSFT of ≥320µm.

The EAG is concerned about the robustness of the subgroup analyses from KITE and KESTREL based on CSFT measurement at baseline, and considers that it may not be appropriate to conclude that the [redacted], although they were *post-hoc* analyses and [redacted]

[redacted], which the EAG's clinical experts reported may be clinically important and influence the results. Nevertheless, the primary outcome for KESTREL and KITE was mean change from baseline in BCVA at 52 weeks, and both trials demonstrated non-inferiority of brolucizumab 6 mg compared to aflibercept 2 mg in the overall DMO population. Additionally,

[redacted]

The EAG's clinical experts also reported that due to potential safety concerns in terms of intraocular inflammation with brolucizumab it may be used as a second-line treatment with preference for aflibercept or ranibizumab as first-line therapy. The EAG notes that in wet age-related macular degeneration (wAMD) safety concerns around intraocular inflammation emerged only during the post-marketing surveillance of brolucizumab and that [redacted]. However, the company reported that their panel of six clinicians considered the primary positioning of brolucizumab would be as a first-line treatment and highlighted an absence of clinical trial data for brolucizumab use at second-line.

[redacted]

Economic

The EAG are concerned that the company's base case analysis incorporates an indirect treatment effect as this is inconsistent with the cost-comparison modelling approach. As discussed in Section 4.2.5.4, the model structure allows for fellow eye DMO incidence to occur only in patients remaining on anti-vascular endothelial growth factor (anti-VEGF) treatment but patients discontinue brolucizumab, aflibercept and ranibizumab at different rates. Hence the patient cohort in each arm has an unequal risk of developing bilateral DMO. The company (and the EAG) have provided scenario analyses applying the same discontinuation rate to all treatment arms, this adjustment suitably equalises the risk of developing bilateral DMO across all treatment arms.

Another major area of uncertainty is the positioning of brolucizumab as a first-line treatment option for adult patients with visual impairment caused by DMO. The EAG's clinical experts noted that, due

to safety concerns regarding potentially higher intraocular inflammation rates, brolucizumab may be used as second-line treatment following aflibercept or ranibizumab. However, due to a lack of clinical trial data for brolucizumab use at second-line, the company were unable to provide a requested scenario analysis considering relevant second-line comparators. The company considered aflibercept and ranibizumab to be appropriate comparators for second-line brolucizumab as well as first-line. However, as discussed in Section 4.2.3, the EAG considers dexamethasone to be a relevant comparator to second-line brolucizumab as dexamethasone is currently recommended for pseudophakic DMO patients who are unsuitable for/insufficiently responsive to non-corticosteroid (anti-VEGF) treatments.

6 Additional economic analysis undertaken by the EAG

6.1 Model corrections

The Evidence Assessment Group (EAG) has made no corrections to the company's model.

6.2 Scenario analyses undertaken by the EAG

In Section 4 of this report, the EAG has described several scenarios that warrant further exploration (in addition to the company's own sensitivity and scenario analyses) to ascertain the impact of these changes on the incremental costs. The deterministic scenarios that the EAG has performed are presented in Table 19.

Table 19. Results of the EAG's scenario analyses

	Treatment arm	Total costs	Incremental costs
0	Company base case		
	Brolucizumab	[redacted]	[redacted]
	Aflibercept	[redacted]	[redacted]
	Ranibizumab	[redacted]	[redacted]
1	Average of aflibercept and brolucizumab discontinuation rates (weighted by number of patients) from KESTREL trial applied to all treatment arms [Section 4.2.5.4].		
	Brolucizumab	[redacted]	[redacted]
	Aflibercept	[redacted]	[redacted]
	Ranibizumab	[redacted]	[redacted]
2	Year one probability of developing DMO in fellow eye halved from 37.64% (Dhoot *et al*. 2020[24]) to 18.82% [Section 4.2.5.4].		
	Brolucizumab	[redacted]	[redacted]
	Aflibercept	[redacted]	[redacted]
	Ranibizumab	[redacted]	[redacted]
3	Unpooled KESTREL trial injection frequencies applied for brolucizumab and aflibercept, with ranibizumab assumed equal to aflibercept injection frequencies [Section 4.2.6.5].		
	Brolucizumab	[redacted]	[redacted]
	Aflibercept	[redacted]	[redacted]
	Ranibizumab	[redacted]	[redacted]
4	Cost of one additional monitoring visit applied to year one of brolucizumab arm - 6 monitoring visits in the first 6 months of brolucizumab treatment assumed (5 coincide with injection visits) [Section 4.2.6.5].		
	Brolucizumab	[redacted]	[redacted]
	Aflibercept	[redacted]	[redacted]
	Ranibizumab	[redacted]	[redacted]

Note: negative incremental cost results indicate brolucizumab is cost saving

*Caution is advised when interpreting brolucizumab versus ranibizumab results as the EAG did not consider there to be sufficient justification for the brolucizumab versus ranibizumab cost-comparison.

6.3 EAG preferred assumptions

In this section, the EAG presents its preferred base case deterministic results for brolucizumab treatment for adult patients with visual impairment caused by DMO, with a CRT of 400 µm or greater at the start of treatment. Table 20 outlines the assumptions incorporated into the EAG's base case. As functionality was not built into the company model to run probabilistic sensitivity analyses, probabilistic results are not provided.

Table 20. EAG's preferred model assumptions (cumulative deterministic results).

Preferred assumption	Section in EAG report	Cumulative incremental cost of brolucizumab versus	
		aflibercept	Ranibizumab*
Company base case	4.2.4, 4.2.5 & 4.2.6	[redacted]	[redacted]
10-year time horizon	4.2.4.1	[redacted]	[redacted]
Average of aflibercept and brolucizumab discontinuation rates (weighted by number of patients) from KESTREL trial applied to all treatment arms.	4.2.5.4	[redacted]	[redacted]
Relative risk of mortality (1.95) associated with diabetes patients applied	4.2.5.4	[redacted]	[redacted]
Unpooled KESTREL trial injection frequencies applied for brolucizumab and aflibercept, with ranibizumab assumed equal to aflibercept injection frequencies	4.2.6.5	[redacted]	[redacted]
Bilateral DMO administration cost multiplier of 1.15 applied for aflibercept and ranibizumab arms	4.2.6.5	[redacted]	[redacted]
Bilateral DMO administration cost multiplier of 2 applied for brolucizumab arm	4.2.6.5	[redacted]	[redacted]

Aflibercept and ranibizumab monitoring frequency assumed equal to aflibercept injection frequency	4.2.6.5	[redacted]	[redacted]
Cost of one additional monitoring visit applied to year one of brolucizumab arm - 6 monitoring visits in the first 6 months of brolucizumab treatment assumed (5 coincide with injection visits)	4.2.6.5	[redacted]	[redacted]
Additional cost of wide field fundus photography applied at each monitoring visit	4.2.6.5	[redacted]	[redacted]

Abbreviations: EAG, Evidence Assessment Group; DMO, diabetic macular oedema

*Caution is advised when interpreting brolucizumab versus ranibizumab results as the EAG did not consider there to be sufficient justification for the brolucizumab versus ranibizumab cost-comparison.

6.4 EAG preferred base case results

Table 21 presents the EAG's deterministic base case results. The EAG notes that the results versus ranibizumab should be interpreted with caution as, due to the lack of a direct comparison of brolucizumab and ranibizumab and limitations to the company's network meta-analyses, the EAG did not consider there to be sufficient justification for the brolucizumab versus ranibizumab cost-comparison. A further set of EAG base case results, incorporating the aflibercept PAS discount, are provided by the EAG in the confidential appendix.

Table 21. EAG's base case results

Interventions	Total Costs (£)	Incremental costs (£)
Brolucizumab	[redacted]	-
Aflibercept	£31,316	[redacted]
Ranibizumab	[redacted]	[redacted]

Note: negative incremental costs indicate brolucizumab is cost saving.

*Caution is advised when interpreting brolucizumab versus ranibizumab results as the EAG did not consider there to be sufficient justification for the brolucizumab versus ranibizumab cost-comparison.

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8 Appendices

8.1 Baseline characteristics of KESTREL and KITE

Table 22. Baseline demographic, background, diabetes and ocular characteristics of patients in KITE and KESTREL (FAS) (Reproduced from CS, Table 9)

Participant characteristic	KITE			KESTREL			
	Brolucizumab 6 mg (N=179)	Aflibercept 2 mg (N=181)	Overall (N=360)	Brolucizumab 3 mg (N=190)	Brolucizumab 6 mg (N=189)	Aflibercept 2 mg (N=187)	Overall (N=566)
Demographic and background characteristics							
Age group (years), n (%)							
<65 years	100 (55.9)	102 (56.4)	202 (56.1)	97 (51.1)	104 (55.0)	93 (49.7)	294 (51.9)
≥65 years	79 (44.1)	79 (43.6)	158 (43.9)	93 (48.9)	85 (45.0)	94 (50.3)	272 (48.1)
Age (years)							
Mean	62.3	62.2	62.2	64.4	62.4	63.9	63.6
SD	10.55	9.48	[redacted]	9.76	10.14	10.09	[redacted]
Sex, n (%)							
Male	120 (67.0)	115 (63.5)	235 (65.3)	119 (62.6)	110 (58.2)	126 (67.4)	355 (62.7)
Female	59 (33.0)	66 (36.5)	125 (34.7)	71 (37.4)	79 (41.8)	61 (32.6)	211 (37.3)
Race†, n (%)							
White	133 (74.3)	132 (72.9)	265 (73.6)	151 (79.5)	158 (83.6)	153 (81.8)	462 (81.6)
Black or African American	3 (1.7)	1 (0.6)	4 (1.1)	13 (6.8)	4 (2.1)	7 (3.7)	24 (4.2)
Asian	43 (24.0)	48 (26.5)	[redacted]	25 (13.2)	25 (13.2)	27 (14.4)	77 (13.6)
Native Hawaiian or Other pacific Islander	0	0	0	0	2 (1.1)	0	2 (0.4)

American Indian or Alaska native	0	0	0	1 (0.5)	0	1 (0.5)	2 (0.4)
Diabetes characteristics							
Diabetes type (based on primary diagnosis), m (%)							
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Type 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Type 2	160 (89.4)	174 (96.1)	334 (92.8)	180 (94.7)	177 (93.7)	181 (96.8)	538 (95.1)
HbA_{1c}, %							
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean	7.55	7.46	7.50	7.52	7.69	7.44	7.55
SD	1.174	1.161	[redacted]	1.160	1.067	1.132	[redacted]
Ocular characteristics							
BCVA, letters							
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean	66.0	63.7	64.9	65.7	66.6	65.2	65.8
SD	10.77	11.70	[redacted]	11.09	9.67	12.38	[redacted]
BCVA group, m (%)							
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≤65 letters	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>65 letters	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time since DMO diagnosis (months)							
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean	10.4	9.9	10.2	12.5	9.4	9.6	10.5
SD	16.56	20.73	[redacted]	30.82	19.47	24.17	[redacted]
Time since DMO diagnosis group, m (%)							

N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≤3 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>3–<12 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥12 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Macular oedema type, m (%)							
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Focal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diffuse	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Can't grade	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
N/A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CSFT, µM							
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean	481.1	484.4	482.7	456.0	453.1	475.6	461.5
SD	132.46	134.58	133.35	118.04	123.42	135.84	126.11
CSFT group, m (%)							
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
<450 µm	85 (47.5)	82 (45.6)	167 (46.5)	111 (58.4)	107 (56.6)	96 (51.3)	314 (55.5)
≥450 – < 650 µm	74 (41.3)	79 (43.9)	153 (42.6)	64 (33.7)	70 (37.0)	71 (38.0)	205 (36.2)
≥650 µm	20 (11.2)	19 (10.6)	39 (10.9)	15 (7.9)	12 (6.3)	20 (10.7)	47 (8.3)
Leakage on fluorescein angiography, m (%)							
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Present	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Absent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IRF, m (%)							

n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Present	176 (98.3)	179 (98.9)	355 (98.6)	190 (100)	189 (100)	184 (98.4)	563 (99.5)
Absent	3 (1.7)	2 (1.1)	5 (1.4)	0	0	3 (1.6)	3 (0.5)
SRF, m (%)							
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Present	56 (31.3)	67 (37.0)	123 (34.2)	60 (31.6)	62 (32.8)	61 (32.6)	183 (32.3)
Absent	123 (68.7)	114 (63.0)	237 (65.8)	130 (68.4)	127 (67.2)	126 (67.4)	383 (67.7)
DRSS, m (%)							
n	176	177	353	185	186	184	555
1-DR absent	3 (1.7)	1 (0.6)	4 (1.1)	1 (0.5)	0	0	1 (0.2)
2-Microaneurysms only	0	2 (1.1)	2 (0.6)	3 (1.6)	1 (0.5)	3 (1.6)	7 (1.3)
3-Mild NPDR	49 (27.8)	37 (20.9)	86 (24.4)	56 (30.3)	57 (30.6)	52 (28.3)	165 (29.7)
4-Moderate NPDR	55 (31.3)	68 (38.4)	123 (34.8)	51 (27.6)	54 (29.0)	59 (32.1)	164 (29.5)
5-Moderately severe NPDR	30 (17.0)	20 (11.3)	50 (14.2)	25 (13.5)	15 (8.1)	16 (8.7)	56 (10.1)
6-Severe NPDR	26 (14.8)	34 (19.2)	60 (17.0)	39 (21.1)	45 (24.2)	40 (21.7)	124 (22.3)
7-Mild PDR	9 (5.1)	7 (4.0)	16 (4.5)	6 (3.2)	3 (1.6)	7 (3.8)	16 (2.9)
8-Moderate PDR	3 (1.7)	5 (2.8)	8 (2.3)	4 (2.2)	8 (4.3)	5 (2.7)	17 (3.1)
9-High risk PDR	1 (0.6)	2 (1.1)	3 (0.8)	0	3 (1.6)	2 (1.1)	5 (0.9)
10-Very high-risk PDR	0	0	0	0	0	0	0
11-Advanced PDR	0	1 (0.6)	1 (0.3)	0	0	0	0
12-Very advanced PDR	0	0	0	0	0	0	0

[†]A patient can have multiple races.
n=number of patients with an assessment. Percentages are calculated based on n; m=number of patients with an assessment meeting the criterion for the given categorical variable.
Abbreviations: BCVA, best-corrected visual acuity; CSFT, central subfield thickness; DMO, diabetic macular oedema; DR, diabetic retinopathy; DRSS, diabetic retinopathy severity scale; FAS, full analysis set; $HbA_{1c,}$ haemoglobin A_{1c}; IRF, intraretinal fluid; N/A, not applicable; NPDR, non-proliferative diabetic retinopathy; N/R, not reported; OD, oculus dexter; OS, oculus sinister; PDR,

proliferative diabetic retinopathy; SD, standard deviation; SRF, subretinal fluid.
Source: Brown 2022 [32]; KITE and KESTREL Week 52 clinical study reports. [12, 13]

8.2 Quality assessment

Table 23. Quality assessment of KESTREL and KITE trials according to checklist used in CS (Adapted from CS Appendix D, Table 23)

Question on trial design	Company assessment of risk	EAG agrees or disagrees
KESTREL (EudraCT no. 2017-004742-23)[13-15, 32, 33]		
Was randomisation carried out appropriately?	LOW	EAG agrees.
Was the concealment of treatment allocation adequate?	LOW	EAG agrees.
Were the groups similar at the onset of the study in terms of prognostic factors, for example, severity of the disease?	LOW	The EAG considers there may be a risk of bias for this domain as there were some baseline differences between treatment arms: • Proportion with Type 1 diabetes mellitus, 6.3% vs 3.2% in brolucizumab 6 mg and aflibercept 2 mg treatment arms • Proportion with HbA_{1c} levels ≥7.5%, 59.6% vs 42.8% in brolucizumab 6 mg and aflibercept 2 mg treatment arms The difference for HbA_{1c} levels ≥7.5% appears to be a particularly large difference, though one of the EAG's clinical experts advised that HbA_{1c} levels should not have a large impact on treatment efficacy.
Were the care providers, participants, and outcome assessors blind to treatment allocation?	LOW	The EAG notes that, although in their quality assessment the company describes investigators, patients and biostatisticians as being masked, [redacted]

		[redacted]
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	LOW	The EAG agrees that at 52 weeks, study discontinuations are similar between groups, but slightly higher in the brolucizumab 6 mg group compared to the aflibercept 2 mg group. At 100 weeks, [redacted]
Is there any evidence to suggest that the authors measured more outcomes than they reported?	LOW	EAG agrees.
Did the analysis include an ITT analysis?	LOW	The EAG notes that a risk of bias for this domain may be present based on the use of LOCF imputation for missing data; however, the EAG notes that the same issue would be relevant for brolucizumab and aflibercept and the risk of bias may depend on the differences in proportions of missing data between arms. Although missing data is similar between groups at weeks 52 [redacted], reasons for drop-out include those related to the study (for example adverse events) and discontinuing treatment may lead to deterioration in outcome rather than maintenance of effect from previous measurement.
KITE (EudraCT no. 2017-003960-11)[12, 14, 15, 32, 33]		
Was randomisation carried out appropriately?	LOW	EAG agrees.
Was the concealment of treatment allocation adequate?	LOW	EAG agrees.
Were the groups similar at the onset of the study in terms of prognostic factors, for example, severity of the disease?	LOW	The EAG considers there may be a risk of bias for this domain as there were some baseline differences between treatment arms: • [redacted] in brolucizumab 6 mg and aflibercept 2 mg treatment arms • Proportion with [redacted]

		[redacted] in brolucizumab 6 mg and aflibercept 2 mg treatment arms. The difference between groups in terms of proportion with [redacted]
Were the care providers, participants, and outcome assessors blind to treatment allocation?	LOW	The EAG notes that, although in their quality assessment the company describes investigators, patients and biostatisticians as being masked, [redacted]
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	LOW	The EAG agrees that [redacted] in the brolucizumab 6 mg group compared to aflibercept 2 mg [redacted]
Is there any evidence to suggest that the authors measured more outcomes than they reported?	LOW	EAG agrees.

Did the analysis include an ITT analysis?	LOW	The EAG notes that a risk of bias for this section may be present based on the use of LOCF imputation for missing data; however, the EAG note that the same issue would be relevant for brolucizumab and aflibercept and the risk of bias may depend on the differences in proportions of missing data between arms. Although missing data is similar between groups at week 52 [redacted]. Reasons for drop-out at include those related to the study (for example adverse events) and discontinuing treatment may lead to deterioration in outcome rather than maintenance of effect from previous measurement.

Abbreviations: BCVA, best-corrected visual acuity; CSR, Clinical Study Report; EAG, Evidence Assessment Group; HbA_{1c}, glycated haemoglobin; ITT, intention to treat; LOCF, last observation carried forward.

8.3 Other outcomes of relevance to the NICE final scope

This section includes additional outcomes reported in KESTREL and KITE that were relevant to the NICE scope.

8.3.1.1 Disease severity

Severity of diabetic retinopathy was assessed using the Early Treatment Diabetic Retinopathy Scale (ETDRS) Diabetic Retinopathy Severity Scale (DRSS). Severities were categorised from 10 to 85, with 10 representing absent diabetic retinopathy and 85 representing very advanced proliferative diabetic retinopathy. This was converted to a 12-level scale. Treatment difference assessed using logistic regression adjusted for baseline DRSS score categories (≤4 and ≥5), age categories (<65 years vs ≥65 years) and treatment as fixed effect factors, and was within the FAS analysis set, with LOCF used for missing or censored data.

The company reports the proportion in each treatment arm with ≥2 and ≥3-step improvements on this scale compared to baseline at various time-points (see Table 5 of Appendix K of the CS). For

KITE, the company reports that the proportion with a ≥2 or ≥3-step improvement was [redacted] For KESTREL, the proportion was [redacted] Treatment differences for most time-points in both studies indicated [redacted]

Proportions in each treatment arm with a worsening of ≥2 and ≥3-steps compared to baseline at various time-points were also reported (Appendix K of the CS). In both studies, [redacted]; in KITE, [redacted] experienced a ≥2-step worsening by week 100, while in KESTREL [redacted], proportions with a ≥3-step worsening at week 100 [redacted] Treatment differences for week 100 in both studies indicated [redacted]

8.3.1.2 IRF and sub-retinal fluid (SRF)

SRF and IRF are measures of fluid accumulation and disease activity, with reductions indicating better disease activity control. Treatment difference was assessed using logistic regression adjusting for baseline fluid status (SRF and/or IRF), age categories (<65 years vs ≥65 years) and treatment as fixed effect factors and was within the FAS analysis set, with LOCF used for missing or censored data.

The company reported the proportion of patients with SRF and/or IRF in the study eye at each post-baseline visit up to week 100 (Figures 13 and 14 of CS), with results indicating [redacted] In KITE, there were some [redacted]

[redacted] At weeks 52 [redacted] in both trials, treatment differences indicated better outcome in the brolucizumab 6 mg group compared to aflibercept 2 mg (see Table 4 in Appendix K of the CS), with confidence intervals consistent with this conclusion.

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check and confidential information check

Brolucizumab for treating diabetic macular oedema [ID3902]

'*Data owners will be asked to check that confidential information is correctly marked in documents created by others in the technology appraisal process before release; for example, the technical report and ERG report.*' (Section 3.1.29, Guide to the processes of technology appraisals).

You are asked to check the ERG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Wednesday 1 June** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as 'commercial in confidence' in turquoise, all information submitted as 'academic in confidence' in yellow, and all information submitted as 'depersonalised data' in pink.

Issue 1 Inaccurate description of company submission

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 14, lines 31-33	Current wording: "the EAG's clinical experts noted that wide field fundus examinations are conducted at all monitoring visits rather than the single examination assumed in the company base case" Proposed wording: "the EAG's clinical experts noted that wide field fundus examinations are conducted at monitoring visits, but were not included in the company base case"	Wide field fundus examinations were not included in the company base case.	The EAG thanks the company for highlighting this error and has made the proposed amendment.
Page 17, Table 1, population row, EAG comment column, lines 17–19	Current wording: "but the EAG notes that only CSFT data were available from KITE and KESTREL" Proposed wording: "but the EAG notes that the subgroup data are for patients with baseline CSFT ≥400 µm, and the company consider CSFT to be equivalent to CRT"	The original wording suggests that CSFT-related endpoints were the only endpoints provided for the subgroup analysis. This is incorrect, as the primary and key secondary endpoints, change from baseline in BCVA to Week 100, disease severity outcomes (EDTRS-DRSS), and patient reported outcomes (VFQ-25) were also presented. The subgroup was patients with CSFT ≥400 µm, and CSFT is considered by the company to be equivalent to CRT (see response to Page 36, lines 24–26).	The EAG thanks the company for highlighting this and has amended the text to "the EAG notes that the subgroup data from KITE and KESTREL are for patients with baseline CSFT ≥400 µm, and the company consider CSFT to be equivalent to CRT."
Page 23, line 4–5	Current wording: "DMO involving the centre of the macula and central subfield thickness (CSFT) of ≥320µm on SD-OCT"	The proposed wording matches the KITE and KESTREL clinical study reports.	The EAG thanks the company for highlighting this and has made the proposed amendment.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	Proposed wording: “DMO involving the centre of the macula and central subfield retinal thickness (CSFT) of ≥320µm on SD-OCT”		
Page 26, line 14–15	Current wording: “In addition, of the 44 studies originally identified, 14 studies (from 68 publications, including KESTREL and KITE)” Proposed wording: “In addition, of the 44 studies originally identified, 14 studies (from 72 publications, including KESTREL and KITE)”	The current value for the numbers of publications in incorrect. In total, 14 studies from 72 publications were included in the NMA.	The EAG thanks the company for highlighting this error and has made the proposed amendment.
Page 26, line 20	Current wording: “Details of the 30 studies (from 72 publications) identified as meeting the broad inclusion criteria in the NICE scope, including their quality assessment, were provided by the company” Proposed wording: “Details of the 30 studies (from 72 publications) identified as meeting the broad inclusion criteria in the NICE scope (but were not included in the NMA), including their quality	The original wording does not make it clear that the 30 studies referred to are those that met the broad inclusion criteria of the NICE scope, but not the narrower inclusion criteria for the NMA (which included only studies with comparators the company considered the most relevant [aflibercept 2 mg and ranibizumab 0.5 mg]). The proposed wording clarifies this.	The EAG thanks the company for highlighting this and has added the text “(but not included in the NMA)”.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	assessment, were provided by the company"		
Page 36, lines 24–26	Current wording: However, the EAG's clinical experts also reported that CSFT does not necessarily equal CRT, and so it is difficult to draw conclusions for the CRT ≥400 µm population based on the CSFT subgroup. Proposed wording: However, the EAG's clinical experts also reported that CSFT does not necessarily equal CRT, and so it is difficult to draw conclusions for the CRT ≥400 µm population based on the CSFT subgroup. The company consider the terms CSFT and CRT to be used interchangeably in clinical practice and the EAG notes that CSFT and CRT are reported by Waheed *et al.* 2013 (1) to be closely correlated.	The company acknowledges CRT and CSFT measures may slightly differ as CRT is defined as the mean thickness measured at the point of intersection of 6 radial scans whilst CSFT is defined as the mean thickness within the central 1mm diameter area in the ETDRS map. Older trials may typically report CRT values whilst newer trials such as VIVID-DME, VISTA-DME, and protocol T report CSFT values. Some publications have reported that CSFT is the preferred OCT measurement for the central macula in DMO because of its higher reproducibility and correlation with other measurements of the central macula (2). In clinical practice CRT and CSFT are often used interchangeably.	The EAG thanks the company for highlighting this and has added the text "The EAG notes that the company reported that CRT and CSFT could be considered to be equivalent and referenced a paper by Waheed *et al*.2013[16] where it is reported that CSFT and CRT are closely correlated.".
Page 40, line 28	Current wording: "The associated p-values were not provided" Proposed wording: The associated p-values were not	The original wording implies that Novartis did not include any p-values in the submission, however they were provided for the primary and key secondary endpoints according to the multiple testing strategy. The proposed wording clarifies	No change required; the EAG does not consider this to be a factual error.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	provided as the proportion of patients experiencing a change in ≥15 or ≥10 letters from baseline in BCVA was not part of the multiple testing strategy"	that not including p-values was not an oversight, but due to the statistical analysis plan.	
Page 48, line 11	Current wording: [redacted] Proposed wording: [redacted]	The current value is incorrect. Table 13 of Appendix D shows discontinuation due to AEs in [redacted] patients in the brolucizumab arm in KITE	The EAG thanks the company for highlighting this error and has made the proposed amendment.
Page 56, lines 6–9	Current wording: "There was a lack of formal non-inferiority testing for most secondary outcomes, and p-values for significance were also not reported; however, treatment differences with 95% confidence intervals were generally sufficient to indicate whether or not large differences were present and whether there was uncertainty in the direction of the treatment difference" Proposed wording: "The company presented formal non-inferiority testing and p-values for secondary outcomes according to the multiple	The current phrasing implies that the company did not report any p-values for the secondary endpoints; non-inferiority testing and superiority testing were performed according to the multiple testing strategy, and p-values presented accordingly. For analyses that were not part of the multiple testing strategy, confidence intervals are considered most appropriate for interpretation of results.	The EAG thanks the company for highlighting this and has amended the text to: "There was a lack of formal non-inferiority testing for most secondary outcomes, and p-values for significance were also not reported for all outcomes (non-inferiority testing and p-values were reported as per the multiple testing strategy and statistical analysis plan); however, treatment differences with 95% confidence intervals were generally sufficient to indicate whether or not large differences were present and whether there was uncertainty in the direction of the treatment difference."

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	testing strategy. Where these were not reported, as per the multiple testing strategy and statistical analysis plan, treatment differences with 95% confidence intervals were generally sufficient to indicate whether or not large differences were present and whether there was uncertainty in the direction of the treatment difference"		
Page 47, lines 23–25	Current wording: "however, it is noted in Appendix D of the CS (section D4.2) that an NMA was not done for treatment discontinuation and was only performed for study discontinuation." Proposed wording: "however, it is noted in Appendix D of the CS (section D4.2) that an NMA was not done for treatment discontinuation and was only performed for study discontinuation, as very few studies reported treatment discontinuation, so an NMA was not possible for this outcome."	The original wording omits the company's explanation for why an NMA was not performed for treatment discontinuation; the proposed wording clarifies this.	The EAG thanks the company for highlighting this and has added the following text: "The company reported that this was because very few studies reported treatment discontinuation, so an NMA was not possible for this outcome."

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 63, line 10–11	Current wording: "The model structure (**Error! Reference source not found.**) developed by the company aims to estimate the costs associated with DMO both on and off anti-VEGF treatment" Proposed wording: "The model structure (**Error! Reference source not found.**) developed by the company aims to estimate the costs associated with DMO whilst on anti-VEGF treatment"	The current phrasing implies costs are acquired in the 'off anti-VEGF treatment' health state, which is inconsistent with the modelled approach.	The EAG thanks the company for highlighting this error and has made the proposed amendment.
Page 69, line 27 Page 72, line 18	Please correct "2020" to "2021"	The current year reported is incorrect. Modelled costs were inflated to the year 2021 using the Office for National Statistics inflation indices.	This is not a factual error. All costs included in the company base case are sourced from NHS reference costs 2019-20. Costs that were uplifted to 2021 relate to AE costs and were not included in the company base case.
Page 71, line 11 Page 84, line 7	Please correct "ICER" to "incremental costs"	The current wording is inconsistent with the cost-comparison approach taken.	The EAG thanks the company for highlighting this error and has made the proposed amendment.
Page 74, line 27-29	Please remove: "The company did not consider it necessary to include additional ophthalmologist costs for monitoring visits because monitoring would coincide with injection visits."	The company model submitted alongside the response to EAG clarification questions included additional ophthalmologist visits in the scenario in which 6 monitoring visits were included in the first 6 months; see cell DF16 on the 'Calculations' sheet. The EAG scenario in which an additional ophthalmologist visit is included is therefore not required, and results in double counting this cost.	The EAG has amended the text in the EAG report to state that for the base case, the company did not consider it necessary to include additional ophthalmologist costs for monitoring visits because monitoring would coincide with injection visits However, the EAG's scenario simply adds one additional monitoring visit as based on

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
			the dosing schedule, 5 visits would occur in the first 6 months of treatment with brolucizumab. The EAG's scenario is applied independently of the company's scenario and therefore costs are not double counted.
Page 76, line 12-13	Please remove "One-way sensitivity analyses were also not provided by the company."	One-way sensitivity analysis results are presented in Section B.4.4.1 of the company submission.	The EAG thanks the company for highlighting this error and has added the tornado plots to the EAG report.

Issue 2 Clinical pathway of care

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 15, lines 20–23	Current wording: "The EAG's clinical experts reported potential safety concerns in terms of intraocular inflammation with brolucizumab and that brolucizumab may be used as a second-line treatment with preference for aflibercept or ranibizumab as first-line therapy although the company reports there are no clinical data for second-line use of brolucizumab in DMO." Proposed wording: "The EAG's clinical experts reported potential safety concerns in terms of intraocular inflammation with brolucizumab and that brolucizumab may be used as a second-line treatment with preference for aflibercept or ranibizumab as first-line therapy although the company reports there are no clinical data for second-line use of brolucizumab in DMO. However, clinical experts consulted by the company stated that brolucizumab would be considered as a first-line option"	All six clinicians, who participated in clinical insight gathering from 8th-12th April 2022, stated that brolucizumab would be considered as a first line treatment for DMO in UK clinical practice.	No change required; the EAG does not consider this to be a factual error.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 62, lines 27–29	Please remove: “It seems clinically implausible to the EAG that in current clinical practice if patients do not have an adequate response to aflibercept they would be switched to what is considered a less effective treatment”	All six UK clinical experts consulted by Novartis in April 2022 stated that in current clinical practice, DMO patients not responding or experiencing a suboptimal response to first line anti-VEGF treatment are switched to another anti-VEGF treatment (30).	No change required; the EAG does not consider this to be a factual error.
Page 62, line 29-31 to page 63, line 1-2	Current wording: “More plausibly, the EAG notes that dexamethasone is currently available for use in pseudophakic DMO patients who are unsuitable for, or who did not respond to, non-corticosteroid (anti-VEGF) treatment. As such, the EAG consider dexamethasone to be a relevant second-line comparator for pseudophakic DMO patients.” Proposed wording: “The EAG notes that dexamethasone is recommended by NICE for pseudophakic DMO patients who are unsuitable for, or who did not respond to non-corticosteroid (anti-VEGF) treatment. However, the clinical insight gathering conducted by the company confirmed that the most relevant second-line treatment comparator is another anti-VEGF”	This statement does not accurately reflect the evidence submitted by the company. Although dexamethasone is recommended by NICE, the clinical expert opinion presented by the company described the most relevant second-line treatment comparator as anti-VEGF. All six UK clinical experts consulted by Novartis in April 2022 stated that in current clinical practice, DMO patients not responding or experiencing a suboptimal response to first line anti-VEGF treatment are switched to another anti-VEGF treatment (30).	No change required; the EAG does not consider this to be a factual error.

Issue 3 Robustness of the NMA

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 13, lines 22–25	Current wording: [redacted]	The original wording suggests inconsistency was detected in “some outcomes”, which is inaccurate. In addition, although inconsistency between the direct	The EAG thanks the company for highlighting this and has made the proposed amendment.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	Proposed wording: [redacted]	and indirect paths was identified for a single outcome and timepoint, the direction of effect for the point estimate was the same and both direct and indirect estimates showed that RAN 0.5 mg PRN was favoured vs. LP in gain in BCVA letters at 1 year (WMD point estimate direct = [redacted] and indirect = [redacted]). This does not seem to have been noted. There is no apparent difference in baseline characteristics between the two trials that might explain all the identified heterogeneity, except some imbalance in BCVA between arms in KITE, as already noted by the EAG.	
Page 56, lines 26–29	Current wording: [redacted] Proposed wording: [redacted]	There is only one outcome in which inconsistency was detected.	The EAG thanks the company for highlighting this and has made the proposed amendment.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 49, line 7–9	Current wording: "The EAG notes that the company considers the exclusion of KITE from the NMAs not to be appropriate as it omits valid evidence from a pivotal trial; however, the EAG considers the results from KESTREL to be more reliable." Proposed wording: The EAG notes that the company considers the exclusion of KITE from the NMAs not to be appropriate as it omits valid evidence from a pivotal trial and that including KITE data represents a conservative approach; as generally, the higher the baseline BCVA, the smaller the number of letters gained (due to the ceiling effect (3)); however, the EAG considers the results from KESTREL to be more reliable.	The current text suggests the company's only argument for the inclusion of KITE is because it is a pivotal trial. The amended text includes further details on the company's argument against the exclusion of KITE	No change required; the EAG does not consider this to be a factual error.
Page 55, lines 3–8	Current wording: [redacted] Proposed wording: [redacted]	The current wording suggests that the EAG consider the NMA to be flawed methodologically. The suggested rewording will clarify that the issues are not methodological but are data driven. The most robust evidence for brolucizumab comes from KESTREL and KITE, which did not use the same CRT cut-off as used by NICE in its recommendations for aflibercept and ranibizumab. Nevertheless, an NMA incorporating these trials is considered the most appropriate for assessing relative treatment effects and it demonstrated that brolucizumab, aflibercept and	[redacted]

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	[redacted]	ranibizumab share similar efficacy. The company submitted an exploratory NMA in the ≥400 µm subgroup using the best available data, as limited outcomes for the comparison were reported in the identified studies.	
Page 82, lines 12–14	Current wording: [redacted] Proposed wording: [redacted]	As noted above, the current wording suggests inconsistency was identified in multiple outcomes, however this was not the case.	The EAG thanks the company for highlighting this and has made the proposed amendment.

Issue 4 Imbalance in baseline characteristics

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 12, line 22–25 This also applies to:	Current wording: "There were also a number of [redacted]	Regarding the differences in mean BCVA at baseline, a difference of 2.3 ETDRS letters, which was observed, is not generally	No change required; the EAG does not consider this to be a factual error.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 32, Table 3, Summary of KITE column, baseline characteristics row, lines 2–10; Page 54, lines 3–8	[redacted], which the EAG's clinical experts reported may be clinically important and influence the results." Proposed wording: "There were also a number of [redacted], which the EAG's clinical experts reported may be clinically important and influence the results. The EAG notes that the company argued that including KITE data represents a conservative approach, as generally, the higher the baseline BCVA, the smaller the number of letters gained due to the ceiling effect (3)."	considered to be clinically significant as evidenced by several clinical trials which use 3.5 to 5 letters as the margin to demonstrate a significant difference between drugs (IVAN (4), CATT (5), HAWK and HARRIER (6), KITE and KESTREL (7)). In addition, as the proportion of patients in KITE presenting ≤65 letters at baseline was [redacted] compared with the aflibercept arm [redacted] including KITE data represents a conservative approach; generally, the higher the baseline BCVA, the smaller the number of letters gained due to the ceiling effect (3).	
Page 24, lines 1–5 This also applies to: Page 55, lines 23–25; Page 81, lines 25–26; Page 97, Table 23, "Were the groups similar at the onset of the study in terms of prognostic factors, for example, severity of the disease?" row, lines 5–16	Current wording: "However, the EAG has concerns around the population with the KITE study demonstrating some differences in baseline characteristics, in particular for mean best-corrected visual acuity (BCVA) and [redacted]. The EAG therefore considers KESTREL to potentially be more suitable for drawing conclusions on the efficacy of brolucizumab versus aflibercept than KITE."	The company argue that the proportion of patients in KITE presenting ≤65 letters at baseline [redacted] compared with the aflibercept arm [redacted] and therefore including KITE data represents a conservative approach; generally, the higher the baseline BCVA, the smaller the number of letters gained due to the ceiling effect (3).	No change required; the EAG does not consider this to be a factual error.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	Proposed wording: “However, the EAG has concerns around the population with the KITE study demonstrating some differences in baseline characteristics, in particular for mean best-corrected visual acuity (BCVA) and [redacted]. The EAG therefore considers KESTREL to potentially be more suitable for drawing conclusions on the efficacy of brolucizumab versus aflibercept than KITE. However, the company argued that including KITE data represents a conservative approach, as generally, the higher the baseline BCVA, the smaller the number of letters gained due to the ceiling effect (3).”		

Issue 5 Brolucizumab marketing authorisation and licence

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 14, lines 19–22	Current wording: “The company’s application of pooled brolucizumab injection frequency estimates from the KITE and KESTREL studies concerned the EAG as patients in KITE could have their treatment interval extended to 16 weeks, whereas the anticipated license only specifies extension to 12 weeks.” Proposed wording: “The company’s application of pooled brolucizumab injection frequency estimates from the KITE and KESTREL studies	The original wording did not recognise that the Year 1 pooled KITE and KESTREL data are representative of the license. Patients were only allowed to extend to q16w in their second year of brolucizumab treatment. The company maintain that the pooled KITE and KESTREL results are representative of the license.	The EAG thanks the company for highlighting this and amended the EAG report to clarify interval extension occurred at Week 72 in KITE.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	concerned the EAG as patients in KITE could have their treatment interval extended to 16 weeks in their second year of treatment, whereas the licence states that physicians may individualise treatment intervals based on disease activity and that in patients without disease activity, 12 weeks should be considered."		
Page 17, EAG comments column, Intervention row, line 1	Please remove "anticipated" from: "The EAG notes that the anticipated posology for brolucizumab"	Brolucizumab received MHRA approval for DMO on the 27th of April 2022	The EAG thanks the company for highlighting this and has made the proposed amendment.
Page 18, Table 1, intervention row, EAG comment column, lines 13–20	Current wording: "The EAG notes that in KITE the maintenance treatment could be extended up to 16 weekly dosing and the company presented results for the proportion of patients who remained on the different maintenance treatment regimens in KESTREL and KITE." Proposed wording: "The EAG notes that in KITE the maintenance treatment could be extended up to 16 weekly dosing in Year 2 and the company presented results for the proportion of patients who remained on the different maintenance treatment regimens in KESTREL and KITE."	The original wording did not recognise that the Year 1 KITE and KESTREL data are representative of the license. Patients were only allowed to extend to q16w in their second year of brolucizumab treatment. The company maintain that the pooled KITE and KESTREL results are representative of the license.	The EAG thanks the company for highlighting this and amended the EAG report to clarify interval extension occurred at Week 72 in KITE.
Page 24, line 13	Please remove "anticipated" from: "In addition, brolucizumab is anticipated to be licensed"	Brolucizumab received MHRA approval for DMO on the 27th of April 2022	The EAG thanks the company for highlighting this and has made the proposed amendment.
Page 24, line 15–16	Current wording: "marketing authorisation expected to be granted by the European Commission in April 2022 and MHRA approval is expected in April 2022."	Brolucizumab received MHRA approval for DMO on the 27th of April 2022, and marketing authorisation was received by the	The EAG thanks the company for highlighting this and has amended the EAG report accordingly.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	Proposed wording: "marketing authorisation was granted by the European Commission on 6th April 2022 and MHRA approval was received on 21st April 2022"	European commission on the 6th April 2022	
Page 24, line 25–26	Current wording: "were generally consistent with the anticipated posology for brolucizumab." Proposed wording: "were generally consistent with the licensed posology for brolucizumab."	Brolucizumab received MHRA approval for DMO on the 27th of April 2022	The EAG thanks the company for highlighting this and has made the proposed amendment.
Page 24, line 29	Please remove "anticipated" and "anticipated to be" from: "that the 16-week treatment interval is not anticipated to be included in the anticipated posology in the Summary of Product Characteristics (SmPC). "	Brolucizumab received MHRA approval for DMO on the 27th of April 2022	The EAG thanks the company for highlighting this and has made the proposed amendment.
Page 30, lines 11–13	Please remove "anticipated" from: KESTREL also included a 3 mg brolucizumab arm and although the company included the results in the CS, they are not discussed by the EAG as the anticipated licensed dose is 6 mg.	Brolucizumab received MHRA approval for DMO on the 27th of April 2022	The EAG thanks the company for highlighting this and has made the proposed amendment.
Page 62, line 9–11	Current wording: "Brolucizumab, which is a 6mg IVT injection, is administered 6-weekly for the first 5 doses and either 8- or 12-weekly thereafter for patients with or without disease activity, respectively." Proposed wording: "Brolucizumab, which is a 6 mg IVT injection, is administered 6-weekly for the first 5 doses and based on clinical decision, either 8- or 12-weekly should be considered thereafter for patients with or without disease activity, respectively.	The amended text provides less ambiguity surrounding the brolucizumab licence.	No change required; the EAG does not consider this to be a factual error.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 62, line 11–13	Please remove “anticipated” from: “As discussed in Section 2.2, this posology (outlined in the anticipated marketing authorisation) aligns with dosing in the KESTREL trial but not KITE…”	Brolucizumab received MHRA approval for DMO on the 27th of April 2022.	The EAG thanks the company for highlighting this and has made the proposed amendment.
Page 73, line 5-9	Current wording: “As discussed in Section 3.2.1, patients in KITE could extend the treatment interval to 16 weeks in their second year of brolucizumab treatment. However, the anticipated marketing authorisation only specifies extension to 12-weekly dosing for patients without disease activity. The EAG is concerned that the injection frequency data from KITE, and hence the pooled KITE and KESTREL data, underestimates the injection frequency for patients treated in line with the anticipated licence.” Proposed wording: “As discussed in Section 3.2.1, patients in KITE could extend the treatment interval to 16 weeks in their second year of brolucizumab treatment. However, the marketing authorisation only specifies extension to 12-weekly dosing for patients without disease activity. The EAG is concerned that the Year 2 injection frequency data from KITE, and hence the pooled Year 2 KITE and KESTREL data, underestimates the injection frequency for patients treated in line with the licence”	The original wording did not recognise that the Year 1 pooled KITE and KESTREL data are representative of the license. Patients were only allowed to extend to q16w in their second year of brolucizumab treatment. The company maintain that the pooled KITE and KESTREL results are representative of the license.	The EAG thanks the company for highlighting this and amended the EAG report to clarify injection frequency for year 2 in KITE and has removed the word “anticipated” from the text.

Issue 6 Cross-referencing errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Table 3, page 31–35	Page numbers in Table 3 of the EAG report don't match up with the final submitted version of the CS, please ensure these align with the version shared with the committee	The current cross references may be incorrect	The EAG thanks the company for highlighting this error and has made the proposed amendment.
Page 68, line 21	Please update cross-reference from "Section 0" to "Section 6.2"	The current cross-reference is incorrect	The EAG thanks the company for highlighting this error and has made the proposed amendment.

Issue 7 Typographic errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 26, lines 11–13	Current wording: "Of these studies matching the broad inclusion criteria of the NICE scope, two RCTs (from four publications) directly comparing outcomes with brolucizumab to aflibercept (KESTREL and KITE studies) were identified." Proposed wording: Of the studies matching the broad inclusion criteria of the NICE scope, two RCTs (from four publications) directly comparing outcomes for brolucizumab with aflibercept (KESTREL and KITE studies) were identified.	Correction of the typographic error will improve the clarity of the report.	The EAG thanks the company for highlighting this error and has made the proposed amendment.
Page 51, lines 19–20	Please add [redacted]	Correction of the typographic error will improve the clarity of the report.	No change required; the EAG does not consider this to be a factual error.
Page 51, line 22	Please add [redacted]	Correction of the typographic error will improve the clarity of the report.	No change required; the EAG does not consider this to be a factual error.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 51, lines 24	Please add [redacted]	Correction of the typographic error will improve the clarity of the report.	No change required; the EAG does not consider this to be a factual error.
Page 51, line 30	Please add [redacted]	Correction of the typographic error will improve the clarity of the report.	No change required; the EAG does not consider this to be a factual error.
Page 52, Table 7, header row, KITE and KESTREL columns Page 52, Table 7, header row, Excluding KITE columns	Please add "relative": "Median mean relative difference (95% CrI)" and "Mean relative mean difference" Please add "relative": "Median mean relative difference (95% CrI)" and "Mean relative mean difference"	Correction of the typographic error will improve the clarity of the report.	No change required; the EAG does not consider this to be a factual error.
Page 66, line 16	Current wording: "…because patients discontinue brolucizumab, aflibercept, and ranibizumab at difference rates…" Proposed wording: "…because patients discontinue brolucizumab, aflibercept, and ranibizumab at different rates…"	Correction of the typographic error will improve the clarity of the report.	The EAG thanks the company for highlighting this error and has made the proposed amendment.
Page 67, line 17	Please remove "an" from: "However, the company did provide two scenario analyses wherein an equal discontinuation rates were applied to all anti-VEGF treatments…"	Correction of the typographic error will improve the clarity of the report.	The EAG thanks the company for highlighting this error and has made the proposed amendment.
Page 69, line 25	Current wording: "administrations" to "administration" from "The costs included in the economic model consist of drug acquisition costs, administrations costs and disease monitoring costs."	Correction of the typographic error will improve the clarity of the report.	The EAG thanks the company for highlighting this error and has made the proposed amendment.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	Proposed wording: "The costs included in the economic model consist of drug acquisition costs, administration costs and disease monitoring costs."		
Page 70, line 6	Current wording: "For the proportion of patients estimates to receive bilateral treatment…" Proposed wording: "For the proportion of patients estimated to receive bilateral treatment…"	Correction of the typographic error will improve the clarity of the report.	The EAG thanks the company for highlighting this error and has made the proposed amendment.
Page 76, lines 3–4	Current wording: "…inconsistent cost-comparison modelling." Proposed wording: "… inconsistent with cost-comparison modelling."	Correction of the typographic error will improve the clarity of the report.	The EAG thanks the company for highlighting this error and has made the proposed amendment.
Page 78, Table 18, scenario column, injection frequency – years 1& 2 row, line 3	Current wording: "Pooled aflibercept KITE and KESTREL data used, ranibizumab assumed equal." Proposed wording: "Pooled aflibercept KITE and KESTREL data used, ranibizumab assumed equal to aflibercept."	Correction of the typographic error will improve the clarity of the report.	The EAG thanks the company for highlighting this error and has made the proposed amendment.

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