NICE National Institute for Health and Care Excellence

Fast Track Appraisal

Brolucizumab for treating wet age-related macular degeneration [ID1254]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

FAST TRACK APPRAISAL (FTA)

Brolucizumab for treating wet age-related macular degeneration [ID1254]

Contents:

The following documents are made available to consultees and commentators:

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

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

3. **Company response to NICE's request for clarification**
   a. Clarification response
   b. Clarification response addendum for question A3

4. **Patient group, professional group and NHS organisation submission** from:
   a. Macular Society
   b. Royal College of Ophthalmologists
   c. NHS Bury CCG
   d. NHS Luton CCG

5. **Expert personal perspectives** from:
   a. Ben Burton – clinical expert, nominated by the Royal College of Ophthalmologists
   b. Priya Boparai – clinical expert, nominated by the UK Ophthalmic Pharmacy Group
   c. Bryan Naylor – patient expert, nominated by Macular Society

6. **Evidence Review Group report** prepared by **Warwick Evidence**

7. **Evidence Review Group – factual accuracy check**
   a. ERG response to company factual accuracy check proforma – February 2020
   b. ERG response to company factual accuracy check proforma – July 2020

8. **Company response to ERG dosing and monitoring assumptions**

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

Technical briefing

Brolucizumab for treating wet age-related macular degeneration

This slide set is the technical briefing for this appraisal. It has been prepared by the technical team and it is sent to the appraisal committee before the committee meeting as part of the committee papers. It summarises:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the appraisal committee meeting and is expected reading for committee members. The submissions made by the company, consultees and nominated experts as well as the ERG report are available for committee members, and are optional reading.

Authors:
Thomas Paling, Charlie Hewitt - Technical Leads

Nicola Hay, Lucy Beggs - Technical Advisers

Issues for consideration

1. Dose frequency

What approach should be used to estimate dose frequency?

- **Company:** a weighted calculation of flexible and continuous regimens
- **ERG preferred:** a dual base-case based on TREX and PRN regimens?

How should brolucizumab year 3+ dose frequency be calculated?

- **Company:** assumed equivalent to year 2 dosing frequency
- **ERG:** based on TA294 (aflibercept) year 3 dose frequency, or
- **Scenario:** based on % of patients dosed q8w at w92 in HAWK/HARRIER?

How should comparator year 3+ dose frequency be calculated?

- **Company:** assumed to be the same as year 2, or
- **ERG:** based on TA294 (aflibercept) year 3 dose frequency, or
- **Scenario:** based on the NARMD data?

2. Monitoring visits

How many monitoring visits would be expected in clinical practice for comparator PRN / PRNX regimens?

- **Company:** apply total clinic visits from NG82
- **ERG:** apply additional monitoring visits from NG82?

3. Fast Track Appraisal (FTA) decision

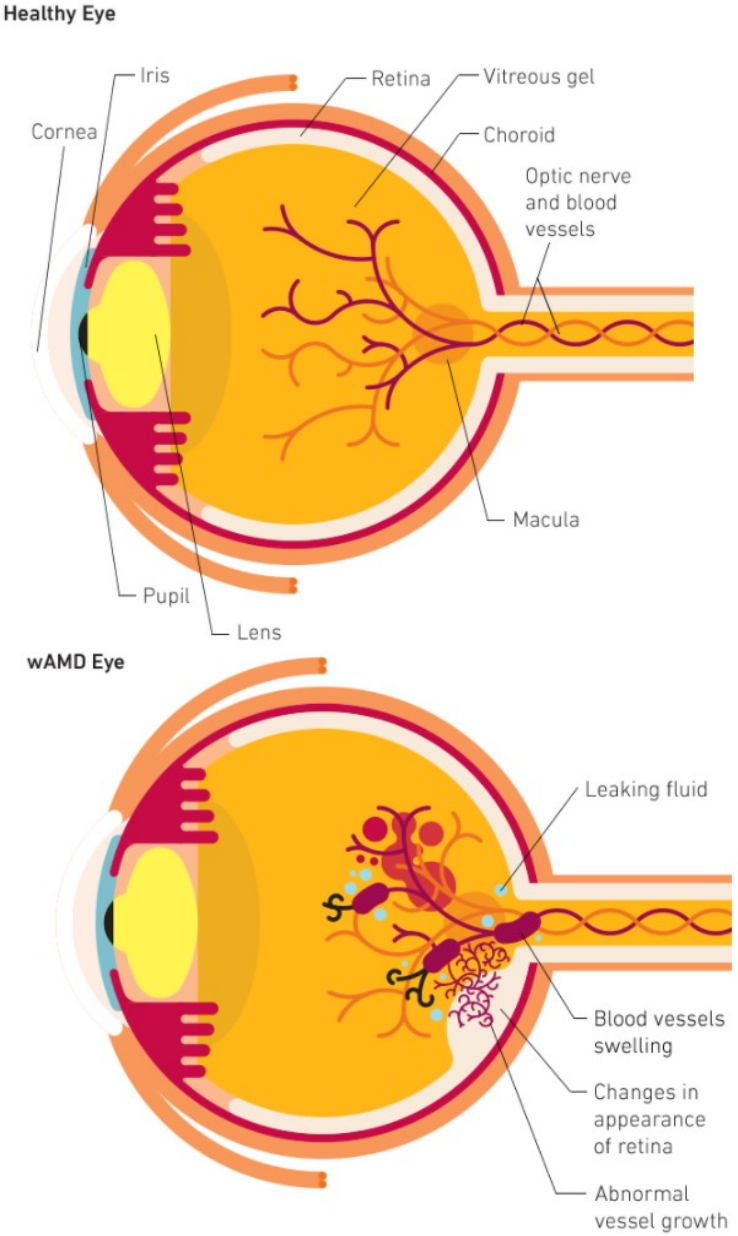
- Does brolucizumab provide similar or greater health benefits than the comparators?
- Is brolucizumab likely to result in a similar or lower cost than the comparators?

Cost comparison overview

- A company may apply for a cost-comparison fast track appraisal if the drug provides similar/greater benefits at a similar/lower overall cost than a comparator recommended in NICE technology appraisal guidance
- For this appraisal, the comparators presented by the company are aflibercept (TA294) and ranibizumab (TA155) (see slides 5-6)
  - Cost-effectiveness needs only be demonstrated against one of these
  - Both comparators have confidential commercial arrangements
- Any FTA recommendation for brolucizumab can only cover the same population recommended in TA155 and TA294 which includes people with:
  - wet age-related macular degeneration (wAMD)
  - best-corrected visual acuity (BCVA) between 6/12 and 6/96
  - no permanent central fovea damage
  - lesion size ≤ 12 disc areas
  - evidence of recent disease progression.
- FTA was deemed to be a suitable process by the scrutiny panel (see slide 4)
  - The objective of today's appraisal is to decide whether brolucizumab is likely to have similar or lower costs compared with aflibercept or ranibizumab

Wet age-related macular degeneration

- Age-related macular degeneration (AMD) is a chronic and progressive eye condition characterised by macula degeneration
  - The macula is the area of the retina responsible for sharp, central vision
- If untreated AMD can lead to severe visual impairment or blindness
- Neovascular (wet) AMD (wAMD) accounts for 10-20% of AMD cases, but is responsible for 80-90% of vision loss associated with AMD
  - It is the leading cause of vision loss in people aged over 65 years
- wAMD occurs when abnormal blood vessels grow under the macula and retina; they leak blood and fluid causing problems with vision
- wAMD incidence in over 50s is estimates to be 1.4 and 2.3 per 1,000 for men and women → incidence increases with age



The technologies

	Brolucizumab	Aflibercept	Ranibizumab
Mechanism of action	Inhibits vascular endothelial growth factor-A [VEGF-A]	Inhibits VEGF-A, VEGF-B and placental growth factor	Inhibits VEGF-A
Marketing authorisation	Indicated in adults for the treatment of neovascular (wet) age-related macular degeneration (wAMD)		
Administration and dose	6 mg (intravitreal injection) once a month for 3 months, then extend depending on absence/presence of disease activity	2 mg (intravitreal injection) once a month for 3 months, then extend	0.5 mg (intravitreal injection) once a month until maximum visual acuity is achieved then extend
Monitoring	Patients should be monitored for elevation in intraocular pressure	No monitoring requirement. Based on physicians' judgement	Based on disease activity, as assessed by visual acuity and/or anatomical parameters

TA294: Aflibercept for wAMD (2013)
Key drivers of cost-effectiveness

Clinical outcomes (VIEW 1 and VIEW 2)	• Proportion of patients losing <15 ETDRS letters from Baseline at Week 52 (and Week 96) • Proportion of patients gaining ≥15 letters from Baseline to Week 52 (and Week 96) • Mean change in BCVA from Baseline at Week 52 (and Week 96)
Key clinical drivers	• Drug acquisition costs • Proportion in one-stop or two-stop models • The relative risk of gaining or losing visual acuity with ranibizumab treatment • Frequency of injections and monitoring
Clinical uncertainties	• Exclusion of bevacizumab as a comparator (accepted as consistent with TA155) • Comparative effectiveness at 24 months
Resource use assumptions	• Both treatment groups need 8 treatment visits in year 1 of the model • 50% need separate monitoring visits
Resource use uncertainties	• Cost of treatment and monitoring visits

TA155; Ranibizumab for wAMD (2008)
Key drivers of cost-effectiveness

Clinical outcomes (MARINA, ACHOR, PIER)	• Proportion of patients losing <15 ETDRS letters from Baseline to 12 months (and 24 months) • Gain of more than 15 ETDRS letters of visual acuity from Baseline to 12 months (and 24 months) • Mean change in visual acuity (mean number of ETDRS letters lost or gained) from Baseline to 12 months (and 24 months)
Key clinical drivers	• The costs of blindness • The costs of administering the injections • The number of injections of ranibizumab • The utility values used in the analysis
Clinical uncertainties	• Whether the clinical benefit achieved in the trials could be achieved with fewer injections
Resource use assumptions	• Ranibizumab treatment stops after year 2, with benefit declining at the same rate as usual care
Resource use uncertainties	• The costs of administering the injections

FTA: cost-comparison overview

- 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
- FTA comparators are aflibercept (TA294) and ranibizumab (TA155):
  - Cost-effectiveness needs only be demonstrated against one of these
  - Both comparators have confidential commercial arrangements
- Any FTA recommendation for brolucizumab can only cover the same population recommended in TA155 and TA294:
  - people with wAMD, and
  - best-corrected visual acuity (BCVA) between 6/12 and 6/96
  - no permanent central fovea damage
  - lesion size ≤ 12 disc areas
  - evidence of recent disease progression.

Scrutiny panel agreed to proceed as FTA

The objective of today's appraisal is to decide whether brolucizumab provides similar or greater health benefits at a similar or lower cost than the comparators

Clinical expert & professional group comments

Royal College of Ophthalmologists

- Aim of treatment is to improve visual outcomes usually by preventing disease progression
- The need for long-term repeated injections is well established
  - Treat and extend (TREX), pro re nata (PRN) and fixed dosing provides flexibility But, regime choice is based on capacity issues not outcomes/results (see notes)
- Brolucizumab may require fewer injections – more research is required
- No additional investment required to introduce brolucizumab
- Superior retinal drying achieved with brolucizumab could benefit some patients
- NICE guidelines (TA155, TA294) require vision drops below 6/12 before starting treatment, although there are advantages to starting treatment before vision loss

Clinical expert statements

- Unmet need for a treatment with lower injection frequency, to improve capacity
- Brolucizumab use and resource use is expected to be similar to existing practice
- Improvements in quality of life expected from reducing injection frequency

Notes: continuous dosing regimens used in clinical practice

- **PRN:** Patients monitored frequently, treatment administered as needed
- **PRNX:** PRN, but with potential to extend treatment interval
- **TREX:** Treatment interval extended in stepwise manner based disease activity

Clinical effectiveness evidence

HAWK and HARRIER trials

- **Design:** compare the safety and efficacy of brolucizumab with aflibercept
- **Population**: anti-VEGF treatment-naive patients aged 50 years or more with active choroidal neovascularisation (CNV) caused by AMD
- **Primary outcome:** BCVA change from baseline to Week 48
- **Trial dosing:** monthly for 3 months (both arms), maintenance phase (brolucizumab [q12w or q8w* if disease activity], aflibercept [q8w*])
- **Clinical practice dosing (aflibercept and ranibizumab)**
  - There is a range of dosing schedules for aflibercept and ranibizumab
  - No standard regimen is used
  - After an initial loading phase (LP) the most common regimens used in clinical practice include
  - A survey of 50 retinal experts suggested TREX is the most commonly used regimen in practice

Aflibercept	Ranibizumab
• q4w*	• q4w*
• q8w*	• q4w*→PRN
• q8w*→PRN	• PRN
• TREX	• TREX

Note: *qXw, one injection every X weeks

NICE

Company's clinical effectiveness evidence

Company conclusion:

- Brolucizumab non-inferior to aflibercept in mean change in BCVA (baseline to week 48):
  - **HAWK:** BROL 6.6 (95% CI 5.2 to 8.0) vs. AFLI 6.8 (95% CI 5.4 to 8.2)
  - **HARRIER:** BROL 6.9 (95% CI 5.7 to 8.1) vs. AFLI 7.6 (95% CI 6.4 to 8.8)
- Brolucizumab superior to aflibercept in improvement in CSFT, retinal fluid and disease activity
- 30% fewer people receiving brolucizumab had disease activity
- Similar improvements in health-related quality of life
- Safety profile comparable to aflibercept. No new AEs vs. other anti-VEGFs

ERG review:

- No major concerns → HAWK and HARRIER were considered of high quality
- Brolucizumab non-inferiority to aflibercept supported by trial evidence
- Data for rare adverse events is sparse
- Adverse effects are likely to be similar for both treatments

Network meta-analysis (NMA)

Overview

- An NMA was performed to assess the efficacy and safety of brolucizumab compared with aflibercept and ranibizumab
  - No head-to-head evidence comparing brolucizumab with ranibizumab
  - 14 studies were included in the company base case. VIEW 1 and VIEW 2 (aflibercept) were pooled, given the similarity in study designs

Outcomes

- Given the variety of dosing regimens included in the NMA (LP, PRN, PRNX, TREX, fixed), naive baseline pooling was conducted to estimate absolute treatment effects. Alternative pooling for other outcomes included:
- **Regimen-based pooling:** Pooled dosing regimens from different trial arms, for:
  - Mean change in BCVA (Baseline [BL] to 1 year; BL to 2 years)
  - Injection frequency (BL to 1 year; BL to 2 years)
- **Molecule-based pooling:** Pooled trial arms for the same drug (all regimens), for:
  - Treatment discontinuation (BL to 2 years). Also assessed without BL pooling
- Adverse events (both regimen and molecule-based pooling) and mean change in central retinal thickness (BL to 1 year; BL to 2 years) were also assessed

Network meta-analysis (NMA)

Company conclusion:

- Brolucizumab treatment leads to comparable changes in BCVA compared with aflibercept and ranibizumab
- Brolucizumab superior in decreasing retinal thickness with lower injection frequency
- Comparable safety profile and probability of discontinuation for all treatments

ERG review:

- Considered the NMA robust → results supports claims of non-inferiority
- No notable differences in age, sex, and race/ethnicity between studies
- Inclusion of additional studies could have strengthened the network, though unlikely to alter direction of results (cost-saving or cost-increasing)
- Differences in distribution of CNV lesion type and size between studies could modify treatment effect estimates, though unlikely to alter direction of results
- Baseline pooling (slide 11) does not preserve randomisation → subject to bias as no adjustments were made for baseline imbalances

A retinal vasculitis and/or retinal vascular occlusion safety issue has been confirmed

- The company has conducted a review of spontaneously reported cases of significant vision loss, retinal artery occlusion and potential vasculitis in patients who have had treatment with brolucizumab in the USA
  - As of 28 February 2020, the company had received reports of 44 cases of interest, from a total estimated vial use of around 56,000
  - The company considers that there is a validated signal of an emerging new safety issue of retinal vasculitis and/or retinal vascular occlusion with or without intraocular inflammation, which may result in severe vision loss
- SmPC update:

  "Retinal vasculitis and/or retinal vascular occlusion, typically in the presence of intraocular inflammation, have been reported with the use of [brolucizumab] … In patients developing these events, treatment with [brolucizumab] should be discontinued and the events should be promptly managed"
- ERG considers that events are sufficiently rare that they are unlikely to affect the its view that brolucizumab has a similar AE profile to the comparators

Cost-comparison analysis

Features of the company cost-comparison analysis

Component	Approach
Population	Adults aged ≥50 years with wAMD (reflecting the populations included in the HAWK and HARRIER trials)
Intervention	Brolucizumab
Comparators	Aflibercept and ranibizumab
Outcomes	Incremental per-patient costs and total per-patient costs
Perspective	NHS and personal social services (PSS) in England and Wales
Time horizon	Lifetime – 30 years (maximum age of 100 years)
Discounting	Costs discounted at 3.50%

Source: Table 4.1 company submission

Economic model

- Markov cohort model with 3 states: On treatment (unilateral [one eye] or bilateral [both eyes]); discontinued treatment (no treatment); and death
  - Patients enter the model with either unilateral or bilateral disease
  - Patients with unilateral disease can develop bilateral disease over time according to an annual probability of neovascularisation
  - Once patients developed bilateral disease they cannot revert to unilateral

Company base-case cost-comparison
Costs, dosing and monitoring assumptions

	Brolucizumab	Aflibercept	Ranibizumab
Acquisition cost*	[redacted]	[redacted]	[redacted]
Dose	6 mg	2 mg	0.5 mg
Dosing regimen	Loading phase [LP] → quarterly [q12w] or bi-monthly[q8w] dosing	Weighted average of continuous and flexible dosing regimens**	Weighted average of continuous and flexible dosing regimens***
No. of injections	Year 1: 6.66 Year 2: 4.76 Year 3+: 4.76	Year 1: 8.82 Year 2: 6.85 Year 3+: 6.85	Year 1: 9.16 Year 2: 7.91 Year 3+: 7.91
Total no. of visits (incl. monitoring)	Year 1: 6.66 Year 2: 4.76 Year 3+: 4.76	Year 1: 8.82 Year 2: 8.17 Year 3+: 8.17	Year 1: 10.97 Year 2: 10.12 Year 3+: 10.12

*Includes PAS discounts; ** includes PRN and TREX; ***includes PRN, PRNX and TREX

PRN: Frequent monitoring, treatment administered as needed

TREX: Treatment interval extended in stepwise manner based on disease activity

PRNX: PRN, but with potential to extend treatment interval

Summary company and ERG base-case assumptions

Assumption	Company	ERG
Brolucizumab dosing frequency	Years 1 and 2 frequency taken from NMA using pooled HAWK and HARRIER data	
Comparator dosing regimen	Weighted average of continuous and flexible dosing regimens (weights determined from survey of retinal experts)	Individual comparison vs PRN* and TREX regimens
Year 3+ dose frequency	**Same as year 2** Brolucizumab: 4.76 Aflibercept: 6.85 Ranibizumab: 7.91	**Based on TA294** Brolucizumab: 4.0 Aflibercept: 4.0 Ranibizumab: 4.0
Monitoring visits for PRN/PRNX regimens	**Applying the <u>total</u> clinic visits from NG82** PRN: 12.7 total visits in each of years 1-3+ PRNX: 10.1 visits in each of years 1-3+ 0.2 year 1 loading phase visits No additional monitoring for continuous regimens	**Applying the <u>additional</u> clinic visits from NG82** Year 1: 6.1 additional visits in for ranibizumab Year 2+: 4.5 additional visits for aflibercept and ranibizumab The above additional visits are applied 2 years later for brolucizumab

* Aflibercept: LP → q8w → PRN; Ranibizumab: LP → PRN

Dosing and monitoring frequencies

	Company (weighted approach)			ERG base case 1 (TREX)			ERG base case 2 (PRN)		
	BROL	AFLI	RANI	BROL	AFLI	RANI	BROL	AFLI	RANI
Dosing frequencies									
Year 1	6.7	8.8	9.2	6.7	9.7	9.5	6.7	7.1	7.1
Year 2	4.8	6.9	7.9	4.8	7.3	8.2	4.8	5.0	5.6
Year 3	4.8	6.9	7.9	4.0	4.0	4.0	4.0	4.0	4.0
Monitoring frequencies (total visits)									
Year 1	6.7	8.8	11.0	6.7	9.7	9.5	6.7	7.1	13.2
Year 2	4.8	8.2	10.1	4.8	7.3	8.2	4.8	9.5	10.1
Year 3	4.8	8.2	10.1	4.0	4.0	4.0	10.1*	8.5	8.5
Year 4+	4.8	8.2	10.1	4.0	4.0	4.0	8.5	8.5	8.5

* Brolucizumab is assumed to transition from fixed dosing to PRN dosing in year 3, the additional monitoring visits outlined above are applied from year 3+

Dosing and monitoring frequency *ERG scenarios*

1. **Brolucizumab year 3+ dose frequency**
   - Company assumed year 3+ brolucizumab dose frequency to be equivalent to injections observed in year 2 (4.76)
   - HAWK/HARRIER permitted an increase in brolucizumab dosing frequency when insufficient treatment response: [redacted] increased frequency q12w→q8w
   - ERG scenario: assumes [redacted] q8w, [redacted] q12w (average 5.7 doses/year)
     - *But in HAWK/HARRIER, once people moved to q8w dosing, not permitted to move back to q12w but expected this would be tried in practice → scenario likely biases against brolucizumab*
2. **Aflibercept and ranibizumab year 3+ dose frequency (NG82 approach)**
   - NG82 used an alternative approach to estimate year 3+ dosing frequencies
   1. Calculate a ratio of year 2 dose frequencies for AFLI and RANI continuous regimen (TREX/PRN) from year 2 frequencies observed in the clinical trials
   2. Find a report of year 3 dose frequency for any continuous regimen
   3. Apply the ratio (step 1) to reported year 3 dose frequency (step 2) to estimate year 3+ dose frequency for other continuous regimens
   - *ERG applies this approach in a scenario analysis, but notes this approach resulted in lower than expected estimates of comparator dose frequency*

Other resource use assumptions	
Treatment discontinuation	• Company assumed treatment discontinuation to be constant over time, with different annual discontinuation rates for each treatment → brolucizumab (7.86%) aflibercept (8.95%) and ranibizumab (7.89%) • ERG noted that if brolucizumab dosing intervals cannot be lengthened beyond 12 weeks, discontinuation rates become more important. A higher dose frequency than comparators may produce greater long-term costs
Bilateral (both eyes) treatment multipliers	• The company assumed bilateral treatment assumed takes place in a one-stop appointment. Cost multipliers: drug costs (x2); administration costs (x1.5) • The ERG agreed that these assumptions align with NG82, and are unlikely to alter conclusions
Adverse event costs	• No significant differences in adverse events were observed versus aflibercept in HAWK/HARRIER. Adverse event costs were not included in company base case, and the ERG agreed that including them has little impact on results • Vasculitis safety reports were made after the company submission and ERG report, and related costs were not included in the model. The ERG considers that these AEs are sufficiently rare and unlikely to affect the CEA outcomes

Company base-case cost comparison outputs (comparator PAS prices)

Costs	Brolucizumab	Aflibercept	Ranibizumab
Drug	[redacted]	[redacted]	[redacted]
Admin	[redacted]	[redacted]	[redacted]
OCT	[redacted]	[redacted]	[redacted]
FFA	[redacted]	[redacted]	[redacted]
AE	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]
Incremental	-	[redacted]	[redacted]

Source: tech team calculated, ERG checked
Abbreviations: AE, adverse events; FFA, fluorescein angiography; OCT, optical coherence tomography; PAS, patient access scheme

Brolucizumab has [redacted] compared with aflibercept and ranibizumab

- Analysis incorporates the following confidential commercial arrangements:
  - Brolucizumab PAS discounts
  - Aflibercept and ranibizumab PAS discounts

ERG base-case cost comparison outputs

- ERG base case amendments:
  1. Dual base-case vs TREX and PRN comparator regimens
  2. 4.0 injections in year 3+ for brolucizumab, aflibercept and ranibizumab
  3. Applying the additional clinic visits from NG82

Costs	TREX			PRN		
	BROL	AFLI	RANI	BROL	AFLI	RANI
Drug	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Admin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OCT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FFA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental		[redacted]	[redacted]		[redacted]	[redacted]

Source: calculated by tech team, ERG checked
Abbreviations: see s18

Brolucizumab has [redacted] compared with aflibercept and ranibizumab (TREX and PRN regimen)

ERG scenario analyses: dosing regimens

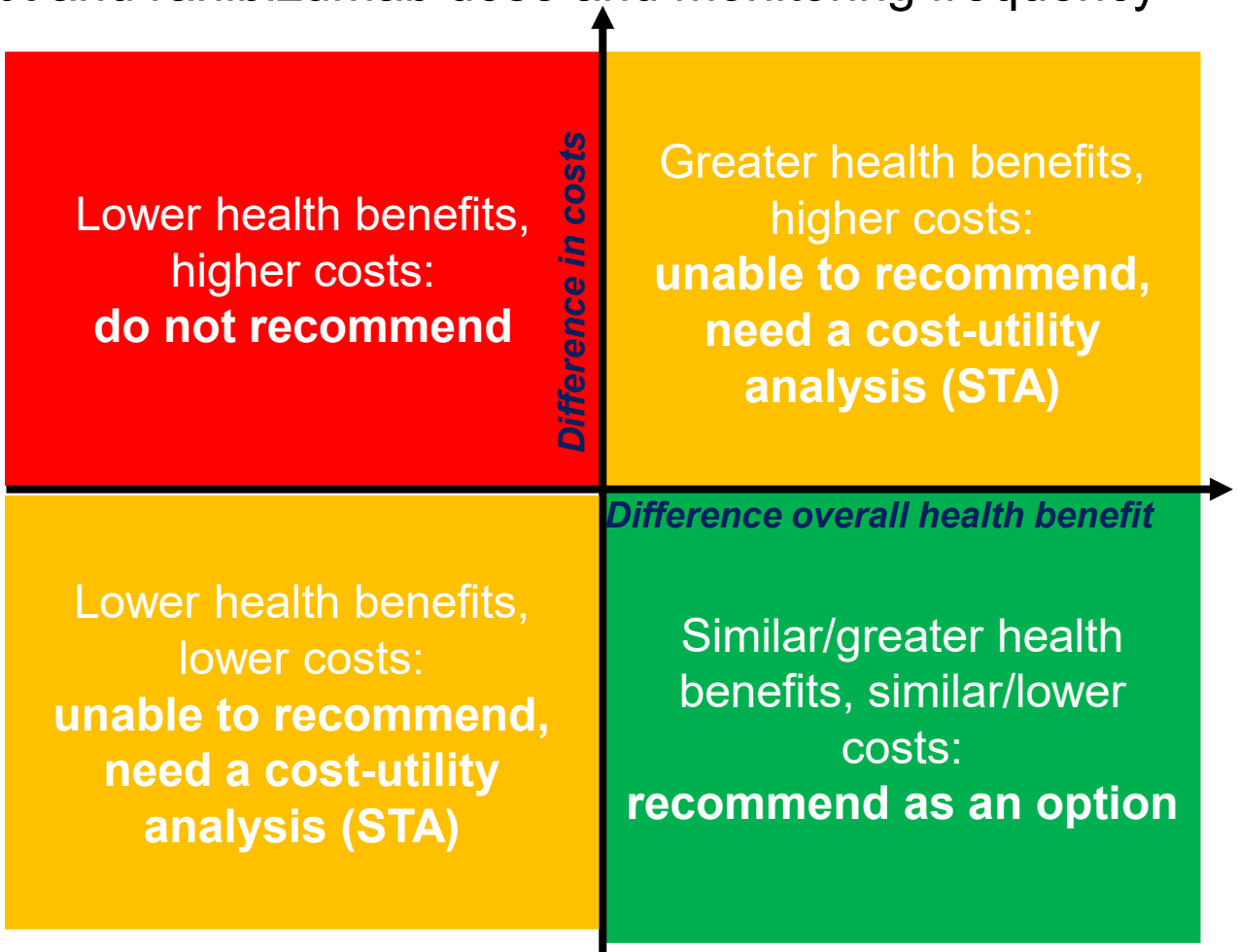
Scenario analyses (SA)				
SA	Dosing and monitoring frequencies *Assumptions or regimen applied in the model*		Brolucizumab incremental cost	
	Brolucizumab	Comparator	AFLI	RANI
1a:	• Company estimates in years 1 and 2 • **ERG scenario:** *5.7 doses for brolucizumab in year 3+.*	q4w	[redacted]	[redacted]
1b:		q4w > PRN	[redacted]	[redacted]
1c:		LP > q8w	[redacted]	N/A
1d:		PRN	N/A	[redacted]
1e:		PRNX	N/A	[redacted]
2a:		• TREX in years 1 and 2 • NG82 derived in year 3	[redacted]	[redacted]
2b:		• PRN in years 1 and 2 • NG82 derived in year 3	[redacted]	[redacted]
3a:	• Company estimates in years 1, 2 and 3+ *4.76 doses for brolucizumab in year 3+.*	• TREX in years 1 and 2 • NG82 derived in year 3	[redacted]	[redacted]
3b:		• PRN in years 1 and 2 • NG82 derived in year 3	[redacted]	[redacted]

Source: Tech team calculated, ERG checked

Potential recommendations: cost comparison

Key issues

- Brolucizumab dose and monitoring frequency
- Aflibercept and ranibizumab dose and monitoring frequency



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1. Dose frequency

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How many monitoring visits would be expected in clinical practice for comparator PRN / PRNX regimens?

- **Company:** apply total clinic visits from NG82
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3. Fast Track Appraisal (FTA) decision

- Does brolucizumab provide similar or greater health benefits than the comparators?
- Is brolucizumab likely to result in a similar or lower cost than the comparators?

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Fast track appraisal: cost-comparison case

Brolucizumab for treating wet age-related macular degeneration

[ID1254]

Document B

Company evidence submission

Novartis Pharmaceuticals Ltd

October 2019

File name	Version	Contains confidential information	Date
ID1254_Brolucizumab_Doc B_FINAL [ACIC]	FINAL	Yes	16th October 2019

Instructions for companies

This is the template for submission of evidence to the National Institute for Health and Care Excellence (NICE) when a cost-comparison case is made as part of the fast track technology appraisal process. Please note that the information requirements for submissions are summarised in this template; full details of the requirements for pharmaceuticals and devices are in the fast track appraisal user guide.

This submission must not be longer than 100 pages, excluding appendices and the pages covered by this template. If it is too long it will not be accepted.

Companies making evidence submissions to NICE should also refer to the NICE guide to the methods of technology appraisal, the NICE guide to the processes of technology appraisal and the NICE process and methods addenda.

In this template any information that should be provided in an appendix is listed in a box.

Highlighting in the template (excluding the contents list)

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Grey highlighted text in the footer does not work as an automatic form field, but serves the same purpose – as prompt text to show where you need to fill in relevant details. Replace the text highlighted in [grey] in the footer with appropriate text. (To change the footer, double click over the footer text. Double click back in the main body text when you have finished.)

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List of abbreviations

AE	Adverse event
Afli	Aflibercept
AMD	Age-related macular degeneration
ANOVA	Analysis of variance
BCVA	Best-corrected visual acuity
Bev	Bevacizumab
BNF	British National Formulary
Bro	Brolucizumab
CDR	Complementarity-determining regions
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
C_L	Constant domain, light-chain
CNV	Choroidal neovascularisation
CRC	Central Reading Center

CSFT	Central subfield retinal thickness
CSR	Clinical study report
CST	Central subfield thickness
DAA	Disease activity assessment
DIC	Deviance information criterion
DSA	Deterministic sensitivity analysis
eCRF	Electronic case report form
EMA	European Medicines Agency
EQ-5D	5-dimension European Quality of Life questionnaire
ERG	Evidence Review Group
ETDRS	Early Treatment Diabetic Retinopathy Study chart
EURETINA	European Society of Retina Specialists
FA	Fluorescein angiography
Fab	Fragment, antigen-binding
FAS	Full analysis set
Fc	Fragment crystallizable
FDA	Food and Drug Administration
FE	Fixed-effects
FFA	Fluorescein angiography
FTA	Fast track appraisal
HES	Hospital Episodes Statistics
HRG	Healthcare resource group
HRQoL	Health-related quality of life
ICG	Indocyanine green
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
Ig	Immunoglobulin
IRF	Intra-retinal fluid
IRT	Interactive response technology
ITT	Intention to treat
IVT	Intravitreal
kDa	Kilodalton
LOCF	Last observation carried forward
LP	Loading phase
LS	Least squares
LSM	Least squares mean
LSMD	Least squares mean difference
mg	Milligram
mL	Millilitre
NA	Not applicable
NCT	National Clinical Trial
NEI	National Eye Institute
NHS	National Health Service
NI	Non-inferiority
NICE	National Institute for Clinical Excellence
NMA	Network meta-analysis
NR	Not reported
OCT	Optical coherence tomography
ONS	Office for National Statistics

PAS	Patient Access Scheme
PCV	Polypoidal choroidal vasculopathy
PDS	Port delivery system
PDT	Photodynamic therapy
PICOS	Population, intervention, comparator, outcome and study type framework
PPS	Per protocol analysis set
PRN	Pro re nata dosing regimen
PRNX	Pro re nata and extend dosing regimen
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
q12w	One injection every 12 weeks
q8w	One injection every 8 weeks
QALY	Quality-adjusted life year
qXw	One injection every X weeks
RAN	Randomised analysis set
Rani	Ranibizumab
RCT	Randomised controlled trial
RE	Random-effects
RPE	Retinal pigment epithelium
SAE	Serious adverse event
SAF	Safety analysis set
scFv	Single-chain variable fragment
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
SRF	Sub-retinal fluid
TA	Technology appraisal
TREX	Treat-and-extend dosing regimen
TTT	Transpupillary thermotherapy
UK	United Kingdom
VA	Visual acuity
VAT	Value-added tax
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor
VFQ	Visual function questionnaire
V_H	Variable domain, heavy-chain
V_L	Variable domain, light-chain
wAMD	Wet age-related macular degeneration

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

B.1.1 Decision problem

This fast track appraisal (FTA) cost-comparison submission covers the full marketing authorisation for brolucizumab in the following indication: 'In adults for the treatment of neovascular age-related macular degeneration';[1] hereafter referred to as wet age-related macular degeneration (wAMD).

The decision problem addressed within this submission is presented in Table 1.1 and is consistent with the National Institute for Clinical Excellence (NICE) final scope for this appraisal. Any differences between the decision problem addressed within this submission and the NICE final scope are outlined in Table 1.1.

The relevant comparators to brolucizumab in this appraisal are aflibercept and ranibizumab, as the two licensed therapies already available for this indication. This submission covers the full populations for aflibercept and ranibizumab, as recommended by NICE in TA294 and TA155.[2, 3]

Table 1.1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with choroidal neovascularisation secondary to AMD	Adults with wAMD	• The patient population addressed in this submission aligns with the final NICE scope and is consistent with the anticipated licensed indication for brolucizumab as a treatment for wAMD, as well as the patient populations of the pivotal clinical trials for brolucizumab in this indication (HAWK and HARRIER)[4, 5]
Intervention	Brolucizumab	Brolucizumab	N/A – in line with the final NICE scope
Comparator(s)	• Aflibercept • Ranibizumab • Bevacizumab (does not currently have a marketing authorisation in the UK for this indication) • Best supportive care	• Aflibercept • Ranibizumab	• Bevacizumab is not a relevant comparator to brolucizumab in this appraisal as it is neither standard of care nor has a marketing authorisation in the UK for wAMD. Whilst aflibercept and ranibizumab are licensed treatments for wAMD and have also been assessed to be clinically and cost-effective by NICE, bevacizumab is not licensed for wAMD as it has not undergone the rigorous regulatory scrutiny and related risk/benefit analysis for use in such indication • In addition, bevacizumab has an estimated market share in wAMD of [redacted] in the UK – this is derived from national

			market share data from January 2018–April 2019;[6] therefore, bevacizumab cannot be considered established clinical practice in the NHS for wAMD • Best supportive care is not an appropriate comparator to brolucizumab in this appraisal, given that patients with wAMD should be offered treatment with aflibercept or ranibizumab in line with NICE TA294 and NICE TA155[2, 3] • The comparators considered relevant to this appraisal were also confirmed by feedback from UK clinical experts experienced in the management of wAMD[7, 8]
Outcomes	• VA (the affected eye) • Overall visual function • Central subfield foveal thickness • Adverse effects of treatment • HRQoL	• Best-corrected VA (BCVA; the affected eye) • Overall visual function • Central subfield foveal thickness • Adverse effects of treatment • HRQoL (measured via the NEI VFQ-25)	N/A – in line with the final NICE scope.
Economic analysis	• The cost effectiveness of treatments should be expressed in terms of incremental cost per QALY • 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 time horizon should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared	• A cost-comparison model has been developed to undertake a cost-comparison of brolucizumab versus aflibercept and ranibizumab • A lifetime time horizon of 30 years has been adopted, in line with the previous NICE appraisal for aflibercept in this indication (25 years).[3] This time horizon is therefore considered to be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared • All costs are considered from an NHS and PSS perspective	• Brolucizumab should be appraised through the NICE FTA cost-comparison process, with aflibercept and ranibizumab as the existing licensed and NICE-recommended comparators • The results of the HAWK and HARRIER trials demonstrate brolucizumab to be associated with comparable efficacy in terms of BCVA versus aflibercept that is achieved with a lower injection frequency, as well as a comparable safety profile • The results of the NMA detailed in Section B.3.9.3 also demonstrate brolucizumab to be associated with comparable efficacy in terms of BCVA and safety versus both aflibercept and ranibizumab • The NMA also demonstrated brolucizumab to be statistically significantly superior in terms of reduction in retinal thickness versus aflibercept and ranibizumab • A cost-comparison case is therefore considered

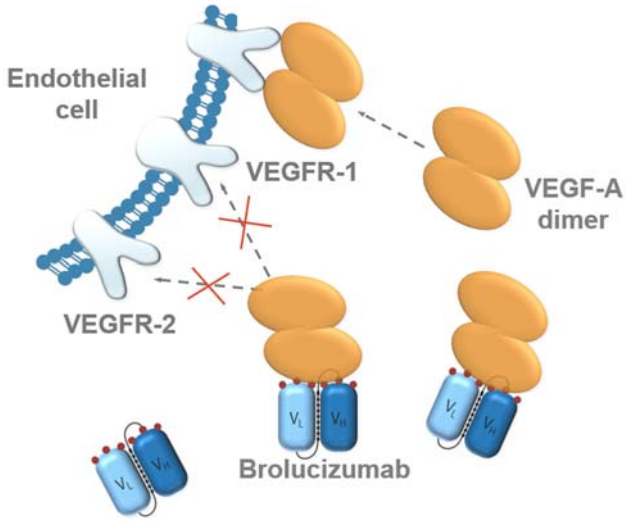
	• Costs will be considered from an NHS and Personal Social Services (PSS) perspective. The availability of any commercial arrangements for the intervention or comparator technologies will be taken into account • Cost-effectiveness analysis should include consideration of the benefit in the best and worst seeing eye	and derived from appropriate sources including NHS reference costs and the BNF	appropriate as brolucizumab will provide similar or greater health benefits at a similar or lower cost than the technologies recommended in published NICE technology appraisal guidance for the same indication (aflibercept [TA294] and ranibizumab [TA155])[2, 3]
Subgroups to be considered	• Lesion is classic or occult neovascularisation in nature	• No economic subgroup analyses are considered relevant to this appraisal	• Results of the subgroup analyses up to Week 48 in the HAWK and HARRIER trials showed a relevant benefit in terms of BCVA improvement from Baseline for brolucizumab patients regardless of lesion type and was not suggestive of subgroup-specific differences. Therefore, this suggested subgroup analysis is not considered appropriate[4, 5]

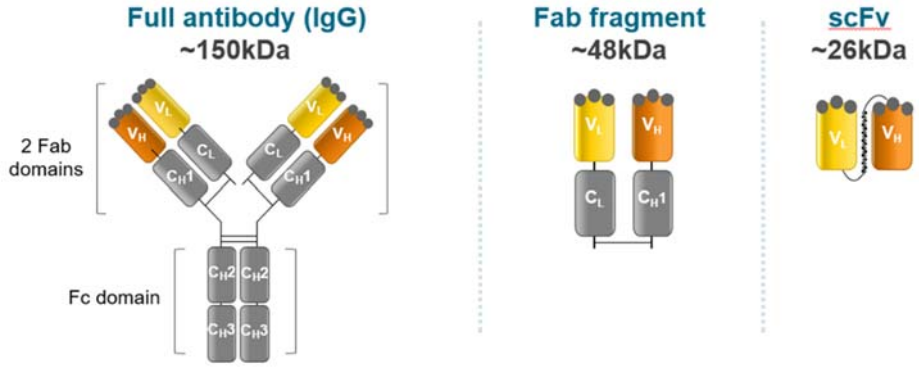
Abbreviations: BCVA: best-corrected visual acuity; BNF: British National Formulary; FTA: fast track appraisal; HRQoL: health-related quality of life; NHS: National Health Service; NEI: National Eye Institute; NICE: National Institute for Health and Care Excellence; PSS: Personal and Social Services; QALY: quality-adjusted life year; TA: technology appraisal; VA: visual acuity; VFQ-25: Visual Functioning Questionnaire; wAMD: wet age-related macular degeneration.
Source: NICE final scope for ID1254.[9]

B.1.2 Description of the technology being appraised

A description of the technology being appraised is presented in Table 1.2.

Table 1.2: Technology being appraised

UK approved name and brand name	Brolucizumab (BEOVU®)
Mechanism of action	The VEGF pathway regulates the development of blood vessels. Increased signalling through the VEGF pathway is associated with the pathological manifestations of wAMD such as CNV and retinal oedema,[10] with VEGF-A emerging as the most important regulator of angiogenesis.[11] The inhibition of the VEGF pathway has been shown to inhibit the growth of neovascular lesions and resolve retinal oedema in patients with chorioretinal vascular diseases, thereby gaining and preserving visual function. Anti-VEGF therapies downregulate angiogenesis via the VEGF pathway, and the anti-VEGF therapies aflibercept and ranibizumab comprise the current standard of care in this indication. Brolucizumab is a humanised single-chain variable fragment (scFv) inhibitor of VEGF-A designed specifically for the treatment of wAMD. Brolucizumab brings innovation to the wAMD treatment pathway as the most clinically advanced, humanised scFv inhibitor of VEGF-A in development.[12, 13] It is administered via intravitreal injection where it binds with high affinity to all isoforms of VEGF-A which prevents the ligand-receptor interaction of VEGF receptors VEGFR1 and VEGFR2, thus preventing activation of the VEGF pathway (Figure 1.1).[14, 15] This reduces the rate of angiogenesis, resulting in superior fluid resolution compared to currently available anti-VEGF therapies and the preservation of visual function. **Figure 1.1: Mechanism of action of brolucizumab**  **Abbreviations**: VEGF-A: vascular endothelial growth factor A; VEGFR: vascular endothelial growth factor receptor; V_H: variable domain, heavy-chain; V_L: variable domain, light-chain. An scFv comprises only the variable domains of the monoclonal antibody (joined by a short flexible linker peptide) that are responsible for binding to its target.[16] An scFv is an autonomous binding agent that is no longer dependent on a heavy molecular support structure and still retains full binding capacity to

	its target. Advantages of scFvs may include achieving more drug in a single injection, effective tissue penetration and rapid systemic clearance (Figure 1.2).[12, 15, 17-19] **Figure 1.2: Structure of a full monoclonal antibody, Fab fragment and scFv**  **Abbreviations**: C_H: constant domain, heavy-chain; C_L: constant domain, light-chain; Fab: fragment, antigen-binding; Fc: fragment crystallizable; Ig: immunoglobulin; kDa: kilodalton; scFv: single-chain antibody fragment; V_H: variable domain, heavy-chain; V_L: variable domain, light-chain. With a molecular weight of ~26 kDa, brolucizumab has been engineered to achieve higher molar dosing than ranibizumab or aflibercept, which can help deliver a long-lasting effect (Figure 1.3). Furthermore, whilst the ocular half-lives of aflibercept and ranibizumab are similar,[20] the small size of brolucizumab may facilitate rapid and more effective penetration of the different retinal layers.[12, 21] Taken together, the advantages of brolucizumab are such that it delivers a long-lasting effect, attributed to the combination of its smaller size and higher molar concentration per injection. As such, brolucizumab is the first anti-VEGF therapy to be administered every 12 weeks (q12w) immediately following the loading dose phase, enabling more patients to be maintained on a longer treatment interval without compromising visual outcomes compared with currently available anti-VEGF therapies. **Figure 1.3: Comparison of anti-VEGF therapies** **Abbreviations**: C_H: constant domain, heavy-chain; C_L: constant domain, light-chain; Fc: fragment crystallizable region; kDa: kilodalton; VEGF: vascular endothelial growth factor; VEGFR: vascular endothelial growth factor receptor; V_H: variable domain, heavy-chain; V_L: variable domain, light-chain.

	Aflibercept	Ranibizumab	Brolucizumab
Format	VEGFR1/2-Fc fusion protein	Fab fragment	single-chain antibody fragment
Molecular structure			
Molecular weight	97-115 kDa	~48 kDa	26 kDa

Marketing authorisation/ CE mark status	• The European Medicines Agency (EMA) centralised procedure was initiated on 28th February 2019 • A positive opinion from the Committee for Medicinal Products for Human Use (CHMP) is expected in December 2019 and regulatory approval from the EMA is anticipated in February–March 2020

	• Approval from the US Food and Drug Administration (FDA) for brolucizumab for the treatment of wAMD was received on 8th October 2019
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Brolucizumab is indicated in adults for the treatment of wAMD.[1] **Contraindications** • Hypersensitivity to the active substance or to the following excipients: sodium citrate, sucrose, polysorbate 80, water for injections • Patients with active or suspected ocular or periocular infections • Patients with active intraocular inflammation[1]
Method of administration and dosage	• Brolucizumab is administered via intravitreal injection using a pre-filled syringe and must be administered by a qualified ophthalmologist experienced in intravitreal injections[1] **The anticipated posology of brolucizumab is as follows:[a]** • The recommended dose is 6 mg (0.05 mL solution) administered every 4 weeks (monthly) for the first three doses. Thereafter, the physician may individualise treatment intervals based on disease activity as assessed by visual acuity and/or anatomical parameters. A disease activity assessment is suggested 16 weeks (4 months after treatment start) • 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. Physicians may further individualise treatment intervals based on disease activity • If visual and anatomical outcomes indicate that the patient is not benefitting from continued treatment, brolucizumab should be discontinued.[1]
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 anticipated list price for brolucizumab is £816.00 (excluding VAT) per 120 mg/ml solution for injection in pre-filled syringe.
Patient access scheme (if applicable)	A confidential simple discount Patient Access Scheme (PAS) will provide brolucizumab at a fixed net price of [redacted] (excluding VAT) per 120 mg/ml pre-filled syringe. This represents a [redacted] discount off the list price.

[a]The draft SmPC and posology wording is subject to ongoing discussion with the EMA.
Abbreviations: CDRs: complementarity-determining regions; CHMP: Committee for Medicinal Products for Human Use; CNV: choroidal neovascularisation; EMA: European Medicines Agency; FDA: Food and Drug Administration; qXw: one injection every X weeks; scFv: single-chain antibody fragment; VEGF: vascular endothelial growth factor; wAMD: wet age-related macular degeneration.

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

Summary

Disease overview

- AMD is a chronic eye disease characterised by the progressive degeneration of the macula that can lead to rapid, irreversible vision loss;[22] whilst wAMD only accounts for 10–20% of all AMD cases, it is responsible for 80–90% of the vision loss associated with AMD[23, 24]
- wAMD is the leading cause of severe vision loss and legal blindness in people over the age of 65 in North America, Europe, Australia and Asia.[25] In the UK, the incidence of wAMD in those over the age of 50 is estimated to be 1.4 and 2.3 per 1,000 people for men and women, respectively, and increases with age[26]
- wAMD is characterised by the leaking of fluid from the formation of abnormal blood vessels underneath the macula, which occurs in response to abnormally high levels of VEGF;[24, 27, 28] symptoms of wAMD include reduced VA, blurred vision and image distortion[29, 30]

Patient and caregiver burden

- The vision loss associated with wAMD has a profound negative impact on health-related quality of life (HRQoL) through its negative impact on independence, productivity and vision-related activities, as well as medical and psychosocial consequences[31]
- Approximately 50% of patients require caregivers' aid with instrumental daily activities such as telephone usage and food preparation[31]

Clinical management

- The control of fluid accumulation is essential to the effective management of wAMD and major clinical guidelines (Europe-wide from the European Society of Retina Specialist [EURETINA] and NICE)[32, 33] recommend that treatment decisions are based around the presence of fluid
- Both of these guidelines recommend the anti-VEGF therapies aflibercept and ranibizumab as the gold standard licensed treatments for wAMD and both therapies have been assessed and recommended for reimbursement for the treatment of wAMD by NICE[2, 3, 33]

Economic and healthcare system burden

- The direct costs of wAMD include treatment costs, ophthalmology clinic visits, informal care and disease diagnostics;[34] indirect costs include productivity losses suffered by both patients and caregivers, which will not be captured in the economic evaluation for this appraisal

Unmet need

- Healthcare resource utilisation by wAMD patients is high due to the high injection and monitoring frequency of currently available anti-VEGF therapies. This impacts patient adherence and ophthalmology clinic capacity, resulting in under-treatment and poorer visual outcomes;[35, 36] up to 22 people per month are permanently losing sight due to delayed and cancelled hospital appointments for conditions including wAMD[37]
- To reduce the treatment burden associated with current therapies, physicians tend to adopt flexible treatment regimens, including pro re nata (PRN), with treatment administered on an 'as-needed' basis, and treat-and-extend (TREX), where the treatment interval length is extended based on disease activity (visual and anatomical outcomes) including BCVA and fluid accumulation.[38] In practice this means that, in some cases, physicians are waiting for the disease to return before providing further treatment, leading to sub-optimal visual outcomes[22, 39]
- Feedback from UK clinical experts indicates that there is a clear unmet need for a therapy with superior fluid reduction and better drying of the macular that can suppress disease activity for longer than currently available anti-VEGF therapies.[8] This would enable the administration of less frequent injections immediately after the loading dose phase without

compromising visual outcomes, and allow ophthalmology clinics to run on time and optimise clinic capacity.

B.1.3.1 Disease overview

AMD is a chronic eye disease characterised by the progressive degeneration of the macula, the area of the retina responsible for sharp, central vision. Left untreated, AMD can lead to rapid, irreversible vision loss and globally, 8.7% of all cases of blindness are attributed to AMD.[39] There are two types of AMD: geographic atrophy/non-exudative (dry) or neovascular/exudative (wet), i.e. wAMD, the indication of relevance to this appraisal. Whilst wAMD only accounts for 10–20% of all AMD cases, it is responsible for 80–90% of the vision loss associated with AMD.[23, 24]

Epidemiology

wAMD is the leading cause of severe vision loss and legal blindness in people over the age of 65 in North America, Europe, Australia and Asia, impacting an estimated 20-25 million people worldwide.[25] In the UK, the incidence of wAMD in those over the age of 50 is estimated to be 1.4 and 2.3 per 1,000 people for men and women, respectively, and this increases with age.[26] Further risk factors strongly associated with the incidence of the disease include smoking status and genotype expression.[39] With 85% of incident patients estimated to be eligible for treatment,[40] the total number of incident wAMD patients in England is estimated to be ~33,000. Full details of the estimated number of patients eligible for treatment with brolucizumab are presented in the budget impact analysis template.

Pathophysiology

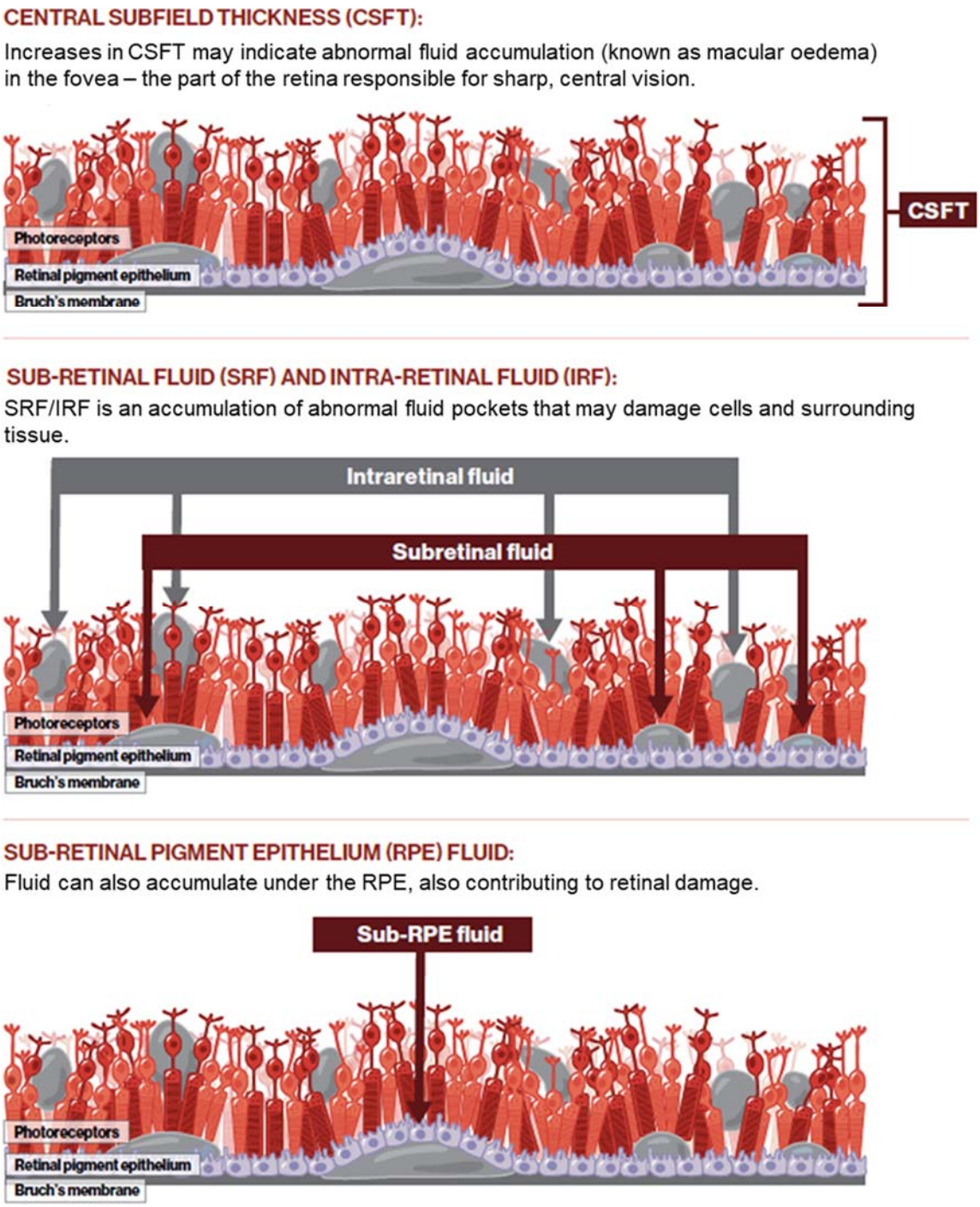
wAMD is an acute onset and rapidly progressing disease characterised by the leaking of fluid from the formation of abnormal blood vessels underneath the macula.[24, 27, 28] This phenomenon, known as choroidal neovascularisation (CNV), is the defining feature in wAMD and occurs in response to abnormally high levels of VEGF.[28] The newly formed blood vessels are fragile and leak fluid (Figure 1.4), and progressive exudation from the macula can lead to the separation of Bruch's membrane, retinal pigment epithelium (RPE) and retina, and the accumulation of sub-RPE, sub-retinal and/or intra-retinal fluid. This leads to a generalised thickening of the retina (central subfield thickness [CSFT]) and the generation of cystic spaces.[32, 41] Unresolved fluid accumulation consequently leads to the disruption to the anatomical architecture of the retina and the progressive damage of photoreceptors, resulting in severe, irreversible vision loss.[32, 41] Patients may also experience metamorphopsia, scotoma, photopsia, dark adaptation difficulties, and eventually, irreversible vision loss.[29, 30, 32, 42, 43] The control of fluid accumulation is therefore essential to the effective management of wAMD and improving and maintaining vision.

Clinical signs and diagnosis

The early and intermediate stages of AMD usually occur without symptoms, with minimal or no vision loss.[44] As the disease progresses into late AMD, the symptoms of wAMD include reduced VA, blurred vision and image distortion.[29, 30, 45] Basic visual function tests such as Snellen's chart, the Amsler grid and the Early Treatment Diabetic Retinopathy Study chart (ETDRS) are the most commonly used tools to determine the symptomatic impact of wAMD on patients' best-corrected visual acuity (BCVA).[32] Early detection of disease onset, prompt therapeutic intervention and continuous follow-up are essential as visual loss becomes irreversible with delayed diagnosis and (re)treatment.[32, 33] In the past, time domain optical coherence tomography (OCT) was predominantly used to diagnose wAMD, but advances in OCT scanning techniques including SD-OCT and OCT angiography (OCT-A) are now more commonly being used, and will aid the earlier

detection of fluid accumulation, a key factor in the effective management of wAMD and maintaining and improving vision.

Figure 1.4: Fluid accumulation in wAMD



Abbreviations: CST: central subfield thickness; SRF: sub-retinal fluid; IRF: intra-retinal fluid; RPE: sub-retinal pigment epithelium.

Patient and caregiver burden

wAMD is a debilitating, chronic disease that significantly impacts patients' HRQoL, independence and functional ability. Several studies have shown overall HRQoL to be significantly associated with the degree of visual impairment suffered.[46-48] Patients with wAMD commonly have difficulty

carrying out activities of daily living, including reading, driving, meal preparation and self-care activities such as dressing, bathing and toileting.[31] As a result, wAMD patients have also been shown to be significantly more likely to develop anxiety and depression than those without wAMD.[46, 47] In addition, wAMD patients are associated with an increased risk of vision-related comorbidities and falls and fractures, the need to access community support services, nursing home placement and increased mortality.[49-51]

The impaired ability to perform daily activities increases the likelihood of patients requiring caregiver assistance, and approximately 50% of patients with wAMD require caregiver support with instrumental daily activities such as telephone usage and food preparation.[31] As a result, the wAMD-associated caregiver burden can be substantial, and is reported to be equivalent to that of conditions such as rheumatoid arthritis and atrial fibrillation, and higher than the burden for colorectal cancer patients.[31]

Finally, the administration of currently available anti-VEGF therapies involves high treatment frequency and regular monitoring, which contributes substantially to the patient and caregiver burden of the disease. Several studies have demonstrated reduced patient adherence as a result of the treatment burden associated with current anti-VEGF therapies, due to factors such as injection fear, anxiety and the inconvenience of travelling to and from regular clinic appointments.[35, 36]

Economic and healthcare system burden

The visual impairment associated with wAMD causes patients to utilise considerable resources from the healthcare system and community in order to function adequately in society. The main direct costs of wAMD include treatment costs, ophthalmology clinic visits, informal care and disease diagnostics.[34] Furthermore, healthcare resource utilisation by wAMD patients is high due to the requirement for frequent monitoring and injection visits with currently available anti-VEGF therapies. Treatment with aflibercept and ranibizumab requires frequent intravitreal injections which results in a significant burden to patients, ophthalmology clinics and healthcare systems. With an increase in the ageing population, the prevalence and incidence rates for wAMD are expected to increase substantially.[39] The number of patients being prescribed anti-VEGF therapies for wAMD is therefore also likely to increase, further contributing to the overall costs associated with the disease.

Finally, indirect costs form a large proportion of the overall economic burden of wAMD, including productivity losses suffered by both patients and caregivers, which will not be captured in the economic evaluation for this appraisal. Indirect medical costs also include the treatment of conditions related to wAMD or worsened by disease progression, such as mental health or fractures from falls.

B.1.3.2 Clinical pathway of care

The aim of wAMD treatment is to resolve the accumulation of retinal fluid and subsequently recover and/or preserve visual function, whilst slowing disease progression.[32, 52] Early detection of disease onset, prompt therapeutic intervention and continuous follow-up to detect fluid accumulation are critical, as vision loss becomes irreversible with delayed diagnosis and treatment.[32] Various diagnostic tools including SD-OCT and FA are used to confirm diagnosis of late wAMD.[5, 32]

Following diagnosis, clinical guidelines on the treatment of wAMD are available Europe-wide from EURETINA and from NICE (NICE clinical guideline NG82).[32, 33] Both guidelines recommend the anti-VEGF therapies, aflibercept and ranibizumab, for the first-line treatment of wAMD, and

both therapies have also been assessed and recommended for reimbursement for the treatment of wAMD by NICE.[2, 3, 33] Photodynamic therapy (PDT) may be offered as an adjunct to anti-VEGF therapy only as second-line treatment in the context of a randomised controlled trial.[33] PDT is therefore not considered a relevant comparator to brolucizumab in the context of this appraisal.

A summary of the pharmacological management of patients with wAMD after diagnosis is shown in Figure 1.5. Brolucizumab is anticipated to be used in clinical practice in accordance with its full licensed indication, for the treatment of wAMD. Therefore, the relevant comparators to brolucizumab in this position, and in the context of this appraisal, are aflibercept and ranibizumab. The development of the anti-VEGF therapies, aflibercept and ranibizumab, has revolutionised the management of wAMD and several studies have demonstrated that both therapies have equal efficacy and similar safety profiles.[53-55]

However, despite a reduction in the incidence of blindness due to wAMD since the availability of anti-VEGF therapies,[56, 57] the current management of wAMD is associated with distinct challenges relating to the need for regular monitoring and injection frequency of these therapies. Real-world evidence demonstrates that visual outcomes with current anti-VEGF therapies are related to injection frequency; however, the high treatment burden impacts both patient adherence (due to factors such as injection fear, anxiety and the inconvenience of attending clinic appointments) as well as ophthalmology clinic capacity, which can lead to delay in follow-up of wAMD patients, placing these patients at risk of symptom exacerbation and vision loss.[58-60] Up to 22 people per month are permanently losing sight due to delayed and cancelled hospital appointments for conditions including wAMD, glaucoma and diabetic eye disease.[37] Taken together, the high treatment and monitoring burden results in undertreatment, with mean injection frequency of anti-VEGF therapy being lower in real-world practice than in pivotal clinical trials, which can lead to poorer visual outcomes.[22, 58]

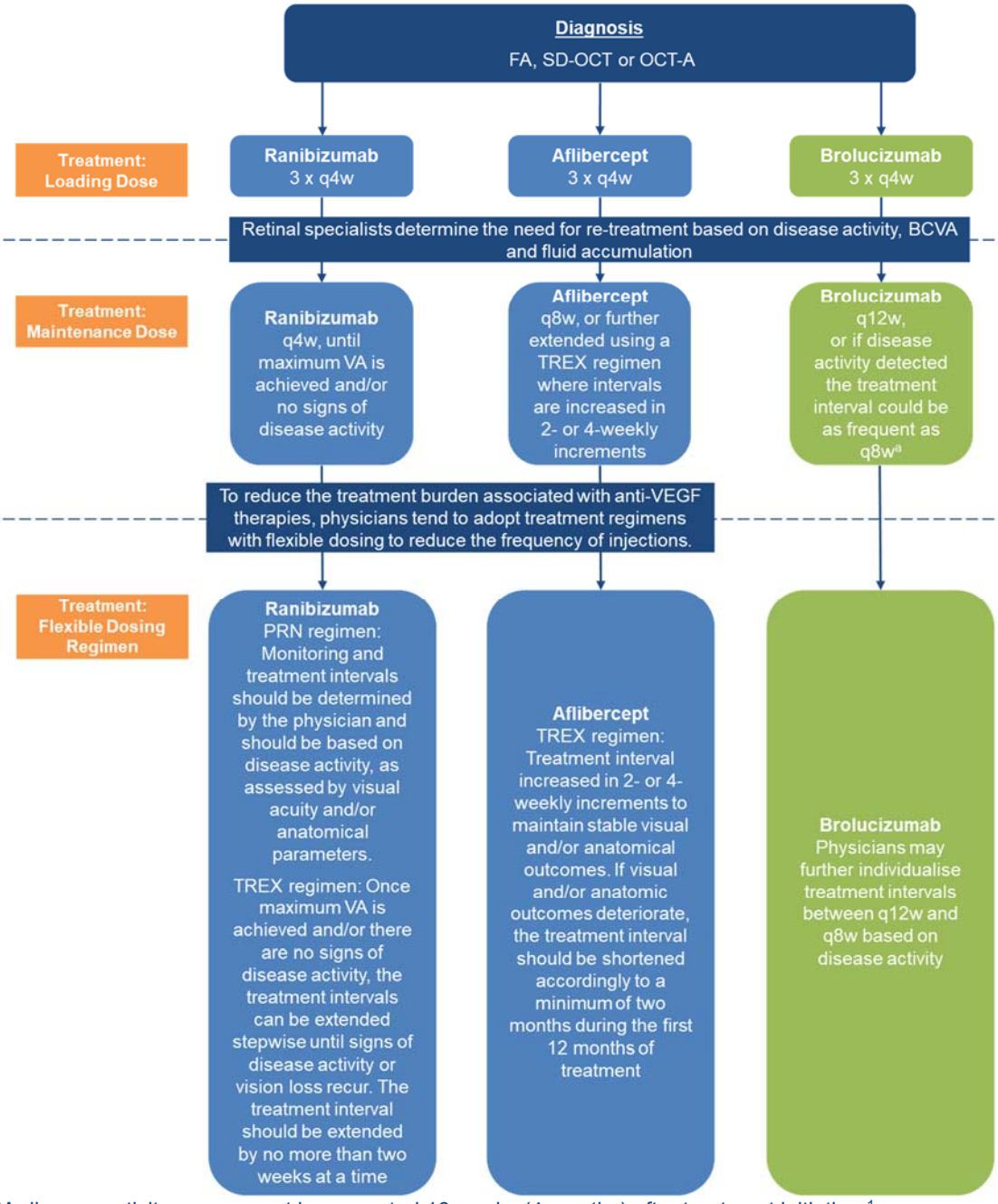
To reduce the treatment burden associated with current anti-VEGF therapies, the adoption of flexible treatment regimens is now more common, including pro re nata (PRN) and treat-and-extend (TREX). With a PRN regimen, patients are monitored frequently (as often as every month) and treatment is administered reactively on an ‘as-needed’ basis based on disease activity, as assessed by visual acuity and/or anatomical parameters, including the accumulation of sub-RPE, sub-retinal and/or intra-retinal fluid and CSFT increases secondary to the presence of fluid.[61] In practice, this means that, in some cases, clinicians following a PRN regimen are waiting for disease activity to return before administering additional treatment. If clinical capacity is not available to enable regular monitoring, patients may experience a delay with their treatment and therefore experience poorer outcomes. With a TREX regimen, the treatment interval may be extended in a stepwise manner until signs of disease activity or visual impairment recur; at this point, the interval is shortened and only re-extended when the disease activity/visual impairment is controlled. Whilst the use of flexible treatment regimens may help to reduce the treatment burden of these therapies, issues with ophthalmology clinical capacity still remain, and clinicians are unable to predict which patients can be maintained on a longer treatment interval.[58-60]

The limitations associated with current anti-VEGF therapies are therefore two-fold: a risk of under-treatment leading to symptom exacerbation and vision decline, and a need to maintain visual and anatomical outcomes whilst reducing the burden on ophthalmology clinic capacity. There is a clear unmet need for a therapy that suppresses disease activity (fluid accumulation and CSFT) for longer than currently available anti-VEGF therapies, enabling the administration of less frequent injections immediately following the loading dose phase without reducing visual outcomes. Furthermore, the earlier identification of patients who are able to be maintained on a longer treatment interval is critical, to enable ophthalmology clinics to plan ahead with regards to

clinic capacity. In turn, this may lead to better patient adherence and a reduced risk of undertreatment, leading to improved visual outcomes, patient independence and HRQoL.

As the first anti-VEGF therapy to have an anticipated licensed q12w maintenance dose immediately following the loading phase, brolucizumab addresses the unmet need associated with currently available anti-VEGF therapies, by providing patients and physicians with a therapy with superior fluid reduction and better drying of the macular that suppresses disease activity for longer than currently available anti-VEGF therapies. In turn, this allows for an earlier extension in the treatment interval immediately following the loading dose phase based on lasting disease control, and the earlier identification of patients who are able to be maintained on a longer treatment interval may allow ophthalmology clinics to run on time and optimise clinic capacity.[8, 62]

Figure 1.5: Pharmacological management of patients with wAMD after diagnosis



[a]A disease activity assessment is suggested 16 weeks (4 months) after treatment initiation.[1]

Abbreviations: BCVA: best corrected visual acuity; FA: fluorescein angiography; OCT-A: Optical coherence tomography angiography; qXw: one injection every X weeks; SD-OCT: spectral domain optical coherence tomography; TREX: treat-and-extend dosing regimen; VA: visual acuity; VEGF: vascular endothelial growth factor.
Source: NICE Guideline (NG82);[33] Ranibizumab SmPC;[63] Aflibercept SmPC;[64] Brolucizumab draft SmPC.[1]

B.1.4 Equality considerations

Visual impairment resulting from wet AMD is a legally recognised disability, as stated in the Equality Act 2010. The patient population addressed in this submission is a protected group under this act.

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

A summary of the clinical outcomes and measures included within the cost-effectiveness analyses conducted for the NICE appraisals for aflibercept (TA294) and ranibizumab (TA155), followed by the key drivers of the cost-effectiveness analyses is presented in this section.[2, 3]

B.2.1 Clinical outcomes and measures

The comparators to brolucizumab in this appraisal are the licensed anti-VEGF therapies aflibercept and ranibizumab. Both therapies have been evaluated by NICE and recommended for patients with wAMD in NICE TA294 (aflibercept; published in 2013) and NICE TA155 (ranibizumab; published in 2008), respectively.[2, 3]

Aflibercept (TA294)

The pivotal clinical trials for aflibercept considered in TA294 were VIEW 1 and 2.[65] VIEW 1 and 2 were international, multicentre, randomised, double-masked, parallel-group, active-controlled, phase III non-inferiority studies. Patients with active primary subfoveal CNV lesions secondary to AMD were randomised into one of four treatment arms: aflibercept 2 mg q4w, aflibercept 0.5 mg q4w, aflibercept 2 mg q8w, and ranibizumab 0.5 mg q4w. Both studies consisted of an initial 48-week dosing phase and a subsequent follow-up phase through to Week 96. From Weeks 52 to 96, patients received their original dosing assignment using an as-needed regimen with defined re-treatment criteria and mandatory dosing at least every 12 weeks. The primary endpoint of both studies was the proportion of patients who maintained vision at Week 52, defined as a loss of <15 letters in terms of ETDRS letters compared to Baseline.

Ranibizumab (TA155)

The pivotal trials for ranibizumab considered in TA155 were MARINA, ANCHOR and PIER.[55, 66-68] MARINA, ANCHOR and PIER were two year, multicentre, randomised, double-masked, studies of the efficacy and safety of ranibizumab 0.3 mg and 0.5 mg. MARINA was sham-controlled and in patients with minimally classic or occult wAMD; in ANCHOR, ranibizumab was compared to photodynamic therapy and in patients with predominantly classic wAMD; and PIER was sham-controlled and in patients with subfoveal CNV secondary to AMD. Both MARINA and ANCHOR evaluated ranibizumab 0.3 mg q4w and 0.5 mg q4w, whilst PIER evaluated a reduced dosing frequency of IVT injections at q4w for the first three doses, followed by a q12w regimen up to 12 months. The primary endpoint of MARINA and ANCHOR was the loss of <15 ETDRS letters from Baseline to 12 months, and the primary endpoint of PIER was the mean change in BCVA from Baseline to 12 months.

Table 2.1 presents the key clinical outcomes and measures considered in TA294 and TA155 from the trials detailed above.

Table 2.1: Clinical outcomes and measures appraised in published NICE guidance for the comparators

TA	Outcome category	Outcome	Used in cost-effectiveness model of previous appraisal?	Source
NICE TA294[3]	VA (the affected eye)	Proportion of patients losing <15 ETDRS letters from Baseline at Week 52 (and Week 96)	Yes	VIEW 1, VIEW 2
		Mean change in BCVA from Baseline at Week 52 (and Week 96)	Yes	VIEW 1, VIEW 2
		Proportion of patients gaining ≥15 letters from Baseline to Week 52 (and Week 96)	Yes	VIEW 1, VIEW 2
	Overall visual function	Change in CNV area from Baseline to Week 52 (and Week 96)	No	VIEW 1, VIEW 2
		Mean change in CSFT from Baseline to Week 52 (and Week 96)	No	VIEW 1, VIEW 2
	AEs	Ocular AEs; non-ocular AEs	No (inclusion of ocular AEs explored in a scenario analysis only)	VIEW 1, VIEW 2
	HRQoL	Change in total NEI VFQ-25 from Baseline to Week 52 (and Week 96)	No	VIEW 1, VIEW 2
		Change in EQ-5D from screening	Yes	VIEW 2 only
NICE TA155[2]	VA (the affected eye)	Proportion of patients losing <15 ETDRS letters from Baseline to 12 months (and 24 months)	Yes	MARINA, ANCHOR, PIER
		Gain of more than 15 ETDRS letters of visual acuity from Baseline to 12 months (and 24 months)	Yes	MARINA, ANCHOR, PIER
		Mean change in visual acuity (mean number of ETDRS letters lost or gained) from Baseline to 12 months (and 24 months)	Yes	MARINA, ANCHOR, PIER
	Overall visual function	Mean change in area of leakage from CNV and total area of CNV from Baseline over time	Yes	MARINA, ANCHOR, PIER
	AEs	Ocular AEs; non-ocular AEs	Yes (only ocular AEs deemed clinically and economically important)	MARINA, ANCHOR
	HRQoL	Change in total NEI VFQ-25 from Baseline over time	No	MARINA, ANCHOR, PIER

Abbreviations: AE: adverse event; BCVA: best corrected visual acuity; CNV: choroidal neovascularisation; CSFT: central subfield thickness; ETDRS: Early Treatment Diabetic Retinopathy Study; EQ-5D: 5-dimension European Quality of Life questionnaire; FA: fluorescein angiography; HRQoL: health-related quality of life; ICH: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; NEI: National Eye Institute; OCT: Optical coherence tomography; VA: visual acuity; VFQ-25: Visual Functioning Questionnaire.

B.2.2 Summary of the key drivers of the cost effectiveness of the comparators

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

The key drivers of the aflibercept cost-effectiveness analysis, as described in TA294, included: the cost of aflibercept and ranibizumab injections; the risk ratio of gaining vision, as the main determinant of treatment effect, the frequency of monitoring and the proportion of patients in a one-stop and two-stop model, and the number of injections. A summary of the key assumptions and parameters used in the base case cost-comparison analysis for this appraisal is presented in Table 4.11 in Section B.4.2.7.

Table 2.2 presents the key assumptions and parameters used in the base case economic analyses conducted for TA294 and TA155. A summary of the key assumptions and parameters used in the base case cost-comparison analysis for this appraisal is presented in Table 4.11 in Section B.4.2.7.

Table 2.2: Resources and associated costs appraised in published NICE guidance for the comparators[a]

TA	Cost category	Item	Unit cost (£)	Manufacturer's assumptions	Committee's preferred assumptions
NICE TA294[3]	**Diagnosis**	All patients were assumed to receive one FA before starting treatment	£117.26[69]	NR	• No comment was made by the Committee
	Drug administration	Outpatient visit (44.87%)[70]	£79.74[69]	The manufacturer assumed that the administration of both aflibercept and ranibizumab occurred as a weighted average of a day case visit and outpatient visit	• No comment was made by the Committee
		Day case visit (55.13%)[70]	£402.08[69]		
	Injection frequency	**Aflibercept**: **Year 1:** 7 (SmPC)[64] **Years 2–5:** 4 (SmPC,[64] VIEW 2, conservative assumption) **Ranibizumab**: **Year 1:** 8 (TA155,[2] EMA report) **Year 2:** 6 (TA155,[2] EMA report)	NA	The manufacturer assumed that patients receiving aflibercept had 7 injections in the first year and 4 injections in the second year based on the treatment frequency recommended in SmPC and the VIEW 2 study. It was assumed that patients receiving ranibizumab had 8 injections in the first year and 6 injections in the second year based on previous NICE guidance and the ranibizumab SmPC. Based on clinical expert opinion, it was assumed that patients in both	• The Committee considered in the absence of longer-term data, it was reasonable to assume both treatment groups would have the same number of treatment and monitoring visits in Years 3 to 5 of the model • The Committee agreed with the ERG that it was more likely that patients treated with aflibercept would need 8 treatment visits in the first year based on the average number of injections received in the VIEW 2 study. The Committee also considered it would

		Years 3–5: 4 (Expert clinical opinion)		treatment groups had 4 injections in Years 3 to 5	be fairer to use the same data that were used to estimate the relative clinical effectiveness of aflibercept and ranibizumab to inform assumptions about the number of treatment and monitoring visits in the model • The Committee concluded it was reasonable to assume patients in both treatment groups would need 8 treatment visits in the first year
	Monitoring costs	Ophthalmologist visit	£79.74[69]	The manufacturer assumed that separate monitoring visits included the cost of an ophthalmologist outpatient visit and an OCT	• No comment was made by the Committee
		OCT	£117.26[69]		
	Monitoring visits	**Aflibercept**: **Year 1:** 6 (100% one-stop model) (SmPC)[64] **Year 2:** 7 (50% one-stop model [2 separate monitoring visits]; 50% two-stop model [6 separate monitoring visits]) **Ranibizumab**: **Year 1:** 12 (50% patients follow a one-stop model [4 separate monitoring visits]; 50% patients follow a two-stop model [12 separate monitoring visits]) (SmPC)[63] **Year 2:** 12 (50% one-stop model [4 separate	NA	• The frequency of monitoring visits in the first two years was based on the SmPC for aflibercept and ranibizumab. Patients receiving aflibercept had 7 monitoring visits in Year 1 and 6 monitoring visits in Year 2, and patients receiving ranibizumab had 12 monitoring visits in Years 1 and 2. • Patients receiving aflibercept in a one-stop model had their treatment and monitoring at the same visit and therefore needed no separate monitoring visits in the first year and 2 separate visits in the second year. Patients receiving aflibercept in a two-stop model in the second year had their treatment and monitoring at separate visits and therefore needed 6 separate monitoring visits in the second year. • Patients receiving ranibizumab had	• The Committee heard from the specialists that, in future clinical practice, it is expected that fewer patients treated with anti-VEGF therapies would need separate treatment and monitoring visits. The Committee also noted that, if a higher proportion of patients in both treatment groups had their treatment administration and monitoring at the same visit, this would bias the results in favour of aflibercept because of the higher number of monitoring visits needed by patients treated with ranibizumab in the first 2 years of the model. • The Committee concluded that, based on current clinical practice, it was reasonable to assume that 50% of patients in both treatment groups would need separate monitoring visits

		monitoring visits]; 50% patients two-stop model [6 separate monitoring visits)] (SmPC)[63] **Years 3–5**: Aflibercept and ranibizumab: (50% one-stop model [3 separate monitoring visits]; 50% two-stop model [7 separate monitoring visits]) (conservative assumption and expert opinion)		4 separate monitoring visits in the first year and 6 separate visits in the second year in a one-stop model and 12 separate monitoring visits in the first 2 years in a two-stop model. On the basis of clinical expert opinion, patients in Years 3 to 5 in both treatment groups had 3 separate monitoring visits in the one-stop model and 7 separate monitoring visits in a two-stop model	
	AEs	Vitreous haemorrhage (0.20%)[71]	£1,270.97[69]	Based on the low incidence of AEs reported in the VIEW 1 and 2 studies, the manufacturer did not apply the costs of AEs in the base case analysis. The costs listed here were adopted in a scenario analysis	• No comment was made by the Committee
		Endophthalmitis (0.10%)[71]	£674.91[69]		
		Cataract (0.10%)[71]	£851.43[69]		
		Retinal detachment (0.10%)[71]	£411.44[69]		
		Retinal haemorrhage (0.30%)[71]	£474.89[69]		
	Cost of blindness	Low vision aids (33.00%)[72]	£136.33[73]	The manufacturer estimated the costs associated with blindness for patients defined as being blind in both eyes from a published UK costing study of blindness in patients with wAMD [72]	• No comment was made by the Committee
		Low vision rehabilitation (11.00%)[72]	£205.30[73]		
		Depression (38.60%)[72]	£391.97[73]		
		Hip replacement (5.00%)[72]	£3,669.00 [73]		
		Total weighted cost of blindness	£548.95		
	Development of bilateral disease	NA	NA	• Clinical effectiveness in the treated eye was assumed to be independent of effectiveness in the second eye • Bilateral disease was assumed to be 0% at Baseline but could only be developed from Year 3 onwards	• The Committee agreed with the ERG that it was unrealistic to assume no second-eye involvement in the first two years of the model because a large proportion of patients in the VIEW 1 and 2 trials had visual impairment in their second eye at the

				(based on a 0.65% monthly probability of developing wAMD in the second eye); all bilateral disease was assumed to be treated • Patients were assumed to start developing wAMD in the fellow eye after Year 3 • Clinical experts advised that treating the fellow eye is a case-by-case decision, but simplification for model purposes was an acceptable assumption	start of treatment • The Committee concluded that the ERG's exploratory approach, which involved separate analyses depending on whether the study eye was a better-seeing eye or worse-seeing eye, was more reasonable
NICE TA155[2]	**Drug administration**	Outpatient visit (base case: 100%)	£55[74]	100% of injections would be carried out as outpatient procedures	• Feedback from clinical specialists indicated the cost of injection administration would be higher than that assumed in the base case (£90.20) by the Assessment Group • The Committee also preferred an assumption of 75% day case/25% outpatient procedure
		Day case visit	£395[74]		
	Injection frequency	**Ranibizumab**: **Year 1:** 8 **Year 2:** 6	NA	• A different dosing schedule from that used in the clinical trials was adopted. The MARINA and ANCHOR trials involved 24 injections over two years and 12 injections over one year respectively. In the base case analysis, 8 injections in Year 1 and 6 injections in Year 2 were assumed. • The manufacturer assumed the same clinical efficacy would be achieved with this lower dosing frequency. • Treatment with ranibizumab (and pegaptanib) was also assumed to stop at the end of Year 2, with	• The Committee noted the number of injections presented by the manufacturer had been accepted by the EMA as a basis for the regimen in the marketing authorisation. Feedback from clinical specialists also stated that such a dosing regimen would be frequently used in practice. The Committee remained concerned whether the clinical benefit achieved in the pivotal trials could be achieved with fewer injections. • The Committee concluded that for some patients it would be appropriate to continue treatment beyond two years into the third or fourth year –

				benefits assumed to decline thereafter at the same rate as usual care.	which would result in additional drug/administration/monitoring costs. • The Committee also concluded that, on balance, it would be reasonable to assume an overall total of 24 injections of ranibizumab.
	Monitoring costs	FA	£162[74]	NR	No comment was made by the Committee
		Indocyanine green angiography	£162[74]		
		OCT	£80[74]		
	Monitoring visits	Retinal specialist	£55[74]	• Patients were assumed to require an optometrist assessment every month to determine whether treatment is necessary (i.e. the cost of an optometrist visit was assumed on the months when they do not receive treatment) • Separate monitoring visits were assumed to include the weighted average cost of a retinal specialist, optometrist, orthoptist and Tel fu ophthalmologists (£69)	No comment was made by the Committee
		Optometrist	£18[74]		
		Orthoptist	£39[74]		
		Tel fu ophthalmologist	£10[74]		
	AEs	Conjunctival haemorrhage	£15.3[74]	The costs of ocular AEs deemed clinically and economically important i.e. leading to a change in medical management and resource utilisation patterns were include	No comment was made by the Committee
		Eye pain	£14.5[74]		
		Vitreous floaters	£20.1[74]		
		Vitreous bleeding	£73.1[74]		
		Retinal bleeding	£51.6[74]		
		Transient increase in ocular pressure	£19.6[74]		
		Uveitis	£98.4[74]		
		Endophthalmitis	£1,964[74]		
		Traumatic cataract	£326[74]		
		Retinal detachment	£1,299[74]		
		Vitreal detachment	£57[74]		
		Retinal vein occlusion	£312[74]		
	Cost of blindness	Low vision aids (33.00%)[72]	£136.3[75]	NR	No comment was made by the Committee

		Low vision rehabilitation (11.00%)[72]	£205.3[75]		
		Depression (38.60%)[72]	£392.0[75]		
		Hip replacement (5.00%)[72]	£3,669.0[75]		
		Community care (6.00%)[72]	£2,848.60[75]		
		Residential care (30.00%)[72]	£15,904.40[75]		
	Treatment of the better-seeing eye	NA	NA	The manufacturer's model assumed that only the better-seeing eye would be treated	The consultees raised concerns that that it would be unacceptable, and clinically inappropriate, not to treat the first eye that comes to clinical attention. The Committee concluded that its considerations of cost effectiveness should relate to starting treatment with the first eye to present clinically

[a]Due to some inconsistencies between the two appraisals in the reporting of references, this table reports varied levels of detail/decimal places. For TA155, HRG codes were not provided in the company submission; the submission stated that unit costs for drug treatments were based on the British National Formulary, interventions and procedures, healthcare professional consultations and hospital or day care admissions were based on the 2004 UK reference costs, and for social services, unit costs were obtained from the 2004 PSSRU.

Abbreviations: AE: adverse event; BNF: British National Formulary; EMA: European Medicines Agency; ERG: Evidence Review Group; FA: fluorescein angiography; HES: Hospital Episodes Statistics; HRG: Healthcare resource group; NR: not reported; OCT: Optical coherence tomography; PSSRU: Personal Social Services Research Unit; SmPC: summary of product characteristics; VA: visual acuity.

B.3 Clinical effectiveness

Summary

- A systematic literature review (SLR) was conducted to identify evidence of the efficacy and safety of brolucizumab and the relevant comparators to this appraisal: aflibercept and ranibizumab
- The evidence base for brolucizumab comprises two phase III randomised head-to-head trials versus aflibercept (HAWK and HARRIER) and one phase II randomised head-to-head trial versus aflibercept (OSPREY)

Clinical effectiveness

- Brolucizumab achieved clinically meaningful and consistent visual gains and a majority of patients were maintained on a q12w dosing interval immediately following the loading phase at Week 48
  - The primary endpoint of non-inferiority for brolucizumab versus aflibercept in terms of mean change in BCVA from Baseline to Week 48 was met in both HAWK and HARRIER with highly significant p-values. At Week 48, the least squares (LS) mean change in BCVA from Baseline was 6.6 versus 6.8 letters, and 6.9 versus 7.6 letters, for brolucizumab 6 mg versus aflibercept 2 mg in HAWK and HARRIER, respectively ($p<0.0001$ for both comparisons, non-inferiority margin of 4 letters)
  - Over 96 weeks, the mean number of active injections administered to patients in the brolucizumab treatment arms of HAWK and HARRIER was between 1 and 1.5 fewer than the number administered in the aflibercept arms. This was driven by more than 50% (56% in HAWK and 51% in HARRIER) of brolucizumab 6 mg patients being exclusively maintained on a q12w regimen from Baseline immediately after the loading dose phase through to Week 48; the remainder were maintained on a q8w regimen and were not able to return to a q12w regimen. For those on a q12w regimen at Week 48, there was a >75% probability of remaining on this regimen at Week 96
- Brolucizumab was statistically superior to aflibercept in terms of improvements in central subfield retinal thickness (CSFT), retinal fluid (intraretinal fluid [IRF] and/or subretinal fluid [SRF]) and disease activity:
  - Brolucizumab was statistically significantly superior to aflibercept in disease activity parameters, with 30% fewer patients receiving brolucizumab had disease activity at Week 16 compared to those receiving aflibercept
  - Statistically significantly fewer patients receiving brolucizumab had IRF and/or SRF at Week 16, with differences maintained to Week 96
  - Brolucizumab showed a statistically significantly superior reduction in CSFT compared with aflibercept at Week 16, with differences maintained to Week 96. Brolucizumab required fewer injections to achieve a similar improvement in HRQoL

Comparative effectiveness

- A network meta-analysis (NMA) was conducted to assess the comparative effectiveness of brolucizumab versus the relevant comparators aflibercept and ranibizumab
- The results of the NMA demonstrated comparable efficacy in terms of BCVA and safety outcomes for brolucizumab, and statistically significantly superior efficacy in terms of reductions in retinal thickness versus aflibercept and ranibizumab. Full details of the NMA are presented in Section B.3.9

Safety

- The overall safety profile of brolucizumab was comparable to the safety profile of aflibercept. The overall incidence of ocular and non-ocular AEs was balanced across all treatment groups in both HAWK and HARRIER trials
- Finally, no new, previously unreported types of AEs were identified compared with other anti-VEGF therapies.

B.3.1 Identification and selection of relevant studies

An SLR was conducted to identify relevant clinical evidence of the efficacy and safety of brolucizumab for the treatment of wAMD. The SLR also identified clinical evidence on the efficacy and safety of the relevant comparators to brolucizumab for this appraisal: aflibercept and ranibizumab.

In total, 6,004 publications were screened, of which 147 publications were reviewed at the full-text stage. After exclusion of publications not meeting the eligibility criteria, 48 publications (reporting on 38 unique RCTs) were included in the SLR. A full list of the 38 RCTs is presented in Appendix D.

B.3.2 List of relevant clinical effectiveness evidence

Of the 38 RCTs included in the SLR, brolucizumab was investigated in three trials: HAWK (NCT02307682),[76] HARRIER (NCT02434328)[76] and OSPREY (NCT01796964).[77]

HAWK and HARRIER were phase III, international, multicentre, randomised head-to-head trials that compared brolucizumab (6 mg or 3 mg) to aflibercept (2 mg). The phase II OSPREY trial also compared brolucizumab 6 mg with aflibercept 2 mg and provides supportive evidence of the efficacy and safety of brolucizumab in this indication. Together, these trials represent the primary sources of evidence for the marketing authorisation for brolucizumab in this indication. A brief overview of the HAWK, HARRIER and OSPREY trials is presented in Table 3.1.

Table 3.1: Clinical effectiveness evidence

Study	HAWK (NCT02307682)	HARRIER (NCT02434328)	OSPREY (NCT01796964)
Reference sources	HAWK CSR[78] Dugel *et al.* (2019)[76]	HARRIER CSR[79] Dugel *et al.* (2019)[76]	OSPREY CSR[80] Dugel *et al.* (2017)[77]
Study design	A two-year, randomised, double-masked, multicentre, three-arm phase III study	A two-year, randomised, double-masked, multicentre, two-arm phase III study	A randomised, double-masked, multicentre, two-arm phase II study
Population	Adults over the age of 50 years with wAMD	Adults over the age of 50 years with wAMD	Adults over the age of 50 years with wAMD
Intervention(s)	Brolucizumab solution for intravitreal injection at doses of 3 mg and 6 mg	Brolucizumab solution for intravitreal injection at a dose of 6 mg	Brolucizumab solution for intravitreal injection at a dose of 6 mg
Comparator(s)	Aflibercept for intravitreal injection at a dose of 2 mg	Aflibercept for intravitreal injection at a dose of 2 mg	Aflibercept for intravitreal injection at a dose of 2 mg
Indicate if trials support application for marketing authorisation (yes/no)	Yes	Yes	Yes
Reported outcomes specified in the decision problem	• BCVA (the affected eye) • Overall visual function • Central subfield foveal thickness	• BCVA (the affected eye) • Overall visual function • Central subfield foveal thickness	• BCVA (the affected eye) • Overall visual function • Central subfield foveal thickness

	(CSFT) • Adverse effects of treatment • HRQoL (measured via the NEI VFQ-25)	(CSFT) • Adverse effects of treatment • HRQoL (measured via the NEI VFQ-25)	(CSFT) • Adverse effects of treatment
All other reported outcomes	• Presence of intra-retinal fluid (IRF)/sub-retinal fluid (SRF) • Proportion of patients receiving q12w injections up to Week 48 in the brolucizumab treatment arms • Predictive value of the first ("initial") q12w cycle for maintenance of q12w treatment up to Week 48 in the brolucizumab treatment arms • Presence of "q8w treatment need" (1 injection every 8 weeks), including assessment of q12w status for patients in the brolucizumab 3 mg and 6 mg treatment arms	• Presence of intra-retinal fluid (IRF)/sub-retinal fluid (SRF) • Proportion of patients receiving q12w injections up to Week 48 in the brolucizumab treatment arms • Predictive value of the first ("initial") q12w cycle for maintenance of q12w treatment up to Week 48 in the brolucizumab treatment arms • Presence of "q8w treatment need" (1 injection every 8 weeks), including assessment of q12w status for patients in the brolucizumab 3 mg and 6 mg treatment arms	• Presence of intra-retinal fluid (IRF)/sub-retinal fluid (SRF)

Abbreviations: HRQoL: health related quality of life; NEI: National Eye Institute; qXw: one injection every X weeks; VFQ: visual function questionnaire; wAMD: wet age-related macular degeneration.
Source: HAWK CSR;[78] HARRIER CSR;[79] OSPREY CSR.[80]

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

B.3.3.1 Trial design and methodology

Given their similarities in trial design and methodology, details of the trial design, methodology and results of the HAWK and HARRIER trials have been presented together in the following sections. Details of the trial design, methodology and results of the phase II OSPREY trial have been presented separately in Appendix I.

HAWK and HARRIER

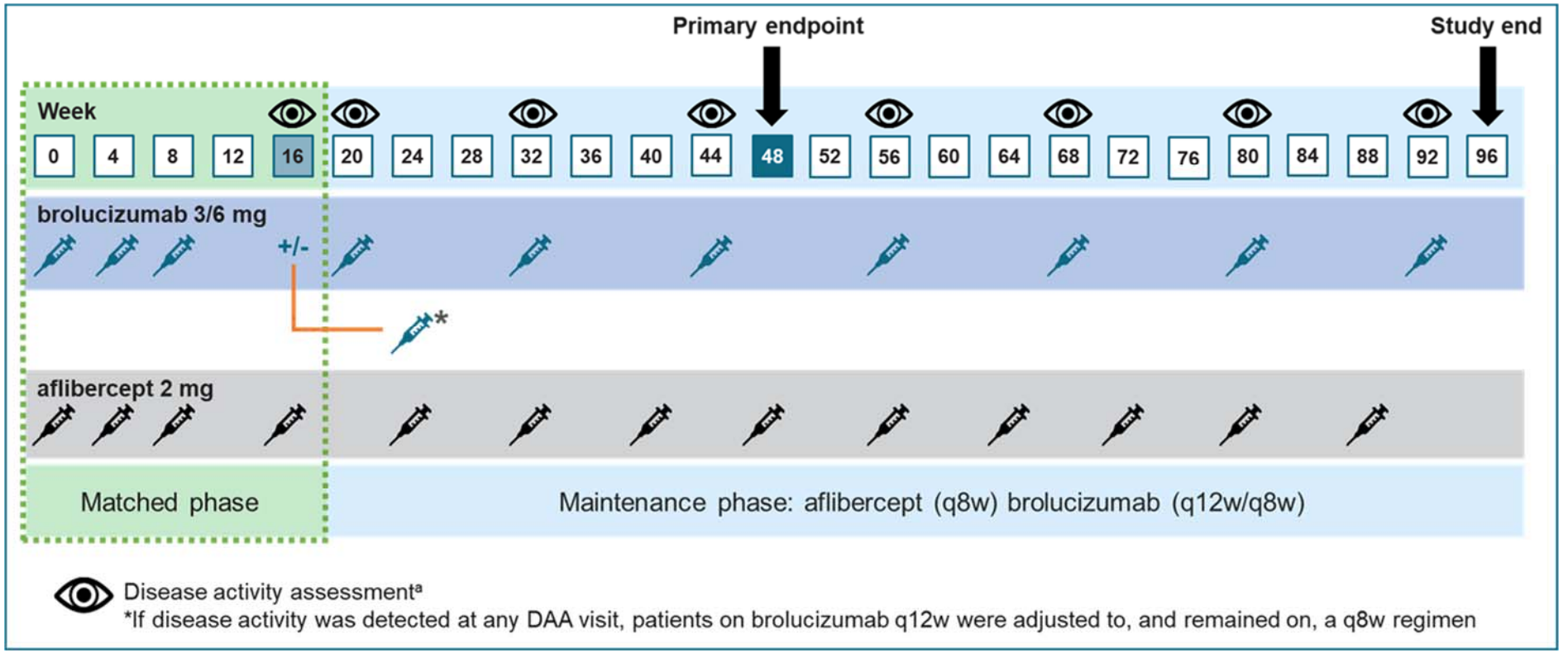
Both the HAWK and HARRIER trials were phase III, two-year, international, multicentre, randomised controlled trials comparing the efficacy and safety of brolucizumab versus aflibercept 2 mg. HAWK investigated the use of brolucizumab at doses of 3 mg and 6 mg whereas HARRIER investigated brolucizumab 6 mg alone. The anticipated licensed dose for brolucizumab is 6 mg; for completeness, results for the 3 mg arm in the HAWK trial are also presented in this submission.

The study populations of both trials consisted of anti-VEGF treatment naïve patients aged ≥50 years of age with active CNV due to AMD. Included patients had to have a Baseline BCVA in the study eye of between 78 and 23 letters (inclusive), assessed using Early Treatment Diabetic Retinopathy Study (ETDRS) testing.

A schematic of the study design of the HAWK and HARRIER trials is presented in Figure 3.1. Both trials primarily followed the same study design, differing only in the dosing of brolucizumab (HAWK investigated the use of brolucizumab at doses of 3 mg and 6mg whereas HARRIER investigated brolucizumab 6mg alone) and in the number of scheduled Disease Activity Assessment (DAA) visits and potential dosing interval adjustments (from Week 20, DAAs were conducted every 12 weeks in both trials; in HARRIER, additional DAAs occurred at Weeks 28, 40, 52, 64, 76 and 88).

Both studies included screening visits (2–14 days prior to Baseline) and a Baseline visit (Day 0), followed by monthly post-Baseline study visits from Week 4 until Week 96. After confirmation of eligibility at Baseline, patients were randomised to receive either brolucizumab 3 mg, brolucizumab 6 mg, or aflibercept 2 mg via IVT injection in a 1:1:1 ratio in HAWK, and randomised to receive either brolucizumab 6 mg or aflibercept 2 mg via IVT injection in a 1:1 ratio in HARRIER. Monthly loading dose injections were given for the first 3 months (Day 0, Week 4, and Week 8) across all arms of both trials, followed by maintenance dosing.

Figure 3.1: HAWK and HARRIER trial design



[a]The maintenance dosing regimen for brolucizumab is denoted as 'q12/q8w' whereby the treatment interval could be adjusted according to the patient's individual treatment need based on disease activity. All patients were allocated to q12w dosing and only re-allocated to q8w dosing if disease activity was detected via disease activity assessments (DAAs). DAAs were performed by masked Investigators at pre-specified visits. Once patients were adjusted to a q8w interval, they stayed on that interval until the end of the study (Week 96/Exit). Presence of disease activity was determined at the discretion of the masked Investigator and supported by protocol guidance based on functional and anatomical criteria. Additional DAAs occurred at Weeks 28, 40, 52, 64, 76, and 88 in HARRIER only, due to a health authority request.
Abbreviations: DAA: disease activity assessment; q8w: 8-week dosing interval; q12w: 12-week dosing interval.
Source: HAWK CSR;[78] HARRIER CSR.[79]

Maintenance dosing for aflibercept in both trials was administered at 8-week intervals (q8w). This was in line with the marketing authorisation for aflibercept in this indication and the guidance issued by NICE in TA294, at the time the trials were initiated.[3, 64]

Maintenance dosing for brolucizumab in both trials was 'q12/q8w', where the treatment interval could be adjusted according to the patient's individual treatment need, from 12- to 8-week intervals, based on DAA. DAAs were performed by masked Investigators at pre-specified visits. For patients receiving brolucizumab, the initial treatment interval following the loading phase was q12w, on which they remained if disease activity was not identified. If disease activity was identified by the Investigator at any of the DAAs, the dosing interval was adjusted to q8w. Once patients were adjusted to a q8w interval, they remained on that interval until the end of the study (Week 96/Exit) and could not return to a q12w interval. This likely represents a conservative strategy, given in UK clinical practice it is likely that patients may return to a q12w treatment interval if stable.

Whilst disease activity identification was at the discretion of the masked Investigator, the protocols provided guidance based on anatomical and functional parameters of disease activity. After Week 16 (first DAA), guidance was based on BCVA decline due to wAMD activity when compared with Week 12 (Table 3.2). Ultimately, the masked Investigator made the final treatment decisions based on clinical judgement, with anatomical assessments such as OCT and FA also used in clinical practice for treatment decisions.

Table 3.2: DAA criteria for HAWK and HARRIER

Study week(s)	DAA criteria
Week 16	• Decrease in BCVA of ≥ 5 letters compared with baseline • Decrease in BCVA of ≥ 3 letters and CSFT increase ≥ 75 µm compared with Week 12 • Decrease in BCVA of ≥ 5 letters due to wAMD disease activity compared with Week 12 • New or worse IRF/intraretinal cysts compared with Week 12
Weeks 20, 28[b], 32, 40[b], and 44	• Decrease in BCVA of ≥ 5 letters due to wAMD disease activity compared with Week 12
Weeks 52[b], 56, 64[b], 68, 76[b], 80, 88[b], and 92	• Decrease in BCVA of ≥ 5 letters due to wAMD disease activity compared with Week 48

[a]DAA criteria used to assign brolucizumab q12w or q8w dosing were developed based on findings from predictive data modelling combined with clinically meaningful vision and anatomical parameters of disease activity. Dynamic criteria identified in analyses of the PIER, EXCITE and CATT studies support DAA at Week 16 for early determination of patients suited to q8w dosing and to minimise patient reassignment at later time points. Subsequent DAA visits coincide with q12w dosing visits to allow reassignment to q8w dosing if patients experience BCVA decline due to wAMD at these time points. [b]Additional DAA visits included in the HARRIER study due to a health authority request.
Key: BCVA: best-corrected visual acuity; CSFT: central subfield thickness; DAA: disease activity assessment; IRF: intraretinal fluid; wAMD: wet age-related macular degeneration.
Source: HAWK CSR;[78] HARRIER CSR.[79]

The primary objective of both trials was to demonstrate that brolucizumab is non-inferior to aflibercept with respect to the mean change in BCVA from Baseline to Week 48. Non-inferiority was demonstrated if the lower limit of the 2-sided 95% confidence interval (CI) for the corresponding treatment difference (brolucizumab [6 mg or 3 mg] − aflibercept 2 mg) was greater than −4 letters.

An overview of the methodology of both trials is presented in Table 3.3.

Table 3.3: Summary of the trial methodology of the HAWK and HARRIER trials

Trial name	HAWK	HARRIER
Locations	International: 212 study centres across 11 countries	International: 147 study centres across 29 countries In the UK, there were [redacted]
Trial design	A two-year, randomised, double-masked, multicentre, three-arm phase III study comparing the efficacy and safety of brolucizumab 3 mg and brolucizumab 6 mg versus aflibercept in patients with wAMD	A two-year, randomised, double-masked, multicentre, two-arm phase III study comparing the efficacy and safety of brolucizumab 6 mg versus aflibercept in patients with wAMD
Eligibility criteria for participants	A summary of the key inclusion and exclusion criteria is provided below: **Key inclusion criteria** • Patients 50 years of age or older at time of screening • Active CNV lesions secondary to AMD that affected the central subfield in the study eye at time of screening • Total area of CNV (including both classic and occult components) must have comprised >50% of the total lesion area in the study eye at time of screening and confirmed by the CRC • IRF/SRF affecting the central subfield of the study eye at time of screening • BCVA between 78 and 23 letters, inclusive, in the study eye at time of screening and Baseline using ETDRS testing **Key exclusion criteria** • Any active intraocular or periocular infection or active intraocular inflammation in either eye at Baseline • Central subfield of the study eye affected by fibrosis or geographic atrophy or total area of fibrosis ≥ 50% of the total lesion in the study eye at time of screening • Subretinal blood affecting the foveal centre point and/or ≥ 50% of the lesion of the study eye at time of screening • Any approved or investigational treatment for wAMD in the study eye at any time • Retinal pigment epithelial rip/tear in the study eye at time of screening or Baseline or current vitreous haemorrhage or history of vitreous haemorrhage in the study eye within 4 weeks prior to Baseline Full details of the inclusion and exclusion criteria are listed in the HAWK (RTH258-C001) and HARRIER (RTH258-C002) CSRs[78, 79]	
Method of study drug administration	Brolucizumab and aflibercept were administered as intravitreal injection Dosing and number of patients • Brolucizumab 3 mg (n=358) • Brolucizumab 6 mg (n=360) • Aflibercept 2 mg (n=360) Loading dose (3 monthly doses) • Brolucizumab 3 mg (Day 0, Week 4, and Week 8) • Brolucizumab 6 mg (Day 0, Week 4, and Week 8) • Aflibercept 2 mg (Day 0, Week 4,	Brolucizumab and aflibercept were administered as intravitreal injection Dosing and number of patients • Brolucizumab 6 mg (n=370) • Aflibercept 2 mg (n=369) Loading dose (3 monthly doses) • Brolucizumab 6 mg (Day 0, Week 4, and Week 8) • Aflibercept 2 mg (Day 0, Week 4, and Week 8) Maintenance regimen • Brolucizumab 6 mg q12/q8w

	and Week 8) Maintenance regimen • Brolucizumab 3 mg q12/q8w • Brolucizumab 6 mg q12/q8w • Aflibercept 2 mg q8w	• Aflibercept 2 mg q8w
Permitted and disallowed concomitant medication	Rescue treatment • Rescue treatment was not permitted in the study eye • Treatment with ranibizumab was allowed in the fellow eye • Treatment with an approved anti-VEGF treatment for exudative AMD in the respective country was permitted in the fellow eye at the discretion of an Investigator Prohibited treatments • Study eye: intraocular or periocular corticosteroids; laser treatment for AMD; anti-VEGF therapy other than the study treatment • Fellow eye: unapproved or investigational treatment • Systemic: use of systemic corticosteroids for 30 or more consecutive days (except low stable doses of corticosteroids [defined as ≤10 mg prednisolone or equivalent dose], inhaled, nasal, or dermal steroids were permitted); anti-VEGF therapy • Any investigational drug, biologic, or device (with the exception of over-the-counter vitamins, supplements, or diets)	
Primary outcome	• The primary objective was to demonstrate that brolucizumab is non-inferior to aflibercept with respect to the change in BCVA from Baseline to Week 48	
Secondary and other outcomes	Key secondary objectives • To demonstrate that brolucizumab is not inferior to aflibercept with respect to the change in BCVA from Baseline averaged over the period Week 36 to Week 48 • To estimate the proportion of patients receiving q12w (1 injection every 12 weeks) up to Week 48 in the brolucizumab treatment arms • To estimate the predictive value of the first (“initial”) q12w cycle for maintenance of q12w treatment up to Week 48 in the brolucizumab treatment arms Other secondary objectives • To evaluate the efficacy of brolucizumab relative to aflibercept over the time period up to Week 96 by assessing changes in: o BCVA o Anatomical parameters of disease activity including CSFT and CNV area, presence of subretinal, intraretinal, and sub-RPE fluid o Presence of “q8w treatment need” (1 injection every 8 weeks), including assessment of q12w status for patients in the brolucizumab treatment arms • To assess visual function-related subject reported outcomes following treatment with brolucizumab relative to aflibercept • To assess the safety and tolerability of brolucizumab relative to aflibercept	
Pre-planned subgroups	• Age category (<75 years and ≥75 years) • Sex (male and female) • Baseline BCVA categories (≤55, 56–70, and ≥ 71 letters) • Baseline CSFT category (<400 and ≥400 µm) • Baseline lesion type (predominantly classic, minimally classic, occult) • Baseline CNV lesion size (<1.3 mm^2, 1.3–3.9 mm^2, >3.9 mm^2) • Baseline lesion size by lesion type	

	• Baseline fluid status (IRF, SRF, sub-RPE fluid) • HAWK only: o Japanese ethnicity: Japanese versus non-Japanese o Baseline polyp status (present/absent) from ICG assessment at Screening (study centres in Japan only)	
Duration of study and follow-up	• 96 weeks • The study was initiated on 8th December 2014 • The study was completed on 28th March 2018	• 96 weeks • The study was initiated on 28th July 2015 • The study was completed on 7th March 2018

Abbreviations: AMD: age-related macular degeneration; BCVA: best-corrected visual acuity; CNV: choroidal neovascularisation; CRC: Central Reading Center; CSFT: central subfield thickness; ETDRS: Early Treatment Diabetic Retinopathy Study; HRQoL: health related quality of life; ICG: indocyanine green; IRF: intraretinal fluid; NEI: National Eye Institute; qXw: one injection every X weeks; RPE: retinal pigment epithelium; SRF: subretinal fluid; VEGF: vascular endothelial growth factor; VFQ: visual function questionnaire; wAMD: wet age-related macular degeneration.
Source: HAWK CSR;[78] HARRIER CSR.[79]

B.3.3.2 Baseline characteristics

HAWK and HARRIER

Baseline demographics and disease characteristics of the patients included in the HAWK and HARRIER trials are presented in Table 3.4.

The demographic and disease characteristics of patients were similar between treatment arms in both trials. The mean age of patients included in HAWK was 76.5 years (range: 50 to 97 years), and in HARRIER was 75.1 years (range: 50 to 95 years), with majority being ≥75 years old (HAWK: 60.9%; HARRIER: 56.4%) at the time of study entry. A greater percentage of the patients were female than male (HAWK: 56.5%; HARRIER: 57.1%), and the patients were predominantly white (HAWK: 81.1%; HARRIER: 92.2%). In the HAWK trial, 14.3% of patients were of Japanese ancestry. The majority of the patients (HAWK: 75.0%; HARRIER: 70.8%) had unilateral wAMD with occult CNV lesions (HAWK: 57.7%; HARRIER: 50.3%) at Baseline.

Table 3.4: Baseline characteristics of patients in the HAWK and HARRIER trials (FAS) – Week 48 analysis

Trial name	HAWK			HARRIER	
Characteristic	**Brolucizumab 3 mg (n=358)**	**Brolucizumab 6 mg (n=360)**	**Aflibercept 2 mg (n=360)**	**Brolucizumab 6 mg (n=370)**	**Aflibercept 2 mg (n=369)**
Age (years)					
Mean (SD)	76.7 (8.28)	76.7 (8.95)	76.2 (8.80)	74.8 (8.58)	75.5 (7.87)
Median (range)	78.0 (50–96)	78.0 (51–97)	77.0 (51–96)	75.0 (50–94)	76.0 (52–95)
Min–Max	50–96	51–97	51–96	50–94	52–95
Age category (years) – n (%)					
<50	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
50-64	31 (8.7)	35 (9.7)	37 (10.3)	44 (11.9)	28 (7.6)
65-74	103 (28.8)	103 (28.6)	112 (31.1)	124 (33.5)	126 (34.1)
75-84	162 (45.3)	155 (43.1)	148 (41.1)	150 (40.5)	167 (45.3)
≥85	62 (17.3)	67 (18.6)	63 (17.5)	52 (14.1)	48 (13.0)
Sex – n (%)					
Male	148 (41.3)	155 (43.1)	166 (46.1)	160 (43.2)	157 (42.5)
Female	210 (58.7)	205 (56.9)	194 (53.9)	210 (56.8)	212 (57.5)
Race – n (%)					
White	302 (84.4)	285 (79.2)	287 (79.7)	340 (91.9)	341 (92.4)
Asian	44 (12.3)	61 (16.9)	53 (14.7)	22 (5.9)	23 (6.2)
Other	9 (2.5)	9 (2.5)	17 (4.7)	5 (1.4)	4 (1.1)
Multiple	1 (0.3)	3 (0.8)	1 (0.3)	2 (0.5)	1 (0.3)
Black or African American	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)	0 (0.0)
American Indian or Alaska Native	1 (0.3)	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)
Native Hawaiian or other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ethnicity – n (%)					
Not Hispanic or Latino	323 (90.2)	329 (91.4)	319 (88.6)	321 (86.8)	322 (87.3)
Hispanic/Latino	32 (8.9)	29 (8.1)	40 (11.1)	23 (6.2)	25 (6.8)
Unknown	2 (0.6)	1 (0.3)	1 (0.3)	18 (4.9)	17 (4.6)
Not reported	1 (0.3)	1 (0.3)	0 (0.0)	8 (2.2)	5 (1.4)
Japanese ancestry – n (%)					
Japanese	41 (11.5)	60 (16.7)	53 (14.7)	NR	NR
Non-Japanese	317 (88.5)	300 (83.3)	307 (85.3)	NR	NR

Time since diagnosis of wAMD (months) – n (%)					
<1	155 (43.3)	159 (44.2)	154 (42.8)	136 (36.9)	139 (37.7)
1–3	183 (51.1)	184 (51.1)	190 (52.8)	191 (51.8)	197 (53.4)
>3	20 (5.6)	17 (4.7)	16 (4.4)	42 (11.4)	33 (8.9)
Unilateral versus bilateral wAMD – n (%)					
Unilateral	269 (75.1)	271 (75.3)	268 (74.4)	268 (72.4)	255 (69.1)
Bilateral	89 (24.9)	89 (24.7)	92 (25.6)	102 (27.6)	114 (30.9)
BCVA (letters read)					
Mean (SD)	61.0 (13.57)	60.8 (13.66)	60.0 (13.92)	61.5 (12.59)	60.8 (12.93)
Median (range)	64.5 (23–85)	64.0 (23–85)	63.0 (16–83)	64.0 (22–78)	64.0 (23–79)
Min–Max	23–85	23–85	16–83	22–78	23–79
BCVA (letters read) – n (%)					
≤55	109 (30.4)	101 (28.1)	116 (32.2)	102 (27.6)	107 (29.0)
56-70	138 (38.5)	157 (43.6)	153 (42.5)	171 (46.2)	170 (46.1)
≥71	111 (31.0)	102 (28.3)	91 (25.3)	97 (26.2)	92 (24.9)
CSFT total (µm)					
Mean (SD)	61.0 (13.57)	60.8 (13.66)	60.0 (13.92)	473.6 (171.39)	465.3 (151.21)
Median (range)	427 (168–1392)	417 (217–1204)	425 (215–1082)	434 (200–1192)	442 (206–1319)
Min–Max	168–1392	217–1204	215–1082	200–1192	206–1319
CSFT total (µm) – n (%)					
<400	157 (43.9)	157 (43.6)	146 (40.6)	148 (40.0)	130 (35.2)
≥400	201 (56.1)	203 (56.4)	214 (59.4)	222 (60.0)	239 (64.8)
Type of CNV – n (%)					
Predominantly classic	122 (34.1)	113 (31.4)	116 (32.3)	154 (41.6)	144 (39.5)
Minimally classic	32 (8.9)	39 (10.8)	34 (9.5)	33 (8.9)	34 (9.3)
Occult	204 (57.0)	208 (57.8)	209 (58.2)	183 (49.5)	187 (51.2)
Area of lesion associated with CNV (mm^2)					
Mean (SD)	4.5 (4.7)	4.6 (4.1)	4.4 (3.7)	2.6 (2.8)	2.9 (4.0)
Median (range)	3.2 (0–28)	3.4 (0–20)	3.7 (0–19)	1.5 (0–14)	1.6 (0–34)
Min–Max	0–28	0–20	0–19	0.022–13.9	0–33.6
Presence of fluid – n (%)					
SRF	244 (68.2)	250 (69.4)	245 (68.1)	251 (67.8)	268 (72.6)
IRF/cyst	196 (54.7)	194 (53.9)	194 (53.9)	149 (40.4)	139 (37.7)
SRF and/or IRF	330 (92.2)	334 (92.8)	336 (93.3)	330 (89.2)	332 (90.0)
Sub-RPE fluid	147 (41.1)	168 (46.7)	158 (43.9)	125 (33.8)	127 (34.4)
PCV (Japanese patients only)	20 (50.0)	39 (66.1)	30 (56.6)	NR	NR

Abbreviations: BCVA: best-corrected visual acuity; CSFT: central subfield thickness; CNV: choroidal neovascularisation; FAS: full analysis set; IRF: intraretinal fluid; PCV: polypoidal choroidal vasculopathy; RPE: retinal pigment epithelium; SD: standard deviation; SRF: subretinal fluid.

Source: HAWK CSR;[78] HARRIER CSR;[79] Dugel et al. 2019.[76]

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

B.3.4.1 Trial populations

HAWK and HARRIER

Definitions of the study populations analysed in HAWK and HARRIER are presented in Table 3.5.

Table 3.5: Trial populations used for the analysis of outcomes in HAWK and HARRIER

Analysis set	Description
All enrolled analysis set	• All patients who signed an informed consent and were assigned a subject number. This analysis set was used to summarise subject disposition and pre-treatment AEs
All randomised analysis set (RAN)	• All patients who were randomised in the IRT • This analysis set was used to summarise protocol deviations, analysis restrictions, medical history, and prior medications
Full analysis set (FAS)	• All randomised patients who received at least 1 intravitreal injection of study treatment • The FAS served as the primary analysis set for all efficacy analyses, with LOCF imputation of missing/censored (after start of alternative anti-VEGF treatment) BCVA values. • The FAS represented the analysis set that was as close as possible to the intent-to-treat principle of including all randomised patients
Safety analysis set (SAF)	• **A**ll patients who received at least 1 intravitreal injection
Per protocol analysis set (PPS)	• Subset of the FAS that excluded patients with protocol deviations and violations of analysis requirements that were expected to majorly affect the validity of the assessment of efficacy at Week 48

Abbreviations: AE: adverse event; BCVA: best-corrected visual acuity; RAN: randomised analysis set; FAS: full analysis set; IRT: interactive response technology; LOCF: last observation carried forward; SAF: safety analysis set; PPS: per protocol analysis set; VEGF: vascular endothelial growth factor.
Source: HAWK CSR;[78] HARRIER CSR.[79]

In HAWK, a total of 1775 patients were screened, of which there were 693 screen failures. The most common reasons for screening failure were related to the anatomical diagnostic/severity criteria for the study: 227 patients with no active CNV lesion secondary to AMD, 217 patients with total area of CNV ≤50% of the total lesion area, 139 patients with BCVA >78 or <23 letters at screening and/or Baseline, and 112 patients with no IRF or SRF affecting the central subfield.

Overall, 1082 patients were randomised 1:1:1 to brolucizumab 3 mg (n=360), brolucizumab 6 mg (n=361) and aflibercept 2 mg (n=361), of which 1078 patients (99.6%) received study treatment and 994 patients (91.9%) completed the Week 48 visit. In total, 114 patients (10.5%) discontinued study treatment prior to Week 48. The most common reasons for study treatment discontinuation were patient withdrawal, and adverse events. Study treatment discontinuations due to patient withdrawal occurred in 19 patients (5.3%) in the brolucizumab 6 mg arm, 10

patients (2.8%) in the brolucizumab 3 mg arm, and 11 patients (3.0%) in the aflibercept 2 mg arm. Study treatment discontinuations due to adverse events occurred in 11 patients (3.0%) in the brolucizumab 6 mg arm, 8 patients (2.2%) in the brolucizumab 3 mg arm, and 8 patients (2.2%) in the aflibercept 2 mg arm.

In HARRIER, a total of 1048 patients were screened, of which there were 305 screen failures. The most common reasons for screen failures were related to not meeting the anatomical diagnostic/severity criteria for the study: 82 patients with no active CNV lesion secondary to AMD, 118 patients with total area of CNV ≤ 50% of the total lesion area, 62 patients with subretinal blood affecting the central subfield and/or ≥50% of the lesion, 51 patients with central subfield affected by fibrosis or GA, 27 patients had no IRF or SRF affecting the central subfield, and 20 patients had total area of fibrosis <50% of the total lesion.

Overall, 743 patients were randomised 1:1 to brolucizumab 6 mg (n=372) and aflibercept 2 mg (n=371), of which 739 patients (99.5%) received study treatment and 706 patients (95.0%) completed the week 48 visit. In total, 49 patients (6.6%) discontinued study treatment prior to Week 48. The most common reasons for study treatment discontinuation were AEs, occurring in 3.2% of patients in the brolucizumab 6 mg arm and 1.1% of patients in in the aflibercept 2 mg arm (brolucizumab 6 mg: 3.2%; aflibercept 2 mg: 1.1%).

A summary of the numbers of patients included in each analysis set by treatment arm in the HAWK and HARRIER trials is presented in Table 3.6.

Table 3.6: Analysis sets (all enrolled analysis set) – Week 48 analysis

Trial name	HAWK			HARRIER	
Analysis set	**Brolucizumab 3 mg, n (%)**	**Brolucizumab 6 mg, n (%)**	**Aflibercept 2 mg, n (%)**	**Brolucizumab 6 mg, n (%)**	**Aflibercept 2 mg, n (%)**
All enrolled analysis set	360	361	361	372	371
RAN	360 (100.0)	361 (100.0)	361 (100.0)	372 (100.0)	371 (100.0)
FAS	358 (99.4)	360 (99.7)	360 (99.7)	370 (99.5)	369 (99.5)
SAF	358 (99.4)	360 (99.7)	360 (99.7)	370 (99.5)	369 (99.5)
PPS	325 (90.3)	328 (90.9)	312 (86.4)	351 (94.4)	341 (91.9)

Abbreviations: RAN: randomised analysis set; FAS: full analysis set; SAF: safety analysis set; PPS: per protocol analysis set.
Source: HAWK CSR;[78] HARRIER CSR.[79]

B.3.4.2 Statistical analysis

HAWK and HARRIER

The statistical analyses used in the HAWK and HARRIER trials for the primary and secondary endpoints, alongside sample size calculations and methods for handling missing data are presented in Table 3.7.

Table 3.7: Statistical methods for primary analyses of the HAWK and HARRIER trials

Trial name	HAWK	HARRIER
Hypothesis objective	• The primary efficacy endpoint was the change in BCVA from Baseline to Week 48 • The first key secondary efficacy endpoint was the average change in BCVA from Baseline over the period of Week 36 through Week 48 • The statistical hypotheses for the primary and first key secondary efficacy	

	endpoints were intended to demonstrate the non-inferiority of brolucizumab to aflibercept
Statistical analysis	• Non-inferiority was demonstrated (i.e. the null hypothesis was rejected) if the lower limit of the 2-sided 95% CI for the corresponding treatment difference (brolucizumab [6 mg or 3 mg] − aflibercept 2 mg) was greater than −4 letters
Sample size, power calculation	• A sample size of 297 patients per treatment arm was considered sufficient to demonstrate non-inferiority (margin = 4 letters) of brolucizumab 3 mg/6 mg versus aflibercept 2 mg with respect to the change in BCVA from Baseline to Week 48 at a 2-sided alpha level of 0.05 with a power of approximately 90%, assuming equal efficacy and a common SD of 15 letters • A power of at least 90% was expected for the first key secondary efficacy endpoint, assuming that averaging over the 4 time points would not lead to an increase in the SD • To account for a dropout rate of 10%, a total of 330 patients were planned for randomisation into each treatment arm (i.e. a total of 990 and 660 randomised patients in the HAWK and HARRIER trials, respectively)
Data management, patient withdrawals	• Patients could voluntarily withdraw from the study for any reason at any time. A patient could be considered withdrawn if he or she stated an intention to withdraw, failed to return for visits, or became lost to follow-up for any other reason • If premature withdrawal occurred for any reason, the Investigator was obliged to determine the primary reason for the subject's premature withdrawal from the study and record this information on the Study Completion eCRF. Patients who withdrew or were withdrawn from the study should have completed all procedures indicated at the Week 96 visit. Patients who were prematurely withdrawn from the study were not replaced • Patients could voluntarily discontinue study treatment for any reason at any time. Patients who discontinued study treatment were not considered withdrawn from the study. Rather, these patients were expected to continue with the study visits and procedures if such procedures did not pose a risk to the well-being of the patients • For patients who were lost to follow-up (i.e., those patients whose status was unclear because they failed to appear for study visits without stating an intention to withdraw), the Investigator was required to show due diligence by documenting in the source documents all steps taken to contact the subject, e.g., dates of telephone calls, registered letters.

Abbreviations: BCVA: best-corrected visual acuity; eCRF: electronic case report form; SD: standard deviation.
Source: HAWK CSR;[78] HARRIER CSR.[79]

B.3.4.3 Participant flow

Full details of the participant flow (CONSORT diagrams) for the HAWK, HARRIER and OSPREY trials can be found in Appendix D.

B.3.5 Quality assessment of the relevant clinical effectiveness evidence

An overview of the quality assessment conducted for HAWK, HARRIER and OSPREY is presented in Table 3.8, based on the CSRs available for the three trials. All three trials were deemed of high quality, with all elements of the quality assessment reported adequately for assessment.

Table 3.8: Quality assessment of the relevant clinical effectiveness evidence

Trial	HAWK	HARRIER	OSPREY

Was randomisation carried out appropriately?	Yes	Yes	Yes
Was the concealment of treatment allocation adequate?	Yes	Yes	Yes[a]
Where the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes	Yes
Were the care providers, participants, and outcome assessors blind to treatment allocation?	Yes	Yes	Yes
Were there any unexpected imbalances in drop-outs between groups?	Yes	Yes	Yes
Is there any evidence to suggest the authors measured more outcomes than they reported?	Yes	Yes	Yes
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes	Yes

[a]Treatment allocation was unmasked in OSPREY after Week 40, when q12w dosing was explored for brolucizumab.
Source: Adapted from Systematic reviews: CRD's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination).

B.3.6 Clinical effectiveness results of HAWK and HARRIER

Summary

- **Brolucizumab achieved clinically meaningful and consistent visual gains and a majority of patients were maintained on a q12w dosing interval immediately following the loading dose phase**
  - The primary endpoint of non-inferiority for brolucizumab versus aflibercept in terms of mean change in BCVA from Baseline to Week 48 was met in both HAWK and HARRIER with highly significant p-values
  - At Week 48, the least squares (LS) mean change in BCVA from Baseline was 6.6 versus 6.8 letters, and 6.9 versus 7.6 letters, for brolucizumab 6 mg versus aflibercept 2 mg in HAWK and HARRIER, respectively ($p<0.0001$ for both comparisons, non-inferior 4-letter margin)
  - More than 50% (56% in HAWK and 51% in HARRIER) of brolucizumab 6 mg patients were exclusively maintained on a q12w regimen immediately following the loading dose phase through to Week 48, and for those on a q12w regimen at Week 48 there was a >75% probability of maintaining on this regimen at Week 96
- **Brolucizumab was superior to aflibercept in terms of improvements in central subfield retinal thickness (CSFT), retinal fluid (intraretinal fluid [IRF] and/or subretinal fluid [SRF]) and disease activity parameters:**
  - An increase in CSFT or retinal fluid is an important indicator of disease activity, as fluid accumulation and oedema may result in vision deterioration
  - 30% fewer patients receiving brolucizumab had disease activity at Week 16 compared to those receiving aflibercept. At Week 16, the probability of disease activity in patients treated with brolucizumab 6 mg was significantly lower than that for aflibercept 2 mg (24.0% versus 34.5% in HAWK, $p=0.0013$; and 22.7% versus 32.2% in HARRIER, $p=0.0021$)
  - Statistically significantly fewer patients receiving brolucizumab had IRF and/or SRF at Week 16 and Week 48, with differences maintained to Week 96. At Week 16, the proportion of patients with IRF and/or SRF was 33.9% for brolucizumab 6 mg versus 52.2% for aflibercept 2 mg in HAWK ($p<0.0001$), and 29.4% versus 45.1% in HARRIER ($p<0.0001$). At Week 48, the proportion of patients with IRF and/or SRF was 31.2% for brolucizumab 6 mg versus 44.6% for aflibercept 2 mg in HAWK ($p=0.0002$), and 25.8% versus 43.9% in HARRIER ($p<0.0001$)
  - Brolucizumab showed a statistically significantly superior reduction in CSFT compared with aflibercept at Week 16 and Week 48, with differences maintained at Week 96
- **Brolucizumab achieved a similar improvement in HRQoL compared with aflibercept**
  - A comparable change from Baseline in VFQ-25 was observed for brolucizumab 6 mg and aflibercept 2 mg in both HAWK and HARRIER at Weeks 24, 48 and 96
- **Results from the OSPREY trial support the efficacy and safety of brolucizumab in wAMD**
  - During the matched q8w phase, the improvements in BCVA in brolucizumab-treated eyes were comparable to aflibercept-treated eyes, with more stable CSFT reductions, receipt of fewer unscheduled treatments, and higher rates of fluid resolution
  - Full details of the OSPREY trial are presented in Appendix I.

B.3.6.1 Primary endpoint

B.3.6.1.1 Change in BCVA from Baseline to Week 48

Brolucizumab achieved clinically meaningful and consistent visual gains, meeting the primary endpoint of non-inferiority with respect to change in BCVA from Baseline to Week 48 in both the HAWK and the HARRIER trials

In HAWK, treatment with brolucizumab resulted in an LS-mean estimate of the change in BCVA from Baseline to Week 48 of 6.1 letters in the brolucizumab 3 mg arm (95% CI: 4.8–7.5) and 6.6 letters in the brolucizumab 6 mg arm (95% CI: 5.2–8.0), versus 6.8 letters (95% CI: 5.4–8.2) in the aflibercept 2 mg arm ($p<0.0001$, non-inferiority 4-letter margin). In HARRIER, the LS-mean estimate of the change in BCVA from Baseline to Week 48 was 6.9 letters (95% CI: 5.7–8.1) in the brolucizumab 6 mg arm versus 7.6 letters (95% CI: 6.4–8.8) in the aflibercept 2 mg arm (Table 3.9).

The results from both trials for the primary endpoint analysis using the FAS were consistent with the corresponding supporting analysis using the PPS (Table 3.9). All analyses were conducted with LOCF imputation of missing/censored (after start of alternative anti-VEGF treatment) BCVA values.

Treatment with brolucizumab required fewer injections to achieve a similar improvement in BCVA, with a majority of patients maintained on a q12w dosing interval immediately following the loading dose phase

Data on the number of injections received by patients in each arm of the HAWK and HARRIER trials are presented in Section B.3.10.1. Treatment with brolucizumab was associated with a fewer number of injections required versus aflibercept over 2 years. Based on the results of the primary endpoint, treatment with brolucizumab provided comparable efficacy to aflibercept with respect to change in BCVA, which was achieved by administering fewer injections over a 2-year period. The differences in the number of active injections between brolucizumab and aflibercept were driven by differences in the injection schedules, with a majority of brolucizumab 6 mg patients maintained on a q12w dosing schedule immediately following the loading dose phase (see Section B.3.6.2.2).

Table 3.9: BCVA (letters read): summary statistics and ANOVA for change from Baseline at Week 48 for the study eye (FAS-LOCF and PPS-LOCF)

Trial name	HAWK			HARRIER	
FAS population	**Brolucizumab 3 mg (n=358)**	**Brolucizumab 6 mg (n=360)**	**Aflibercept 2 mg (n=360)**	**Brolucizumab 6 mg (n=370)**	**Aflibercept 2 mg (n=369)**
Change in BCVA from Baseline to Week 48					
Mean (SD)	5.9 (13.49)	6.4 (14.40)	7.0 (13.16)	6.9 (11.47)	7.6 (12.47)
Median (range)	7.0 (-57, 51)	7.5 (-69, 52)	8.0 (-57, 54)	8.0 (-57, 38)	8.0 (-37, 50)
95% CI for mean	4.5, 7.3	4.9, 7.9	5.6, 8.3	5.8, 8.1	6.3, 8.9
LSM (Pairwise ANOVA) (brolucizumab 3 mg versus aflibercept 2 mg)					
LSM (SE)	6.1 (0.69)	-	6.8 (0.69)	-	-
95% CI for LSM	4.8, 7.5	-	5.4, 8.1	-	-
LSMD (SE)	-0.6 (0.98)			-	-
95% CI for LSMD	-2.5, 1.3			-	-
p-value for treatment difference (2-sided)	0.5237			-	-
p-value for non-inferiority (4 letter margin) (1-sided)	0.0003			-	-
LSM (Pairwise ANOVA) (brolucizumab 6 mg versus aflibercept 2 mg)					
LSM (SE)	-	6.6 (0.71)	6.8 (0.71)	6.9 (0.61)	7.6 (0.61)
95% CI for LSM	-	5.2, 8.0	5.4, 8.2	5.7, 8.1	6.4, 8.8
LSMD (SE)	-	-0.2 (1.00)		-0.7 (0.86)	
95% CI for LSMD	-	-2.1, 1.8		-2.4, 1.0	
p-value for treatment difference (2-sided)	0.8695			0.4199	
p-value for non-inferiority (4 letter margin) (1-sided)	<0.0001			0.0001	
PPS population	**Brolucizumab 3 mg (n=325)**	**Brolucizumab 6 mg (n=328)**	**Aflibercept 2 mg (n=312)**	**Brolucizumab 6 mg (n=351)**	**Aflibercept 2 mg (n=341)**
Change in BCVA from Baseline to Week 48					
Mean (SD)	6.3 (13.37)	6.6 (14.68)	7.4 (12.71)	7.0 (11.24)	7.8 (12.49)
Median (range)	7.0 (-56, 51)	8.0 (-69, 52)	8.0 (-57, 51)	8.0 (-57, 38)	8.0 (-35, 50)

95% CI for mean	4.9, 7.8	5.0, 8.2	6.0, 8.8	5.8, 8.2	6.5, 9.1
LSM (pairwise ANOVA) (brolucizumab 3 mg versus aflibercept 2 mg)					
LSM (SE)	6.5 (0.71)	-	7.2 (0.73)	-	-
95% CI for LSM	5.1, 7.9	-	5.7, 8.6	-	-
LSMD (SE)	-0.6 (1.02)			-	-
95% CI	-2.6, 1.4			-	-
p-value for treatment difference (2-sided)	0.5355			-	-
p-value for non-inferiority (4 letter margin) (1-sided)	0.0005			-	-
LSM (pairwise ANOVA) (brolucizumab 6 mg versus aflibercept 2 mg)					
LSM (SE)	-	6.9 (0.74)	7.1 (0.76)	7.0 (0.62)	7.8 (0.63)
95% CI for LSM	-	5.4, 8.3	5.7, 8.6	5.8, 8.2	6.6, 9.0
LSMD (SE)	-	-0.3 (1.06)		-0.8 (0.88)	
95% CI	-	-2.4, 1.8		-2.5, 1.0	
p-value for treatment difference (2-sided)	0.7844			0.3771	
p-value for non-inferiority (4 letter margin) (1-sided)	0.0003			0.0001	

Abbreviations: ANOVA: analysis of variance; BCVA: best-corrected visual acuity; CI: confidence interval; FAS: full analysis set; LOCF: last observation carrier forward; LSM: least squares mean; LSMD: least squares mean difference; PPS: per protocol set; SD: standard deviation; SE: standard error.
Source: HAWK CSR;[78] HARRIER CSR;[79] Dugel et al. 2019.[76]

B.3.6.2 Key secondary endpoints

B.3.6.2.1 Average change in BCVA from Baseline over the period Week 36 to Week 48

Brolucizumab demonstrated a non-inferior change in BCVA from Baseline over the period of Week 36–48 in both HAWK and HARRIER versus aflibercept

Both studies confirmed the hypothesis of non-inferiority of brolucizumab to aflibercept for the key secondary endpoint of mean BCVA change from Baseline over the period of Week 36 through to Week 48.

This endpoint was assessed in order to account for differences in the dosing intervals between treatment arms following the matched loading dose phase, where the time from last dose received and Week 48 was not the same between the treatment arms. Outcomes of this analysis therefore demonstrated that non-inferiority with brolucizumab versus aflibercept was not due to differences in time between last dose received and Week 48.

In the HAWK trial, the LS-mean estimate of the change in BCVA from Baseline to the period of Week 36 to Week 48 was 6.2 letters in the brolucizumab 3 mg arm (95% CI: 4.9–7.5), 6.7 letters in the brolucizumab 6 mg arm (95% CI: 5.4–8.0), and 6.7 letters for the aflibercept 2 mg arm (95% CI: 5.4–8.1). In HARRIER, the LS-mean estimate of the change in BCVA from Baseline to the period of Week 36 to Week 48 was 6.5 letters in the brolucizumab 6 mg arm (95% CI: 5.4–7.7) and 7.7 letters for the aflibercept 2 mg arm (95% CI: 6.6–8.9). The results from both trials for the primary endpoint using the FAS were consistent with the corresponding analysis using the PPS (Table 3.10).

Table 3.10: Best-corrected visual acuity (letters read): summary statistics and ANOVA for average change from Baseline over the period Week 36 through Week 48 (FAS-LOCF and PPS-LOCF)

Trial name	HAWK			HARRIER	
FAS population	**Brolucizumab 3 mg (n=358)**	**Brolucizumab 6 mg (n=360)**	**Aflibercept 2 mg (n=360)**	**Brolucizumab 6 mg (n=370)**	**Aflibercept 2 mg (n=369)**
Change in BCVA from Baseline over the period Week 36 through Week 48					
Mean (SD)	6.0 (13.37)	6.5 (13.85)	6.9 (12.61)	6.6 (11.10)	7.7 (11.81)
Median (range)	7.0 (-64, 54)	7.3 (-67, 50)	7.6 (-53, 52)	7.5 (-58, 37)	8.3 (-38, 47)
95% CI for mean	4.6, 7.4	5.1, 8.0	5.6, 8.2	5.4, 7.7	6.5, 8.9
LSM (Pairwise ANOVA) (brolucizumab 3 mg versus aflibercept 2 mg)					
LSM (SE)	6.2 (0.67)	-	6.7 (0.67)	-	-
95% CI for LSM	4.9, 7.5	-	5.4, 8.0	-	-
LSMD (SE)	-0.5 (0.95)			-	-
95% CI for LSMD	-2.4, 1.3			-	-
p-value for treatment difference (2-sided)	0.5829			-	-
p-value for non-inferiority (4 letter margin) (1-sided)	0.0001			-	-
LSM (Pairwise ANOVA) (brolucizumab 6 mg versus aflibercept 2 mg)					
LSM (SE)	-	6.7 (0.68)	6.7 (0.68)	6.5 (0.58)	7.7 (0.58)
95% CI for LSM	-	5.4, 8.0	5.4, 8.1	5.4, 7.7	6.6, 8.9
LSMD (SE)	-	0.0 (0.96)		-1.2 (0.82)	
95% CI for LSMD	-	-1.9, 1.9		-2.8, 0.5	
p-value for treatment difference (2-sided)	0.9791			0.1582	
p-value for non-inferiority (4 letter margin) (1-sided)	<0.0001			0.0003	
PPS population	**Brolucizumab 3 mg (n=325)**	**Brolucizumab 6 mg (n=328)**	**Aflibercept 2 mg (n=312)**	**Brolucizumab 6 mg (n=351)**	**Aflibercept 2 mg (n=341)**
Change in BCVA from Baseline over the period Week 36 through Week 48					
Mean (SD)	6.4 (13.11)	6.8 (13.98)	7.3 (12.20)	6.7 (10.96)	7.9 (11.79)
Median (range)	7.3 (-56, 54)	7.6 (-67, 50)	8.0 (-53, 52)	7.5 (-58, 37)	8.5 (-33, 47)
95% CI for mean	(5.0, 7.9)	(5.2, 8.3)	(5.9, 8.7)	(5.5, 7.8)	(6.6, 9.1)

LSM (pairwise ANOVA) (brolucizumab 3 mg versus aflibercept 2 mg)					
LSM (SE)	6.7 (0.69)	-	7.1 (0.70)	-	-
95% CI for LSM	5.3, 8.0	-	5.7, 8.4	-	-
LSMD (SE)	-0.4 (0.99)			-	-
95% CI	-2.3, 1.5			-	-
p-value for treatment difference (2-sided)	0.6869			-	-
p-value for non-inferiority (4 letter margin) (1-sided)	0.0001			-	-
LSM (pairwise ANOVA) (brolucizumab 6 mg versus aflibercept 2 mg)					
LSM (SE)	-	7.0 (0.71)	7.1 (0.72)	6.7 (0.59)	7.9 (0.60)
95% CI for LSM	-	5.6, 8.4	5.6, 8.5	5.5, 7.8	6.7, 9.0
LSMD (SE)	-	-0.1 (1.01)		-1.2 (0.84)	
95% CI	-	-2.0, 1.9		-2.8, 0.5	
p-value for treatment difference (2-sided)	0.9553			0.1625	
p-value for non-inferiority (4 letter margin) (1-sided)	<0.0001			0.0004	

Abbreviations: ANOVA: analysis of variance; BCVA: best-corrected visual acuity; CI: confidence interval; FAS: full analysis set; LOCF: last observation carrier forward; LSM: least squares mean; LSMD: least squares mean difference; PPS: per protocol set; SD: standard deviation; SE: standard error.

B.3.6.2.2 Source: HAWK CSR;[78] HARRIER CSR;[79] Dugel et al. 2019.[76] Proportion of q12w treatment status at Week 48 for patients randomised to brolucizumab ("maintaining on q12w")

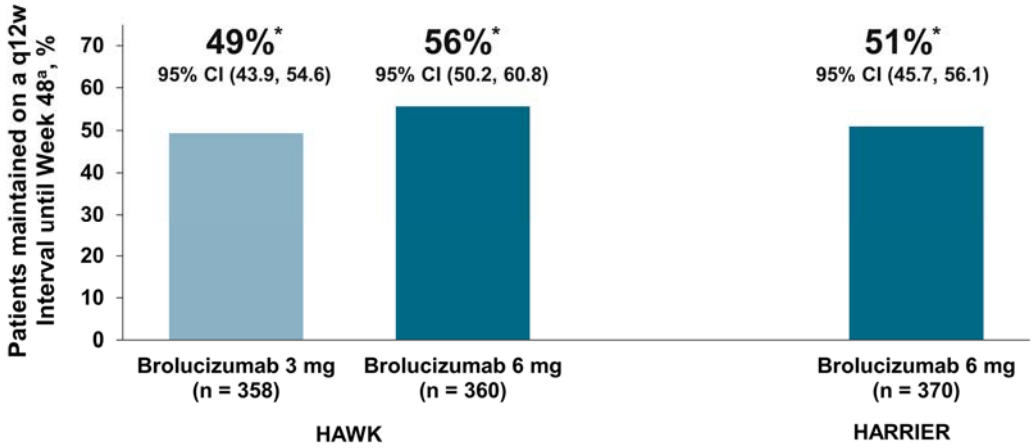
Over 50% of brolucizumab 6mg-treated patients were exclusively maintained on a q12w dose interval (loading through Week 48), requiring a lower frequency of injections than those treated with aflibercept

The third brolucizumab loading injection was followed by a 12-week interval, to identify the subject's individual anti-VEGF therapy need. In this interval, DAAs were performed after 8 and 12 weeks. If disease activity was identified by the Investigator at any of the DAAs, the dosing interval was adjusted to q8w. Once patients were adjusted to a q8w interval, they remained on that interval until the end of the study (Week 96/Exit) and could not return to a q12w interval. Patients without disease activity during the initial q12w cycle were considered to be suitable for q12w and continued on this treatment frequency. Based on the assumption of stable treatment need, subsequent monitoring of the adequacy of the q12w treatment frequency was limited to an assessment of disease activity at the end of each q12w cycle, representing the most likely trough in terms of disease control. Thus, patients remaining on q12w at Week 48 had no detectable disease activity at disease activity assessments from Baseline to Week 48. Overall, the

brolucizumab 6 mg arm showed a higher probability of maintaining on a q12w regimen compared to the brolucizumab 3 mg arm across all subgroups.

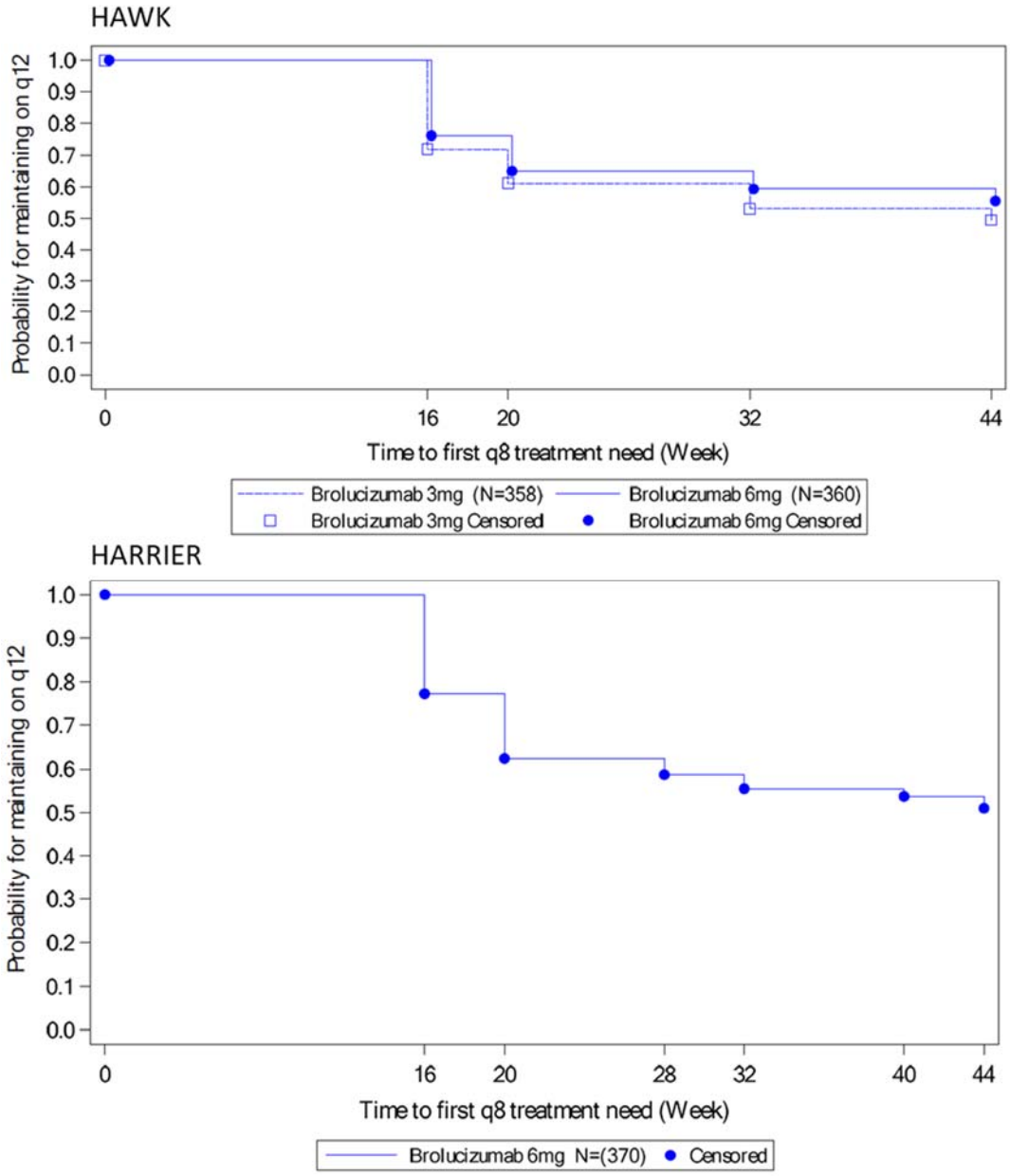
The estimated probability of a patient remaining on the q12w dosing interval up to Week 48 was 49.4% in the brolucizumab 3 mg arm (HAWK), and 55.6% (HAWK) and 51.0% (HARRIER) in the brolucizumab 6 mg arms (Figure 3.3). This estimate was based on the "efficacy/safety" approach, where censored data attributable to a lack of efficacy and/or safety were imputed with "q8w need=yes" at the next DAA visit.

Figure 3.2: Proportion of patients maintained on a q12w interval until Week 48 in HAWK and HARRIER



FAS "Efficacy/Safety approach". The numbers are based on estimated percentages from Kaplan Meier analysis.
*In case of missing/confounded data due to lack of efficacy and/or safety a 'q8-need' is allocated, otherwise censoring is applied.
Abbreviations: CI: confidence interval; q12w: one injection every 12 weeks.
Source: Monés et al. 2018.[81]

Figure 3.3: Time-to-first q8w treatment need: Kaplan-Meier plot for brolucizumab 6 mg patients (FAS-"efficacy/safety" approach)



Abbreviations: FAS: full analysis set; q8w: every 8 weeks.
Source: HAWK CSR;[78] HARRIER CSR.[79]

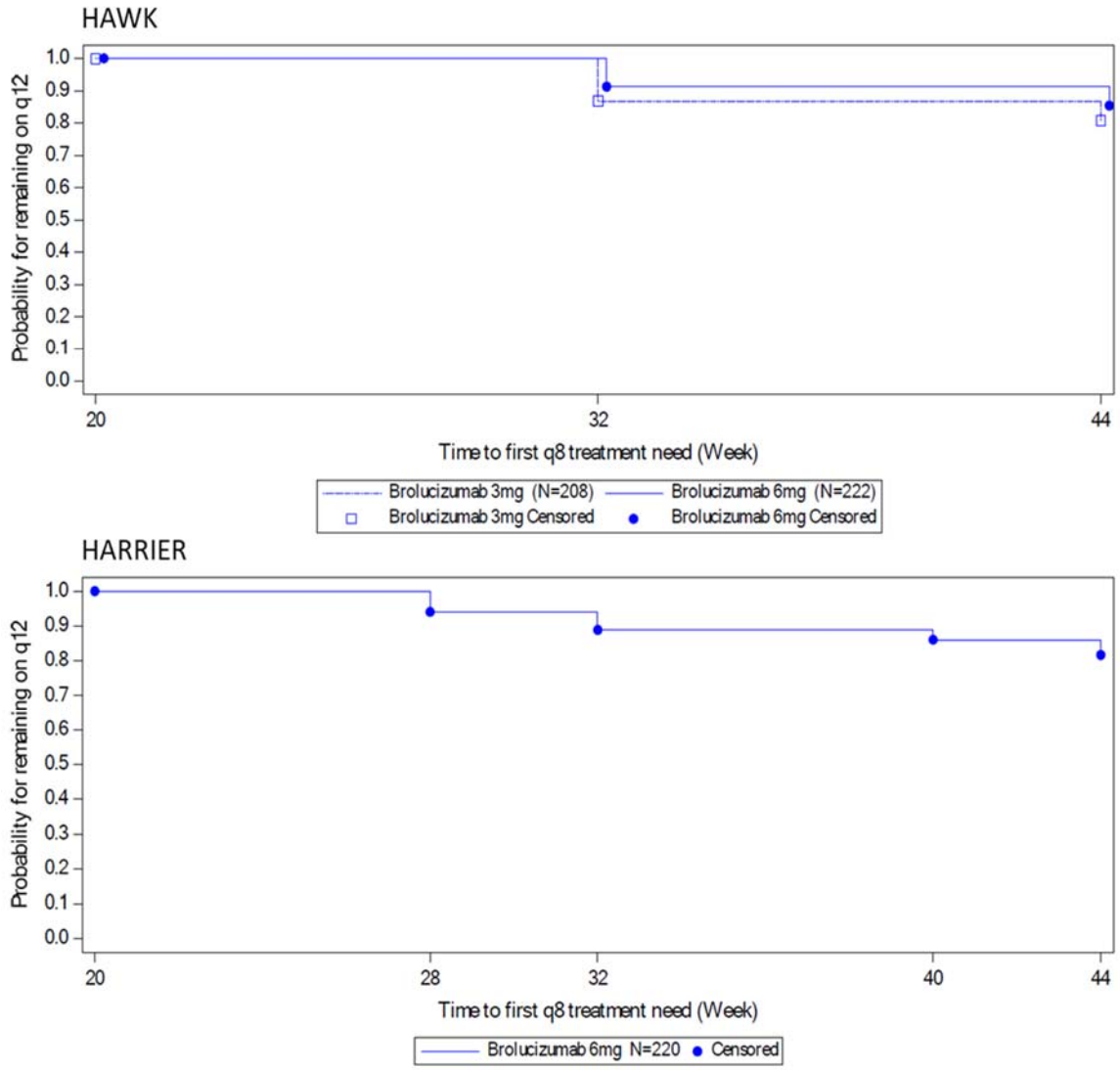
B.3.6.2.3 Predictive value of the initial q12w cycle

A high predictive value was associated with the initial q12w cycle for patients treated with brolucizumab, with over 80% of brolucizumab 6 mg patients who successfully completed the first q12w interval remaining on q12w interval until Week 48, allowing ophthalmology clinics to plan ahead with regards to clinic capacity

Among patients with no q8w need during the initial q12w cycle, the estimate of the probability for a patient to be maintained on q12w regimen up to Week 48 was 80.9% (HAWK) in the brolucizumab 3 mg arm, and 85.4% (HAWK) and 81.7% (HARRIER) in the brolucizumab 6 mg arms, based on the "efficacy/safety" approach (Figure 3.4). Additionally, the majority of q8w need

up to Week 48 was identified during the initial q12w cycle (brolucizumab 3 mg: 77%, [HAWK]; brolucizumab 6 mg: 79% [HAWK], 77% [HARRIER]).

Figure 3.4: Time-to-first q8w treatment need: Kaplan-Meier plot for brolucizumab patients with no q8w need during the initial q12w cycle (FAS-"efficacy/safety" approach)



Abbreviations: FAS: full analysis set; q8w: every 8 weeks; q12w: every 12 weeks.
Source: HAWK CSR;[78] HARRIER CSR;[79] Dugel et al. 2018.[82]

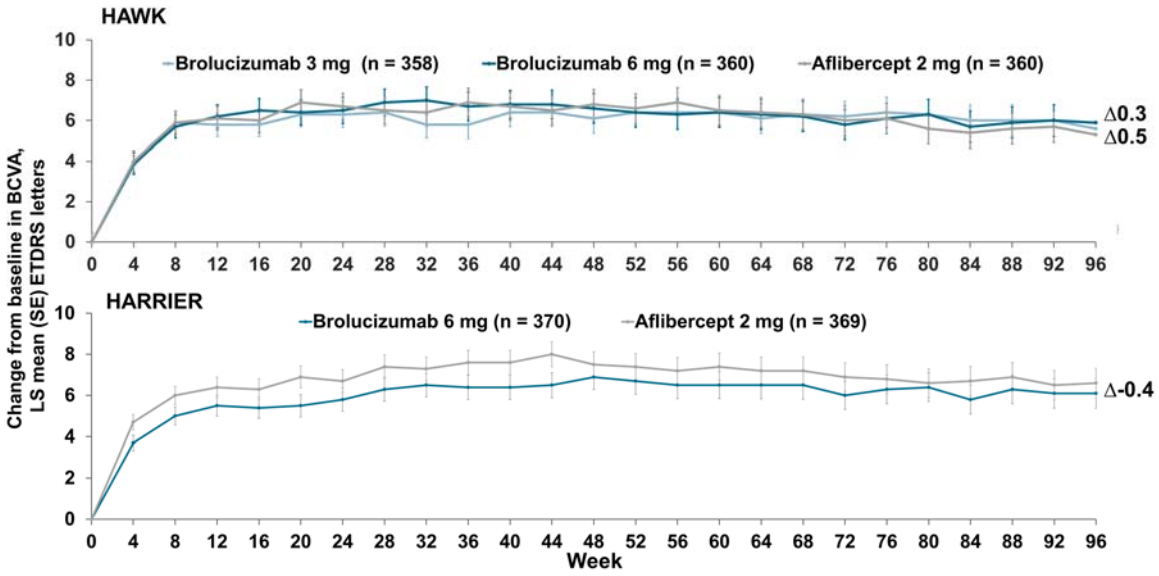
B.3.6.3 Additional secondary endpoints: functional outcomes

Brolucizumab was non-inferior to aflibercept for additional secondary BCVA endpoints, including change in BCVA from Baseline to any post-Baseline visit and the proportion of patients who lost ≥15 letters at any post Baseline visit

B.3.6.3.1 Change in BCVA from Baseline to each post-Baseline visit

The results from both HAWK and HARRIER showed a rapid improvement in change in BCVA from Baseline during the loading phase which was maintained up to Week 48, with no relevant differences observed between treatment arms (Figure 3.5). No relevant fluctuations or treatment arm differences in BCVA changes from Baseline were noted.

Figure 3.5: LS-mean change (SE) in BCVA (letters) from Baseline to Week 96 (FAS-LOCF)



Mean differences in BCVA (brolucizumab–aflibercept, Δ).
Abbreviations: BCVA: best-corrected visual acuity; ETDRS: Early Treatment Diabetic Retinopathy Study; FAS: full analysis set; LOCF: last observation carried forward; LS: least squares; q8w: every 8 weeks; q12w: every 12 weeks; SE: standard error.
Source: HAWK CSR;[78] HARRIER CSR;[79] Dugel et al. 2019.[76]

B.3.6.3.2 BCVA-related secondary outcomes

Results from both HAWK and HARRIER showed brolucizumab 6 mg in the HAWK trial to be advantageous compared to aflibercept (2 mg) at both the 48- and 96-week time point, in terms of the proportion of patients gaining ≥15 BCVA letters or reaching a BCVA of ≥84 letters (Table 3.11). Overall, no relevant differences were identified between brolucizumab (3 mg or 6 mg) and aflibercept (2 mg) in terms of the proportion of patients who lost ≥15 letters at any post Baseline visit up to Week 48, and Week 96.

Table 3.11: Selected secondary endpoints related to BCVA at, and up to, Week 48 and Week 96 (FAS-LOCF)

Trial name	HAWK		HARRIER
Secondary BCVA endpoint	**Brolucizumab 3 mg – aflibercept 2 mg difference (95% CI), p value**	**Brolucizumab 6 mg – aflibercept 2 mg difference (95% CI), p value**	**Brolucizumab 6 mg – aflibercept 2 mg difference (95% CI), p value**
Analysis at Week 48			
Mean change from Baseline (Week 4 – Week 48)	-0.4 (-1.9, 1.1), p=0.6275	0.0 (-1.5, 1.6), p=0.9647	-1.1 (-2.4, 0.3), p=0.1191
Mean change from Baseline (Week 12 – Week 48)	-0.4 (-2.0, 1.2), p=0.6185	0.1 (-1.6, 1.8), p=0.9235	-1.1 (-2.5, 0.4), p=0.1429
≥15 letters gained from Baseline/BCVA of ≥84 letters at Week 48	-0.2 (-6.8, 6.1), p=0.9480	8.2 (2.2, 15.0), p=0.0136	-0.6 (-7.1, 5.8), p=0.8600
≥15 letters loss from Baseline at Week 48	0.3 (-3.2, 3.9), p=0.8583	0.9 (-2.7, 4.3), p=0.6198	-1.0 (-3.9, 2.2), p=0.5079
BCVA of ≥73 letters at Week 48	-3.5 (-9.5, 2.3), p=0.2455	-2.4 (-8.6, 3.6), p=0.4442	0.4 (-5.4, 6.1), p=0.8922
Analysis at Week 96			
Mean change from Baseline at Week 96	0.3 (-1.9, 2.5), p=0.8062	0.5 (-1.6, 2.7), p=0.6326	-0.4 (-2.5, 1.6), p=0.6708
Mean change from Baseline (Week 84 – Week 96)	0.4 (-1.7, 2.5), p=0.7242	0.4 (-1.7, 2.5), p=0.7289	-0.6 (-2.5, 1.4), p=0.5532
Mean change from Baseline (Week 4 – Week 96)	-0.1 (-1.8, 1.6), p=0.8892	0.0 (-1.7, 1.8), p=0.9554	-0.8 (-2.4, 0.7), p=0.2915
Mean change from Baseline (Week 12 – Week 96)	-0.1 (-1.9, 1.7), p=0.8974	0.1 (-1.7, 1.9), p=0.9379	-0.8 (-2.4, 0.8), p=0.3228
≥15 letters gained from Baseline/BCVA of ≥84 letters at Week 96	5.5 (-1.2, 12.3), p=0.1023	7.2 (1.4, 13.8), p=0.0313	-2.4 (-8.8, 4.1), p=0.4765
≥15 letters loss from Baseline at Week 96	1.1 (-2.9, 4.9), p=0.5769	0.7 (-3.6, 4.6), p=0.7210	-0.4 (-3.8, 3.3), p=0.8377
BCVA of ≥73 letters at Week 96	1.7 (-4.7, 7.8), p=0.5950	2.3 (-3.8, 9.0), p=0.4820	-2.0 (-8.1, 4.1), p=0.5295

Abbreviations: BCVA: best-corrected visual acuity; CI: confidence interval; FAS: full analysis set; LOCF: last observation carried forward.

Source: HAWK CSR;[78] HARRIER CSR;[79] Khanani et al. 2018.[83]

B.3.6.4 Additional secondary endpoints: disease activity

Brolucizumab was statistically significantly superior to aflibercept in disease activity parameters; 30% fewer patients receiving brolucizumab had disease activity compared to those receiving aflibercept at Week 16

For disease activity, the prespecified 1-sided alpha for confirmatory testing of superiority was set to 0.01 within the hierarchical testing approach. A Week 16 head-to-head comparison of the presence of disease activity revealed probabilities of: 28.1% (HAWK) for brolucizumab 3 mg; 24.0% (HAWK) and 22.7% (HARRIER) for brolucizumab 6mg; 34.5% (HAWK) and 32.2% (HARRIER) for aflibercept 2mg. Across both trials, 30% fewer patients receiving brolucizumab had disease activity at Week 16 compared to those receiving aflibercept, and statistically significant differences in disease activity were seen between brolucizumab 6 mg and aflibercept 2 mg (HAWK: p=0.0013; HARRIER: p=0.0021).

The overall presence of disease activity from Week 16 through Week 96 (adjusting for differences in time since last active injection) was 63% higher in the aflibercept 2 mg arm compared to the brolucizumab arm (13.6% versus 22.2%) in HAWK, and 25% higher (15.7% versus 19.6%) in HARRIER (Table 3.12).

In HAWK, a total of 7,018 DAAs were performed by masked Investigators, with 1,084 cases of disease activity identified across all treatment arms. Qualitative analysis revealed that in 71.4% of cases, anatomical signs of disease activity were present either alone (35.8%) or in combination with function (35.6%). In the HARRIER trial, a total of 9,005 DAAs were performed by masked Investigators, with 1,421 cases of disease activity identified across all treatment arms. Qualitative analysis revealed that in 67.7% of cases, anatomical signs of disease activity were present either alone (41.9%) or in combination with function (25.8%). With fluid present in the majority of cases of disease activity, this emphasises the importance of monitoring fluid as a symptom of recurring disease activity as reflected in clinical guidelines.[32, 33] This also highlights the importance of the superior fluid control displayed by brolucizumab in comparison to aflibercept, as superior control of fluid suggests greater control of disease activity.

Table 3.12: Overall presence of disease activity across all DAAs

Endpoint/categories	Brolucizumab (overall[a])	Aflibercept 2 mg (8-week)
HAWK		
Number of DAAs performed	2360	1177
Number of disease activity identified by the Investigator	322 (13.6%)	261 (22.2%)
Both, functional and anatomical post hoc disease activity criteria met	121 (5.1%)	101 (8.6%)
HARRIER		
Number of DAAs performed	4494	2266
Number of disease activity identified by the Investigator	707 (15.7%)	444 (19.6%)
Both, functional and anatomical post hoc disease activity criteria met	152 (3.4%)	144 (6.4%)

[a]Combined results for all patients treated with brolucizumab in HAWK (6 mg and 3 mg treatment arms) and HARRIER (6 mg). For aflibercept 2 mg, DAAs performed 8 weeks after the last injection were considered to adjust for the differences in time since last injection.
Abbreviations: DAA: disease activity assessment. **Source:** HAWK CSR;[78] HARRIER CSR.[79]

B.3.6.5 Additional secondary endpoints: anatomical outcomes

B.3.6.5.1 Presence of SRF and/or IRF (central subfield) from Baseline to each post Baseline visit

Significantly fewer patients receiving brolucizumab had SRF and/or IRF at Week 16 and Week 48 compared to patients receiving aflibercept, and this was maintained at Week 96

The increase in VEGF seen in wAMD causes increased retinal fluid accumulation and oedema, which may cause functional deterioration and lead to vision loss due to disruption of the retinal architecture. Therefore, SRF and IRF are important measures of both fluid accumulation and disease activity, with reductions in fluid indicating better control of disease activity.

In both HAWK and HARRIER, consistently lower proportions of patients with SRF and/or IRF were observed for the brolucizumab 6 mg arm compared with the aflibercept 2 mg arm up to Week 96. The exceptions were Week 20, at the end of the initial q12w cycle, and Week 44 (4 weeks since the last aflibercept 2 mg treatment and 12 weeks since the last brolucizumab 6mg treatment for q12w patients) (Figure 3.6). At Week 16, the proportion of patients with IRF and/or SRF was 33.9% for brolucizumab 6 mg versus 52.2% for aflibercept 2 mg in HAWK (p<0.0001), and 29.4% versus 45.1% in HARRIER (p<0.0001). At Week 48, the proportion of patients with IRF and/or SRF was 31.2% for brolucizumab 6 mg versus 44.6% for aflibercept 2 mg in HAWK (p=0.0002), and 25.8% versus 43.9% in HARRIER (p<0.0001) (Table 3.13).

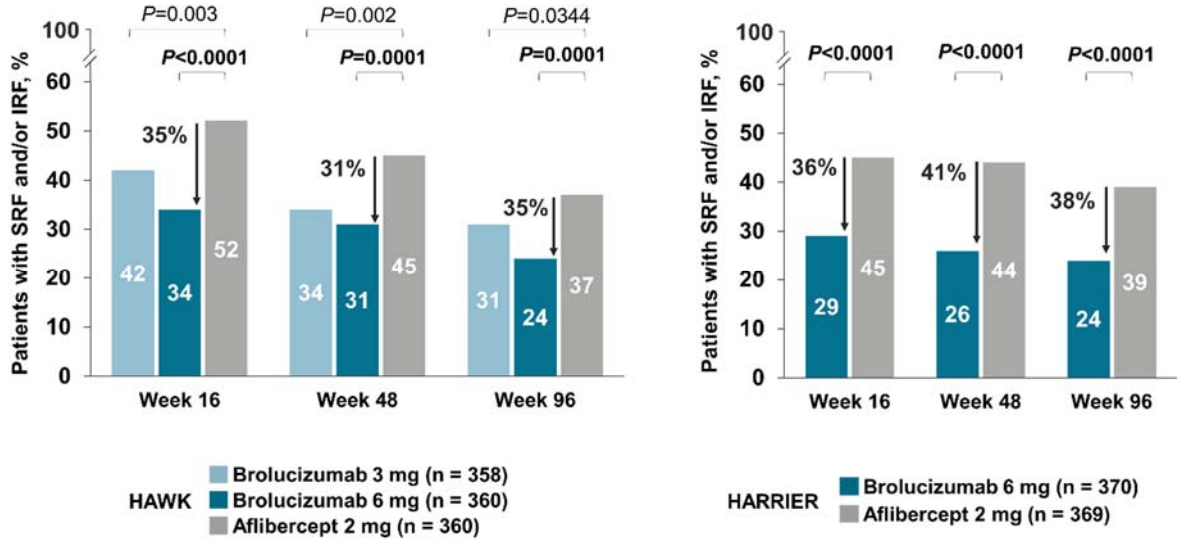
A rapid decline in the proportion of patients with SRF and/or IRF was evident among all treatment arms (both HAWK and HARRIER) following the loading phase. While reductions in SRF and/or IRF from Baseline were seen at all post Baseline visits, fluctuations over the treatment arm-specific treatment intervals were observed. However, these fluctuations were smaller in the brolucizumab treatment arms (Figure 3.6).

Table 3.13: Proportion of subjects with presence of SRF and/or IRF at Week 16 and Week 48 (FAS-LOCF)

Trial name	HAWK			HARRIER	
Time point	Brolucizumab 3 mg, mean (n)	Brolucizumab 6 mg, mean (n)	Aflibercept 2 mg, mean (n)	Brolucizumab 6 mg, mean (n)	Aflibercept 2 mg, mean (n)
Week 16					
Mean (%)	41.8	33.9	52.0	29.4	45.1
Difference (%)	-10.2	-18.2	-	-15.7	-
95% CI for difference (%)	(-17.3, -2.5)	(-25.3, -10.9)	-	(-22.9, -9.0)	-
p-value	0.0059	<0.0001	-	<0.0001	-
Week 48					
Mean	34.1	31.2	44.7	25.8	43.9
Difference	-10.5	-13.5	-	-18.1	-
95% CI for difference	(-17.4, -3.3)	(-20.7, -6.1)	-	(-24.9, -11.8)	-
p-value	0.0039	0.0002	-	<0.0001	-

Abbreviations: FAS: full analysis set; IRF: intraretinal fluid; LOCF: last observation carried forward; SRF: subretinal fluid.
Source: Dugel et al. 2019.[76]

Figure 3.6: Percentage of patients with the presence of SRF and/or IRF at Weeks 16, 48 and 96 in HAWK and HARRIER (FAS-LOCF)



Prespecified secondary endpoint in both HAWK and HARRIER. Confirmatory superiority analysis at Week 16 and Week 48 in HAWK only. 1-sided p-values for HAWK and HARRIER. For confirmatory superiority testing in HAWK, 1-sided p-values below the adjusted significance level (to account for multiplicity) of P<0.01 (for IRF and/or SRF) are regarded as statistically significant. 2-sided p-values for both HAWK and HARRIER at Week 96; P-values are descriptive.
Abbreviations: FAS: full analysis set; IRF: intraretinal fluid; LOCF: last observation carried forward; SRF: subretinal fluid.
Source: HAWK CSR;[78] HARRIER CSR;[79] Singh et al. 2019.[84]

B.3.6.5.2 Presence of sub-RPE fluid (central subfield) at each post Baseline visit

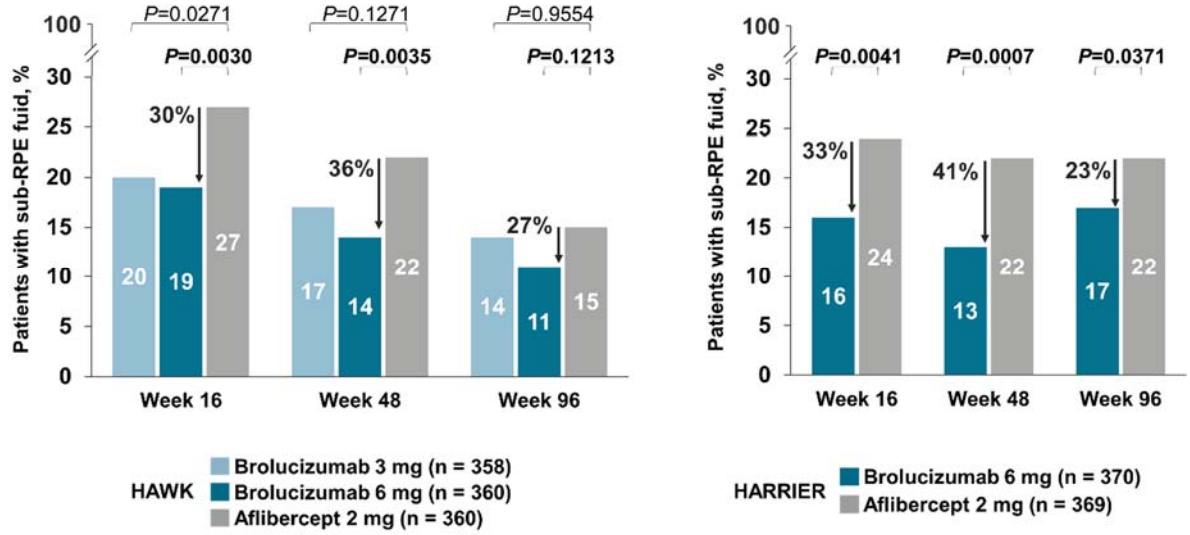
Fewer patients on brolucizumab had sub-RPE fluid at Weeks 16, 48 and 96 versus aflibercept

An increase in sub-RPE fluid in wAMD is an important measure of abnormal fluid accumulation and oedema and may result in reduced vision. Therefore, reductions in sub-RPE fluid indicate better disease control.

Fewer patients on brolucizumab 6 mg had sub-RPE fluid versus aflibercept at Week 16 (p=0.003) and Week 48 (p=0.0035) in HAWK and HARRIER (Week 16, p=0.0041; Week 48, p=0.0007).[76, 84] A lower proportion of patients with sub-RPE fluid for the brolucizumab 6 mg arm compared with the aflibercept 2 mg arm was maintained up to Week 96.

A rapid decline in the proportion of patients with sub-RPE fluid was evident among all treatment arms (both HAWK and HARRIER) following the loading phase. While reductions in SRF and/or IRF from Baseline were seen at all post Baseline visits, fluctuations over the treatment arm-specific treatment intervals were observed. However, these fluctuations were smaller in the brolucizumab treatment arms.

Figure 3.7: Percentage of patients with the presence of sub-RPE fluid by visit at Weeks 16, 48 and 96 in HAWK and HARRIER (FAS-LOCF)



Prespecified secondary endpoint in both HAWK and HARRIER. 2-sided p values for both HAWK and HARRIER. P-values are descriptive.
Abbreviations: FAS: full analysis set; LOCF: last observation carried forward; RPE: retinal pigment epithelium.
Source: HAWK CSR;[78] HARRIER CSR;[79] Singh et al. 2019.[84]

B.3.6.5.3 Change in CSFT from Baseline

Brolucizumab shows a significantly superior reduction in CSFT from Baseline to Week 16 and Week 48, with differences maintained at Week 96

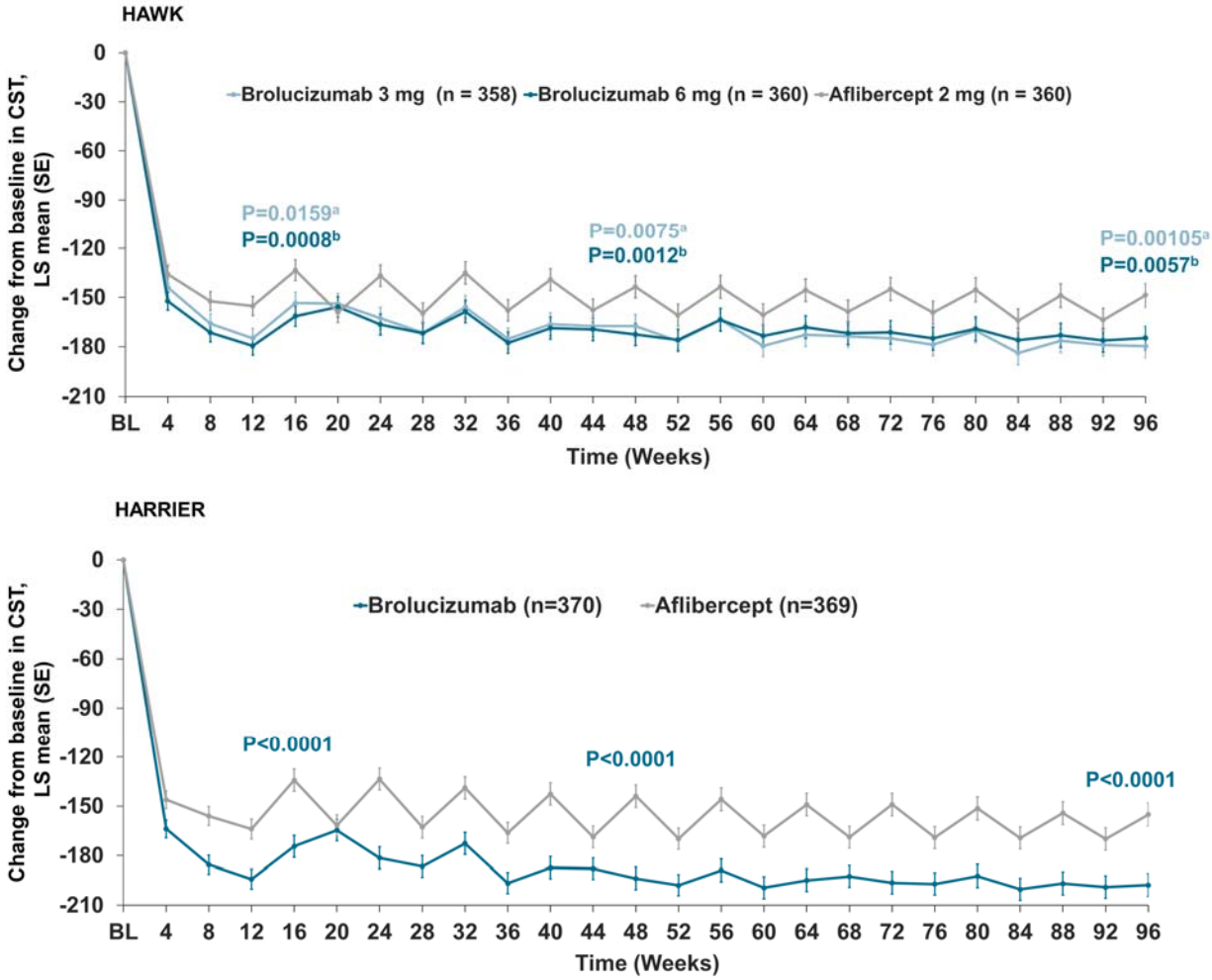
An increase in CSFT in wAMD is an important measure of abnormal fluid accumulation and oedema and may result in reduced vision. Reduction in CSFT therefore indicates better control of disease activity.

Greater reductions in total CSFT were observed for brolucizumab 6 mg versus aflibercept 2 mg at Week 16 and Week 48 in HAWK (p=0.0008 and p=0.0012 respectively) and HARRIER (p<0.0001 for both time points) (Figure 3.8).[84] These superior reductions were reaffirmed by the results from Week 96 for both HAWK (p=0.0115) and HARRIER (p<0.0001).[84] Greater reductions were consistently observed for the brolucizumab 6 mg arm, with the exception of Week 20, which was the end of the initial q12w cycle. The pattern of observed fluctuations with aflibercept followed the treatment schedule with peak reductions occurring 4 weeks after the last active injection and troughs at the end of a treatment interval.

In HAWK, hypothesis testing at Week 16 and Week 48 revealed statistically significant superiority for brolucizumab 6 mg compared to aflibercept 2 mg (differences at Week 16: -28 µm, and at Week 48: -29 µm). Averaging changes from Baseline over the period from Week 36 to Week 48 revealed a difference of -22.4 µm. In HARRIER, averaging across all post-Baseline visits revealed about a 30 µm greater reduction for brolucizumab 6 mg compared with aflibercept 2mg. The greater reductions at Week 16: 40 µm, at Week 48: 50 µm and for the average change over the period Week 36 to Week 48: 36 µm were all assessed with 2-sided p-values of <0.0001.[76]

At Week 96, absolute reductions in CSFT from Baseline were –175 µm for brolucizumab 6 mg versus –149 µm for aflibercept 2 mg in HAWK (p=0.0057) and 198 µm versus –155 µm, respectively, in HARRIER (p<0.0001).

Figure 3.8: Plot of LS-mean change (+/– SE) of central subfield thickness-total (µm) from Baseline by visit through Week 96 (FAS-LOCF)



[a]Brolucizumab 3 mg versus aflibercept 2 mg; [b]brolucizumab 6 mg versus aflibercept 2 mg.
Prespecified secondary endpoint in HARRIER. 1-sided p values for HARRIER. 2-sided p-values at Week 96. P-values are descriptive.
Abbreviations: BL: baseline; FAS: full analysis set; LOCF: last observation carried forward; LS: least squares; SE: standard error.
Source: HAWK CSR;[78] HARRIER CSR;[79] Singh et al. 2019.[84]

B.3.6.5.4 Change in CNV lesion size from Baseline to Week 12, 48 and 96

Treatment with brolucizumab was associated with superior efficacy in CNV lesion size outcomes versus aflibercept

Superior efficacy was observed for brolucizumab 6 mg in terms of CNV lesion size reduction. At Week 12 and Week 48, the number of patients with presence of CNV lesions (lesion size >0 mm^2) was lower for brolucizumab 6 mg patients compared to aflibercept 2 mg.

From Baseline to Week 12, the mean change in CNV lesion size was -3.3 mm^2, -3.8 mm^2 and -3.2 mm^2 (brolucizumab 3 mg, brolucizumab 6 mg, aflibercept 2 mg respectively) in HAWK; and -2.2 mm^2 and -2.5 mm^2 (brolucizumab 6 mg and aflibercept 2 mg respectively) in HARRIER. The difference between the brolucizumab 6 mg and aflibercept 2 mg arms was assessed with a p-value of 0.0024 (HAWK) and 0.0859 (HARRIER).

Similarly, from Baseline to Week 48, the mean change in CNV lesion size was -3.9 mm^2, -4.0 mm^2 and -3.5 mm^2 in HAWK; and -2.3 mm^2 and -2.5 mm^2 in HARRIER. The difference between

the brolucizumab 6 mg and aflibercept 2 mg arms was assessed with a p-value of 0.0344 (HAWK) and 0.1207 (HARRIER). For Baseline to Week 96, the mean change in CNV lesion size was -3.9 mm^2, -4.1 mm^2 and -3.5 mm^2 in HAWK; and -2.5 mm^2 and -2.7 mm^2 in HARRIER. The difference between the brolucizumab 6 mg and aflibercept 2 mg arms was assessed with a p-value of 0.0022 (HAWK) and 0.0366 (HARRIER).

B.3.6.6 Patient-reported outcomes

B.3.6.6.1 Change in subject reported outcomes (VFQ-25)

Brolucizumab achieved a similar improvement in HRQoL compared with aflibercept, with a majority of patients maintained on a q12w dosing interval

VFQ-25 is a patient-reported instrument widely used to measure vision-related HRQoL in wAMD. A positive change in VFQ-25 score indicates benefit.

Both trials (HAWK and HARRIER) showed a similar change in VFQ-25 score from Baseline for both brolucizumab (6 mg and 3 mg) and aflibercept (2 mg) treatment groups. At Week 96, the mean change from Baseline in the VFQ-25 was 3.8 for brolucizumab (6 mg) versus 2.8 for aflibercept in HAWK, and 3.8 versus 2.6 in HARRIER.

The FAS-observed and FAS-LOCF analysis of VFQ-25 showed no relevant differences between treatment arms in terms of mean composite score (Table 3.14). Similar results were seen for all 11 individual VFQ-25 subscales including general vision, ocular pain, near activities, distance activities, social functioning, mental health, role difficulties, dependency, driving, colour vision, and peripheral vision.

Table 3.14: HAWK and HARRIER: mean change in VFQ-25 composite scores from Baseline (FAS-observed)

Trial name	HAWK			HARRIER	
Time point	Brolucizumab 3 mg, mean (n)	Brolucizumab 6 mg, mean (n)	Aflibercept 2 mg, mean (n)	Brolucizumab 6 mg, mean (n)	Aflibercept 2 mg, mean (n)
Week 24	4.4 (n=342)	4.0 (n=341)	3.5 (n=333)	3.9 (n=354)	3.5 (n=355)
Week 48	4.3 (n=328)	4.1 (n=324)	4.5 (n=317)	4.8 (n=347)	3.6 (n=346)
Week 72	4.4 (n=306)	3.9 (n=303)	4.0 (n=298)	5.0 (n=342)	3.2 (n=334)
Week 96	3.8 (n=310)	3.8 (n=301)	2.8 (n=296)	3.8 (n=370)	2.6 (n=369)

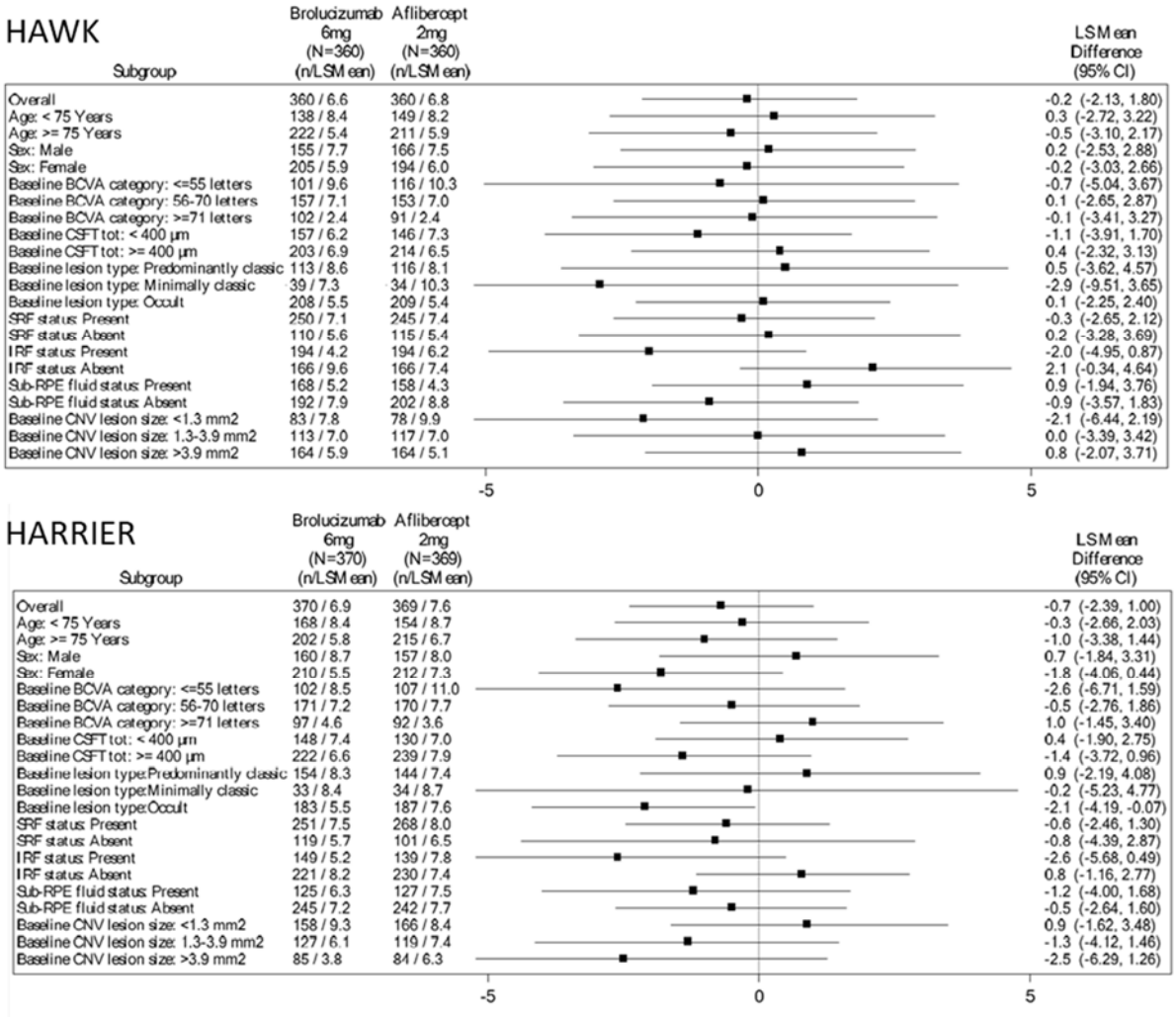
Abbreviations: FAS: full analysis set; VFQ-25: visual function questionnaire-25.
Source: HAWK CSR;[78] HARRIER CSR.[79]

B.3.7 Subgroup analysis

B.3.7.1.1 Change in BCVA from Baseline to Week 48

The results of the subgroup analyses for the primary endpoint of change in BCVA from Baseline to Week 48 showed a relevant improvement in BCVA from Baseline across all brolucizumab subgroups, irrespective of baseline disease characteristics/demographics (Figure 3.9). Additionally, the differences between treatments were not suggestive of relevant subgroup-specific effects for either brolucizumab dose compared with aflibercept 2 mg.

Figure 3.9: Forest plot of summary statistics and ANOVA for change in BCVA from Baseline to Week 48 by subgroups of interest (FAS-LOCF)

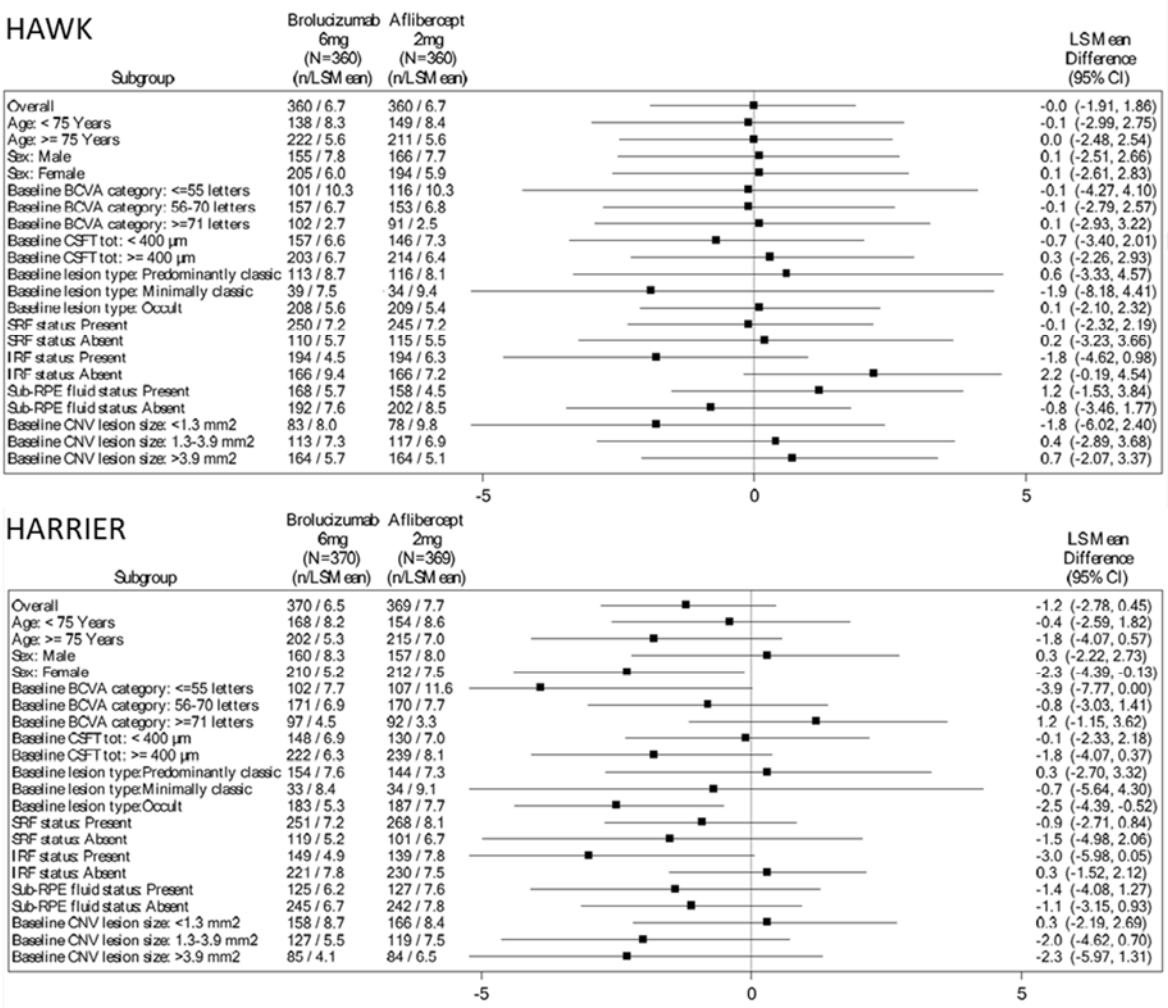


Abbreviations: ANOVA: analysis of variance; BCVA: best-corrected visual acuity; CI: confidence interval; FAS: full analysis set; LOCF: last observation carried forward; LSM: least squares mean.
Source: HAWK CSR;[78] HARRIER CSR.[79]

B.3.7.1.2 Average change in BCVA from Baseline over the period Week 36 to Week 48

Similar to primary efficacy endpoint, subgroup analyses were conducted for the first key secondary endpoint. Overall, results of the subgroup analyses up to Week 48 confirmed relevant improvements for all subgroups in all treatments groups and were not suggestive of relevant differences in treatment effect for either brolucizumab dose (HAWK: 6 mg and 3 mg; HARRIER: 6 mg) compared with aflibercept 2 mg (Figure 3.10).

Figure 3.10: Forest plot of summary statistics and ANOVA for change in BCVA from Baseline over the period of Week 36 through Week 48 by subgroups of interest (FAS-LOCF)



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.
Source: HAWK CSR;[78] HARRIER CSR.[79]

B.3.7.1.3 Proportion of q12w treatment status at Week 48 for patients randomised to brolucizumab ("maintaining on q12w")

Subgroup analyses related to the q12w treatment status at Week 48 suggested that, irrespective of subgroup parameters, >40% of patients qualified for q12w in all subgroups in the brolucizumab arms of both HAWK and HARRIER trials. Overall, the brolucizumab 6 mg arm demonstrated a higher probability of maintaining on a q12w regimen compared to the brolucizumab 3 mg arm across all subgroups.

The most differentiating parameter identified in both trials which impacted the potential of maintaining on the q12w regimen, was baseline CSFT status.

B.3.7.1.4 Predictive value of the initial q12w cycle

Estimates for the probability of remaining on a q12w regimen up to Week 48 amongst patients with no q8w need during the initial q12w cycle were high across all subgroups in patients receiving brolucizumab in both HAWK (>80% in 6 mg treatment group) and HARRIER (>70%). In the Japanese ancestry subgroup, the observed probability at Week 48 was 86.7%. Similar

results were observed in the subgroup analysis for patients in the brolucizumab 3 mg treatment group.

B.3.8 Meta-analysis

Baseline pooling was conducted to estimate the absolute treatment effect for several outcomes for brolucizumab across both the HAWK and HARRIER trials. Full details of the methodology used for the baseline pooling are included within Appendix D.

Key results of the baseline pooling are presented in Section B.3.9.4 (NMA results), and full results are presented in Appendix D.

B.3.9 Indirect and mixed treatment comparisons

Summary

- Following the identification of relevant studies from the clinical SLR, a network meta-analysis (NMA) was performed to assess the efficacy and safety of brolucizumab versus the relevant comparators aflibercept and ranibizumab
- Of the 38 RCTS identified in the SLR, 23 RCTs were excluded from the base NMA, for reasons including the inclusion of a treatment currently unlicensed by the EMA or not recommended by NICE for the treatment of wAMD, as well as trials not using the licensed dose or the dose not being reported
- In total 14 trials were included in the base case NMA were: OSPREY, HARRIER, HAWK, CATT, SALUTE, RABIMO, VIEW1&2 pooled, HARBOR, RIVAL, CAN-TREAT, PIER, MARINA, TREND and TREX-AMD.
- Baseline pooling was conducted to estimate the absolute treatment effect for treatment regimens with more than one trial. Regimen-based pooling was conducted for the mean change in BCVA, patients gaining at least 15 letters, patients losing at least 15 letters, injection frequency, and AEs. Molecule-based pooling was conducted for treatment discontinuation as well as AEs.
- Standard pairwise meta-analyses based on direct comparisons were carried out between pairs of treatments when possible, where two treatments were compared in two or more clinical trials. The relative goodness of fit of the models were assessed using the deviance information criterion (DIC). Both fixed-effects and random-effects models were developed and the one associated with the lowest DIC was selected.
- Results of the NMA demonstrated brolucizumab to be associated with comparable visual outcomes in terms of BCVA and superior anatomical outcomes in terms of decreasing retinal thickness with a lower injection frequency than current standard of care:
  - Brolucizumab was associated with comparable efficacy versus aflibercept and ranibizumab in terms of change in BCVA from Baseline to one and two years
  - Results were comparable for both LP → Bro 6q8w → q12w and LP → Bro 6q12/q8w regimens, where the latter regimen included over 50% of patients on a q12w brolucizumab dosing interval until Week 48 immediately following the initial loading phase
  - The NMA also demonstrated brolucizumab (LP → Bro 6q12/q8w) to be statistically significantly better than all aflibercept and ranibizumab regimens at decreasing retinal thickness from Baseline to one year
  - Results of the arm-based baseline pooling for injection frequency also demonstrated brolucizumab to be associated with the second lowest injection frequency across year one and year two versus most aflibercept and ranibizumab regimens
  - In terms of treatment discontinuation, brolucizumab was associated with comparable odds of discontinuation versus aflibercept and ranibizumab, from Baseline to two years
  - Finally, results of the baseline pooling for serious AEs demonstrated brolucizumab to be associated with a comparable safety profile to both aflibercept and ranibizumab
- Sensitivity analyses were conducted to test the assumptions adopted within the NMA and showed that the results obtained were robust and not significantly affected by the assumptions made. Full details of the methodology of the NMA are presented in Appendix D.

B.3.9.1 Identification and selection of relevant studies

As described in Section B.3.1, an SLR was conducted to identify relevant clinical evidence of the efficacy and safety of brolucizumab and other therapies used in the treatment of wAMD. In total, 6,004 publications were screened, of which 147 publications were reviewed at the full-text stage. After exclusion of publications not meeting the eligibility criteria, 48 publications (reporting on 38 unique RCTs) were included in the SLR. A full list of the 38 RCTs is presented in Appendix D.

Following the identification of relevant studies from the clinical SLR, a network meta-analysis (NMA) was performed to assess the efficacy and safety of brolucizumab versus the relevant comparators to this appraisal: aflibercept and ranibizumab. The SLR and NMA were conducted in line with the NICE guide to the methods of technology appraisal.[85] An overview of the methodology of the NMA is presented in this section. Full details are presented in Appendix D.

B.3.9.2 Feasibility assessment

Of the 38 RCTS included in the SLR, only studies investigating brolucizumab and the relevant comparators were considered for inclusion within the base case NMA:

- Intervention of interest: Brolucizumab 6 mg (and 3 mg)
- Licensed and recommended comparators: Ranibizumab 0.5 mg, Aflibercept 2 mg

In addition, different treatment regimens were also taken into account in the NMA using an attribute-based approach as done in the NICE NMA in wAMD.[86] Each treatment was evaluated separately by its treatment regimen, including if a loading phase was used. The following abbreviations were used to indicate the treatments by their dose and regimen:

- LP: loading phase of three initial monthly injections
- PRN (pro re nata): treatment administered as needed
- PRNX: PRN with the potential to extend the assessment interval
- TREX (treat-and-extend): treat with the potential to extend the treatment interval (when no signs of exudation are present)
- qXw: injections that are administered on a fixed schedule every X weeks, i.e. q4w, q8w, or q12w

For example, in the HAWK and HARRIER clinical trials, patients started treatment with a loading phase, where they received injections at Weeks 0, 4 and 8, with injections every 8 or 12 weeks thereafter. Where regimens have multiple phases, these are separated with an arrow (→). Thus LP→q8w indicates a regimen that starts with a loading phase, then moves to an injection every 8 weeks. A second arrow represents a different regimen is used from the beginning of Year 2. Therefore LP→q8w→PRN indicates a regimen that starts with a loading phase, then patients receive an injection every 8 weeks in the first year followed by a PRN regimen in the second year.

Only studies investigating EU licensed and NICE recommended treatments and doses were included in the NMA. Further detailed of the PICOS criteria applied for the feasibility assessment and the EMA-approved and NICE-recommended doses and regimens for each comparator of interest are provided in Appendix D.

The list of included treatments and their regimens considered within the base case NMA is presented below in Table 3.15.

Table 3.15: List of included treatments and regimens

Treatment	Included regimens
Ranibizumab 0.5mg	Rani 0.5q4w Rani 0.5PRN LP → Rani 0.5PRNX LP → Rani 0.5q8w LP → Rani 0.5PRN LP → Rani 0.5q12w LP → Rani 0.5TREX
Brolucizumab 6mg	LP → Bro 6q8w → q12w[a] LP → Bro 6q12/q8w[a]
Brolucizumab 3mg	LP → Bro 3q12/q8w[a]
Aflibercept 2mg	LP → Afli 2q8w Afli 2q4w LP → Afli 2PRN LP (2q12w) → Afli 2PRN LP → Afli 2TREX

[a] Bro 6q8 → q12 indicates bi-monthly injections until week 40 and every 12 weeks to week 56 (evaluated in OSPREY).[77] Bro q12/q8w indicates injections every 12 weeks unless there were signs of disease progression, in which case the patient switched to bi-monthly injections (evaluation in HAWK and HARRIER).
The treatment names have been shortened and are followed by their dose and then regimen.
Abbreviations: LP: loading phase; PRN: pro re nata; PRNX: pro re nata with the potential to extend the assessment interval; qXw; ome injection every X weeks; TREX: treat and extend.

An overview of the 38 trials included in the SLR, and their subsequent inclusion/exclusion from the base case NMA is presented in Table 3.16.

As part of the feasibility assessment, 23 RCTs were excluded from the base case NMA altogether. 7 RCTs were excluded from the base case NMA because they included a treatment that is currently unlicensed by the EMA. 6 RCTs were excluded for including licensed treatments that are not recommended by NICE for the treatment of wAMD.[86] Other reasons for exclusion were that the dose considered was not the licensed dose (n=5), the time of assessment was not in the specified ranges of 48–52 and 96–104 weeks (n=1), and the treatment doses were not reported (n=2).

In addition, among the trials included in the base case and sensitivity analyses, CLEAR-IT 2 and FLUID did not connect to any of the networks. CLEAR-IT 2 evaluated aflibercept 2PRN with two different loading phases and FLUID evaluated Rani 0.5TREX according to two different TREX regimens (relaxed versus intensive). As such, they were excluded from the analyses (n=2), and therefore aflibercept 2PRN regimen was not evaluated.

Finally, VIEW 1&2 were pooled in the NMAs as the trials are similarly designed and use the same inclusion/exclusion criteria. The main difference between these trials is that they were conducted on different sites, suggesting that any differences can be attributed to random variability. In addition, NICE used the pooled analysis for VIEW 1&2 in their NMA in wAMD.[86] As such, these two trials were considered as one in the networks.

A total of 14 trials were therefore included in the base case NMA: OSPREY, HARRIER, HAWK, CATT, SALUTE, RABIMO, VIEW1&2 pooled, HARBOR, RIVAL, CAN-TREAT, PIER, MARINA, TREND and TREX-AMD.

Table 3.16: Summary of studies included in the SLR and the NMA

Trial ID	Author, year	Time of assessment (months)	Trial name	Sample size (ITT)	Phase	Blinding status	Intervention	Comparator	Included in the base case NMA?	Trial evidence included in NICE technology appraisal for key comparator?
1	**Dugel 2017**	12	OSPREY	90	2	Double-blind	LP → Bro 6q8w → q12w	LP → Afli 2q8w	Included	-
2	**Dugel 2019**	96 weeks	HARRIER	743	3	Double-blind	LP → Bro 6q12/q8w	LP → Afli 2q8w	Included	-
3	**Dugel 2019**	96 weeks	HAWK	1078	3	Double-blind	LP → Bro 3q12/q8w LP → Bro 6q12/q8w	LP → Afli 2q8w	Included	-
4	**Martin 2011 / Martin 2012**	12/24	CATT	1143	NR	Single-blind	Rani 0.5q4w Rani 0.5PRN	Bev 1.25q4w Bev 1.25 PRN	Included	No
5	**Eldem 2015**	12	SALUTE	77	4	Open-label	LP→ Rani 0.5mg PRNX	LP→ Rani 0.5mg PRN	Included	No
6	**Feltgen 2017**	12	RABIMO	40	4	Open-label	LP → Rani 0.5q8w	LP → Rani 0.5PRN	Included	No
7-8	**Heier 2012**	12	VIEW 1/VIEW 2	2412	3	Double-blind	Afli 0.5q4w Afli 2q4w LP → Afli 2q8w	Rani 0.5q4w	Included	Yes (Afli)
7-8	**Yuzawa 2015**	12	VIEW 1/VIEW 2	1202	3	Double-blind	LP → Afli 2q8w	Rani 0.5q4w		
7-8	**Schmidt-Erfurth 2014**	96 weeks	VIEW 1/VIEW 2 (Combined)	1217	3	Double-blind	Afli 0.5q4w→ PRN Afli 2q4w→PRN LP → Afli 2q8w→ PRN	Rani 0.5q4w → PRN		
9	**Ho 2014**	24	HARBOR	1089	3	Double-blind	Rani 0.5q4w Rani 2q4w	LP → Rani 0.5PRN LP → Rani 2PRN	Included	No
10	**Gillies 2019/Hunyor 2018**	12/24	RIVAL	278	3	Double-blind	LP → Rani 0.5TREX	LP → Afli 2TREX	Included	No
11	**Kertes 2019**	24	CAN-TREAT	580	NR	Open-label	LP → Rani 0.5TREX	Rani 0.5q4w	Included	No

Trial ID	Author, year	Time of assessment (months)	Trial name	Sample size (ITT)	Phase	Blinding status	Intervention	Comparator	Included in the base case NMA?	Trial evidence included in NICE technology appraisal for key comparator?
12	**Regillo 2008**	12	PIER	184	3b	Double-blind	LP → Rani 0.5q12w LP → Rani 0.3q12w	Sham IVT	Included	Yes (Rani)
13	**Rosenfeld 2006/ Chang 2007**	24	MARINA	716	3	Double-blind	Rani 0.5q4w Rani 0.3q4w	Sham IVT	Included	Yes (Rani)
14	**Silva 2017**	12	TREND	650	3b	Single-blind	LP → Rani 0.5TREX	Rani 0.5q4w	Included	No
15	**Wykoff 2015 / Wykoff 2017**	12/24	TREX-AMD	60	3b	Open-label	LP → Rani 0.5TREX	Rani 0.5q4w	Included	No
16	**Antoszyk 2007**	24	FOCUS	162	1/2	Single-blind	Vert PDT monthly	Rani 0.5q4w	Excluded (Not recommended by NICE and does not help connect networks)	No
17	**Berg 2015 / Berg 2016**	12/24	LUCAS	441	NR	Double-blind	Bev 1.25TREX	LP → Rani 0.5TREX	Excluded (Not a licensed treatment)	No
18	**Boyer 2009**	12	SAILOR	2378	3b	Single-blind	LP → Rani 0.3 PRN	LP → Rani 0.5 PRN	Excluded (Not a licensed dose)	No
19	**Brown 2009/ Bressler 2009/2013**	24	ANCHOR	423	3	Double-blind	Vert PDT PRN	Rani 0.3q4w Rani 0.5q4w	Excluded (Not a licensed dose and not recommended by NICE and does not help connect networks)	Yes (Rani)
20	**Campochiaro 2019**	9	Ladder	220	2	Open-label	PDS + Rani 10PRN, 40PRN, 100PRN	Rani 0.5q4w	Excluded (No follow-up time of interest)	No

Trial ID	Author, year	Time of assessment (months)	Trial name	Sample size (ITT)	Phase	Blinding status	Intervention	Comparator	Included in the base case NMA?	Trial evidence included in NICE technology appraisal for key comparator?
21	**Guymer 2019**	24	FLUID	349	4	Single-blind	LP → Rani 0.5TREX (relaxed)	LP → Rani 0.5TREX (intensive)	Excluded (Not connected to the network)	No
22	**Hatz 2015**	12	NR	40	3	Double-blind	Vert PDT + Rani 0.3PRN	LP → Rani 0.3PRN	Excluded (Not a licensed dose)	No
23	**Heier 2011**	12	CLEAR-IT 2	157	2	Double-blind	LP (w0-12) → Afli 0.5PRN LP (w0-12) → Afli 2PRN	LP (q12w, w0-12) → Afli 0.5PRN LP (q12w, w0-12) → Afli 2PRN LP (q12w, w0-12) → Afli 4PRN	Excluded (Not connected to the network)	No
24	**Kaiser 2012**	12	DENALI	286	3b	Double-blind	Vert PDT + Rani 0.5q4w	Rani 0.5q4w	Excluded (Not recommended as first-line therapy in wAMD by NICE)	No
25	**Kodjikian 2013**	12	GEFAL	501	NR	Double-blind	LP → Bev 1.25PRN	LP → Rani 0.5PRN	Excluded (Not a licensed treatment)	No
26	**Krebs 2013 (1)**	12	NR	44	NR	Single-blind	Vert PDT + Rani 0.5q4w	Rani 0.5q4w	Excluded (Not recommended as first-line therapy in wAMD by NICE)	No
27	**Krebs 2013 (2)**	12	NR	317	NR	Double-blind	LP → Bev 1.25PRN	LP → Rani 0.5PRN	Excluded (Not a licensed treatment)	No
28	**Larsen 2012**	12	MONT BLANC	255	2	Double-blind	Vert PDT + Rani 0.5q4w	Rani 0.5q4w	Excluded (Not recommended as first-line therapy in wAMD by NICE)	No
29	**Li 2017**	12	SIGHT	304	3	Double-blind	LP → Afli 2q8w	Vert PDT PRN	Excluded (Not recommended by NICE and does	No

Trial ID	Author, year	Time of assessment (months)	Trial name	Sample size (ITT)	Phase	Blinding status	Intervention	Comparator	Included in the base case NMA?	Trial evidence included in NICE technology appraisal for key comparator?
									not help connect networks)	
30	**Mori 2017**	12	NR	58	NR	NR	LP → Afli PRN	LP → Afli q8w	Excluded (Doses not reported)	No
31	**Nunes 2019**	12	NR	45	NR	Open-label	LP → Bev 1.25PRN LP (q2w) → Bev 1.25PRN	LP → Rani 0.5PRN	Excluded (Not a licensed treatment)	No
32	**Schauwvlieghe 2016**	12	BRAMD	327	NR	Double-blind	Bev 1.25q4w	Rani 0.5q4w	Excluded (Not a licensed treatment)	No
33	**Schmidt-Erfurth 2011**	12	EXCITE	233	3b	Double-blind	LP → Rani 0.3q12w	LP → Rani 0.5q12w Rani 0.3q4w	Excluded (Not a licensed dose)	No
34	**Scholler 2014**	12	NR	55	NR	Open-label	LP → Rani 0.5PRN	LP → Bev 1.25PRN	Excluded (Not a licensed treatment)	No
35	**Subramanian 2010**	24	NR	22	NR	Double-blind	Bev 1.25q4w	Rani	Excluded (Dose not reported)	No
36	**Söderberg 2012**	24	NR	92	NR	Double-blind	LP → Rani 0.5PRN	TTT + Rani 0.5PRN	Excluded (Not a licensed treatment)	No
37	**Tano 2010/2011**	12/24	EXTEND-I	76	1/2	Open-label	Rani 0.3q4w	Rani 0.5q4w	Excluded (Not a licensed dose)	No
38	**Weingessel 2015**	12	NR	34	NR	NR	Vert PDT + Rani 0.5PRN	LP → Rani 0.5PRN	Excluded (Not recommended as first-line therapy in wAMD by NICE)	No

[a]The LADDER trial (Campochiaro 2019) should be interpreted with caution as the main objective of the trial was to assess the effect of the PDS, it was included in the SLR as it does still report relevant outcomes.

Abbreviations: Afli: aflibercept; Bev: bevacizumab; ITT: intention to treat; IVT: intravitreal; LP: loading phase; NR: not reported; PDT: port delivery system; PRN: pro re nata; PRNX: pro re nata and extend dosing regimen; qXw: one injection every X weeks; rani: ranibizumab; TREX: treat-and-extend dosing regimen.

B.3.9.3 NMA methodology

Baseline pooling

Baseline pooling was conducted to estimate the absolute treatment effect for treatment regimens with more than one trial. The following outcomes were considered:

- Mean change in BCVA
- Proportion of patients gaining at least 15 ETDRS letters
- Proportion of patients losing at least 15 ETDRS letters
- Overall discontinuation
- Injection frequency
- AEs (intraocular inflammation, endophthalmitis, retinal detachment, retinal tear, retinal pigment epithelial tear, and cataract)

Regimen-based pooling was conducted for the mean change in BCVA, patients gaining at least 15 letters, patients losing at least 15 letters, injection frequency, and adverse events. Molecule-based pooling was conducted for discontinuation as well as AEs. Full details of the baseline pooling methodology are presented in Appendix D.

Direct comparisons

Standard pairwise meta-analyses based on direct comparisons were carried out between pairs of treatments when possible, where two treatments were compared in two or more clinical trials. Direct pairwise comparisons were conducted to assess the heterogeneity between studies when there was more than one study comparing the same treatments.

The NMA was conducted using a Bayesian framework, which preserved the randomisation of each trial. The relative goodness of fit of the models was assessed using the deviance information criterion (DIC). Both fixed-effects and random-effects models were developed and the one associated with the lowest DIC was selected.[85] Full details of the methodology of the NMA, and any assumptions that were adopted, are presented in Appendix D.

Assumptions adopted in the base case NMA

Details of any additional assumptions adopted in the base case NMA are described in Section B.3.9.5 and results of sensitivity analyses testing various of assumptions of the base case NMA are presented in Appendix D.

B.3.9.4 NMA results

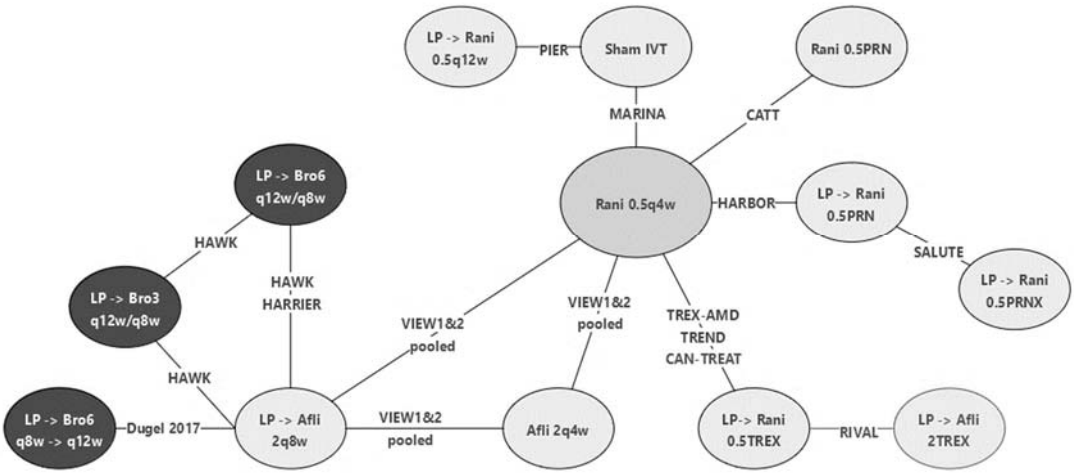
Key results of the NMA and results that feed into the cost-comparison model are presented in this section. All other results from the NMA are presented in Appendix D.

B.3.9.4.1 Mean change in BCVA (Baseline to one year)

At one year, the base case NMA demonstrated brolucizumab to be associated with comparable efficacy to aflibercept and ranibizumab in terms of mean change in BCVA from Baseline

The network for mean change in BCVA from Baseline to one year is displayed in Figure 3.11. A total of 13 studies were included in the analysis. This section presents results from the fixed-effects model of the NMA. The DIC of the fixed-effects model was higher than that of the random-effects model (112.23 versus 108.36) but since the random-effects model encountered convergence issues, the fixed-effects model was chosen.

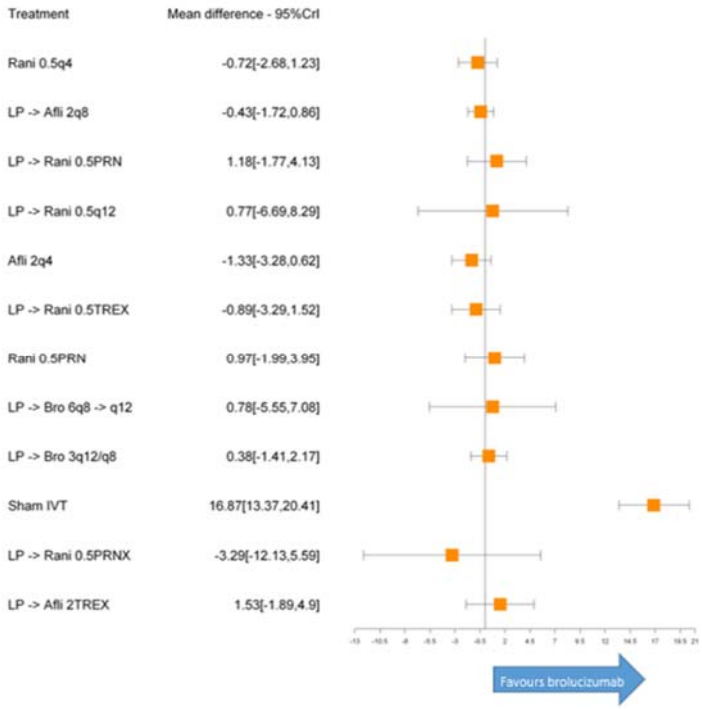
Figure 3.11: Network for mean change in BCVA from Baseline to one year



Note: Dugel 2017 = OSPREY
Abbreviations: Afli: aflibercept; BCVA: best-corrected visual acuity; Bro: brolucizumab; IVT: intravitreal; LP: loading phase; PRN: pro re nata; PRNX: pro re nata and extend dosing regimen; qXw: one injection every X weeks; Rani: ranibizumab; TREX: treat-and-extend dosing regimen.

The indirect comparisons obtained through the NMA are reported in Figure 3.12 for LP → Bro 6q12/q8w versus each comparator. Brolucizumab showed comparable efficacy to aflibercept and ranibizumab for mean change in BCVA from Baseline to one year, with none of the treatment effects for this endpoint significant at a 95% credibility level. Additionally, results for mean change in BCVA at one year indicated that brolucizumab was statistically significantly better than sham IVT.

Figure 3.12: Forest plot of the NMA results comparing the difference in mean change in BCVA from Baseline to one year between LP → Bro 6q12/q8w and each comparator (fixed-effects)



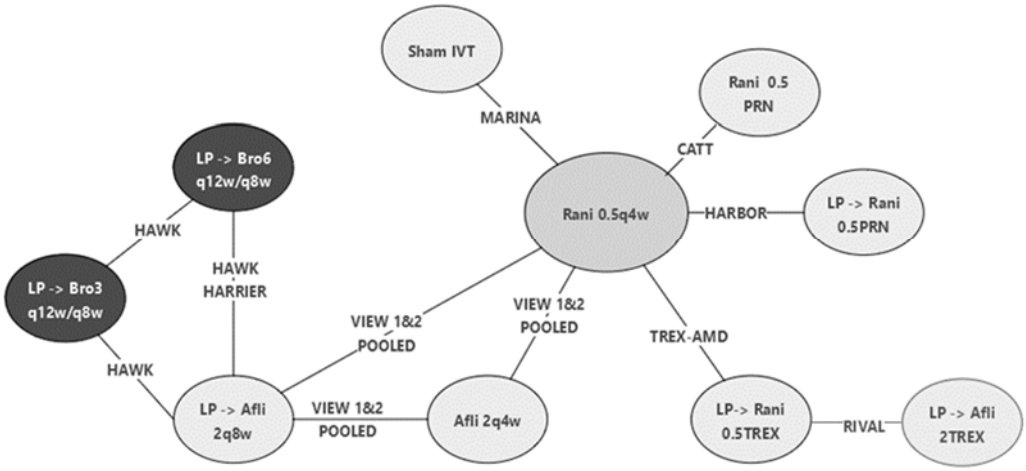
Abbreviations: Afli: aflibercept; BCVA: best-corrected visual acuity; Bro: brolucizumab; IVT: intravitreal; LP: loading phase; NMA: network meta-analysis; PRN: pro re nata; PRNX: pro re nata and extend dosing regimen; qXw: one injection every X weeks; Rani: ranibizumab; TREX: treat-and-extend dosing regimen.

B.3.9.4.2 Mean change in BCVA (Baseline to two years)

At two years, the base case NMA demonstrated brolucizumab to be associated with comparable efficacy to aflibercept and ranibizumab in terms of mean change in BCVA from Baseline

The network for mean change in BCVA at two years is displayed in Figure 3.13. Eight studies were included in the analysis. This section presents the results from the fixed-effects model of the NMA because the DIC was lower than that of the random-effects model (65.93 versus 66.31).

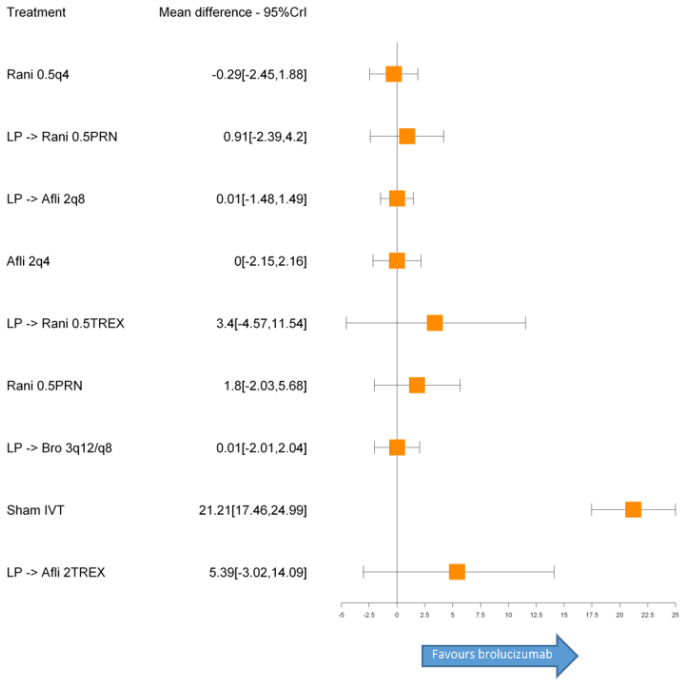
Figure 3.13: Network for mean change in BCVA from Baseline to two years



Abbreviations: Afli: aflibercept; BCVA: best corrected visual acuity; Bro: brolucizumab; IVT: intravitreal; LP: loading phase; PRN: pro re nata; qXw: one injection every X weeks; Rani: ranibizumab; TREX: treat-and-extend dosing regimen.

The indirect comparisons obtained through the NMA are reported in Figure 3.14 (LP → Bro 6q12/q8w versus each comparator). Brolucizumab showed comparable efficacy to aflibercept and ranibizumab for mean change in BCVA from Baseline to two years, with none of the treatment effects for this endpoint significant at a 95% credibility level. Additionally, the results for mean change in BCVA at two years indicated that brolucizumab was statistically significantly better than sham IVT.

Figure 3.14: Forest plot of the NMA results comparing the difference in mean change in BCVA from Baseline to two years between LP → Bro 6q12/q8w and each comparator (fixed-effects)



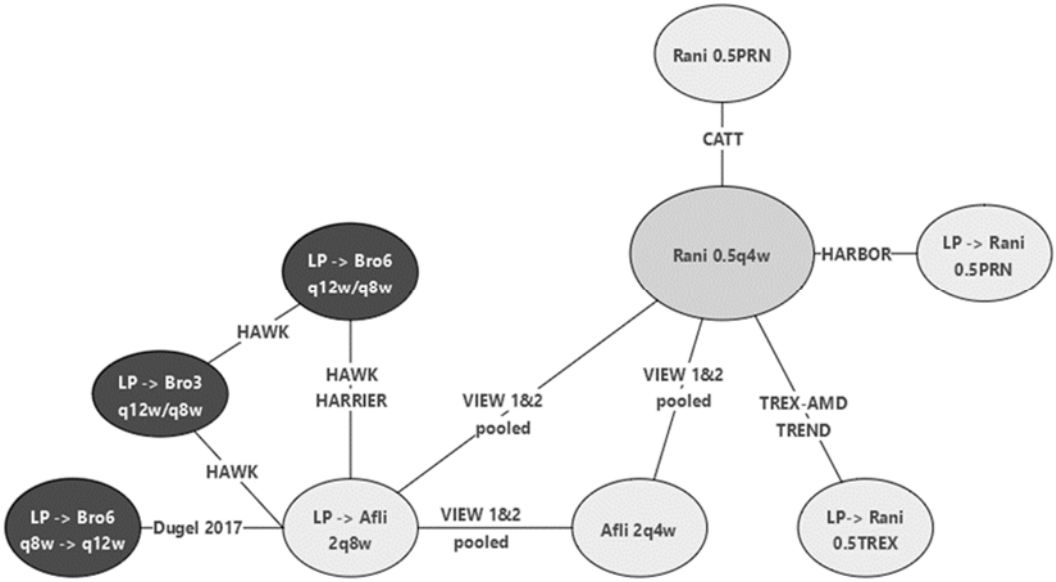
Abbreviations: Afli: aflibercept; BCVA: best corrected visual acuity; Bro: brolucizumab; IVT: intravitreal; LP: loading phase; NMA: network meta-analysis; PRN: pro re nata; qXw: one injection every X weeks; Rani: ranibizumab; TREX: treat-and-extend dosing regimen.

B.3.9.4.3 Mean change in central retinal thickness (Baseline to one year)

At one year, the base case NMA demonstrated brolucizumab (LP → Bro 6q12/q8w) to be statistically significantly better than all aflibercept and ranibizumab regimens at decreasing central retinal thickness from Baseline

The network for mean change in retinal thickness from Baseline at one year is displayed in Figure 3.15. A total of eight studies were included in the analysis. The DIC values were 152.2 and 151.8 for the fixed-effects and random-effects models, respectively. The fixed-effects model was chosen as the random-effects model encountered convergence issues.

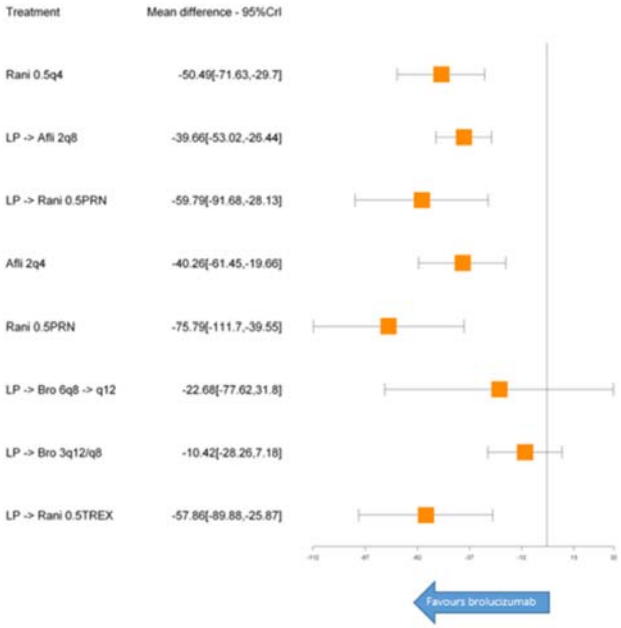
Figure 3.15: Network for mean change in central retinal thickness from Baseline to one year



Note: Dugel 2017 = OSPREY
Abbreviations: Afli: aflibercept; Bro: brolucizumab; IVT: intravitreal; LP: loading phase; NMA: network meta-analysis; PRN: pro re nata; PRNX: pro re nata and extend dosing regimen; qXw: one injection every X weeks; Rani: ranibizumab; TREX: treat-and-extend dosing regimen; TTT: transpupillary thermotherapy.

The indirect comparisons obtained through the NMA are reported in Figure 3.16 for LP → Bro 6q12/q8w versus each comparator. The results for mean change in retinal thickness at one year indicated that brolucizumab (LP → Bro 6q12/q8w) is statistically significantly better at decreasing retinal thickness than every comparator.

Figure 3.16: Forest plot of the NMA results comparing the difference in mean change in central retinal thickness from Baseline to one year between LP → Bro 6q12/q8w and each comparator (fixed-effects)



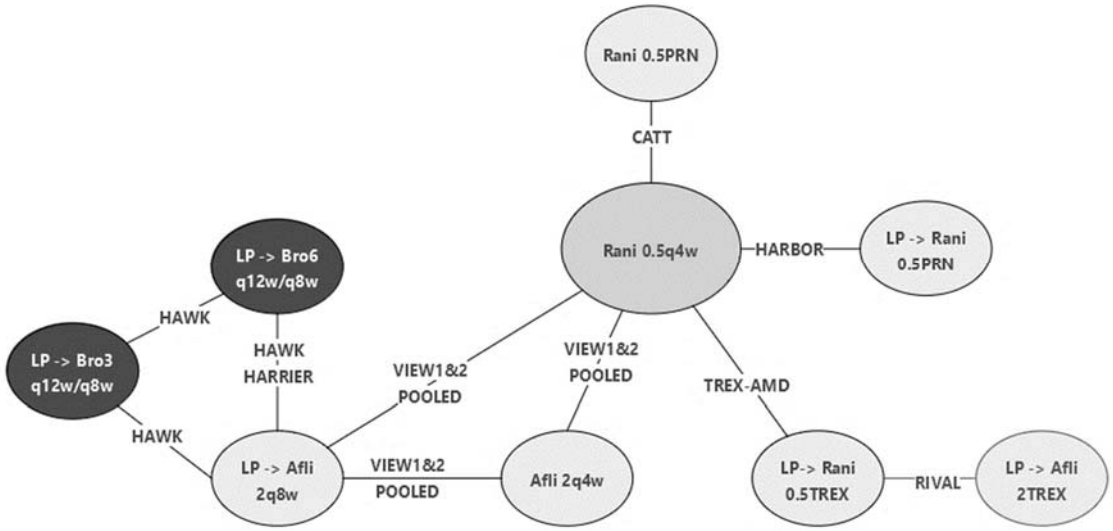
Abbreviations: Afli: aflibercept; Bro: brolucizumab; IVT: intravitreal; LP: loading phase; NMA: network meta-analysis; PRN: pro re nata; PRNX: pro re nata and extend dosing regimen; qXw: one injection every X weeks; Rani: ranibizumab; TREX: treat-and-extend dosing regimen.

B.3.9.4.4 Mean change in central retinal thickness (Baseline to two years)

At two years, the base case NMA demonstrated brolucizumab to be statistically significantly better than most aflibercept and ranibizumab regimens at decreasing retinal thickness from Baseline

The network for mean change in retinal thickness from Baseline to two years is displayed in Figure 3.17. Eight studies were included in the analysis. This section presents the results from the fixed-effects model of the NMA, as the DIC values were 129.4 and 129.2 for the fixed-effects and random-effects models, respectively.

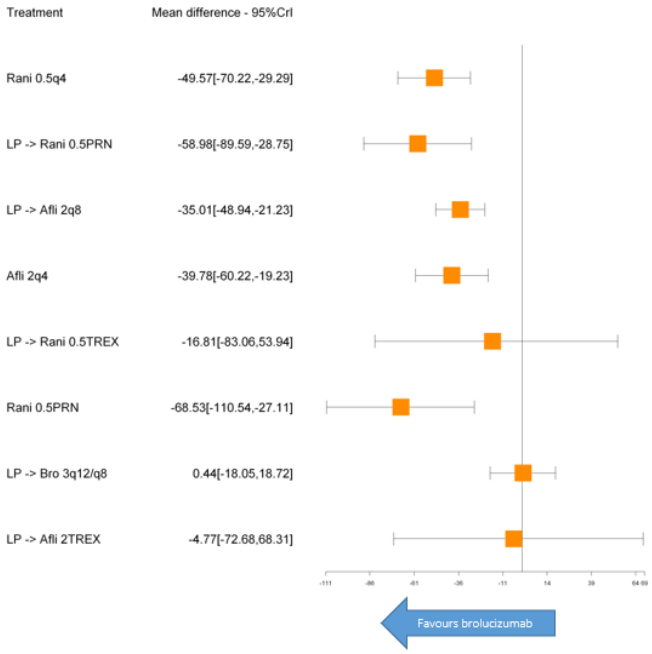
Figure 3.17: Network for mean change in central retinal thickness from Baseline to two years



Abbreviations: Afli: aflibercept; Bro: brolucizumab; LP: loading phase; NMA: network meta-analysis; PRN: pro re nata; qXw: one injection every X weeks; Rani: ranibizumab; TREX: treat-and-extend dosing regimen.

The indirect comparisons obtained through the NMA are reported in Figure 3.18 (LP → Bro 6q12/q8w versus each comparator). The results for mean change in retinal thickness at two years indicated that brolucizumab (LP → Bro 6q12/q8w) is statistically significantly better at decreasing retinal thickness than every comparator other than LP → Rani 0.5TREX and LP → Afli 2TREX (the results for these comparisons were not significant at a 95% credibility level).

Figure 3.18: Forest plot of the NMA results comparing the difference in mean change in central retinal thickness from Baseline to two years between LP → Bro 6q12/q8w and each comparator (fixed-effects)



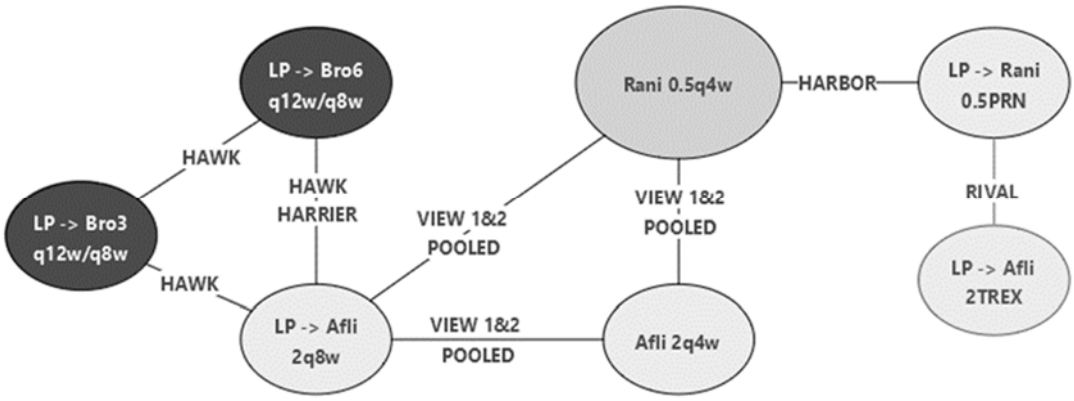
Abbreviations: Afli: aflibercept; Bro: brolucizumab; LP: loading phase; NMA: network meta-analysis; PRN: pro re nata; qXw: one injection every X weeks; Rani: ranibizumab; TREX: treat-and-extend dosing regimen.

B.3.9.4.5 Treatment discontinuation (Baseline to two years)

The base case NMA demonstrated brolucizumab to be associated with comparable odds of discontinuation to aflibercept and ranibizumab, from Baseline to two years

The network for treatment discontinuation from Baseline to two years is displayed in Figure 3.19. Five studies were included in the analysis. This section presents the results from the fixed-effects model of the NMA because the DIC was lower than that of the random-effects model (76.3 versus 77.5).

Figure 3.19: Network for overall treatment discontinuation at 2 years

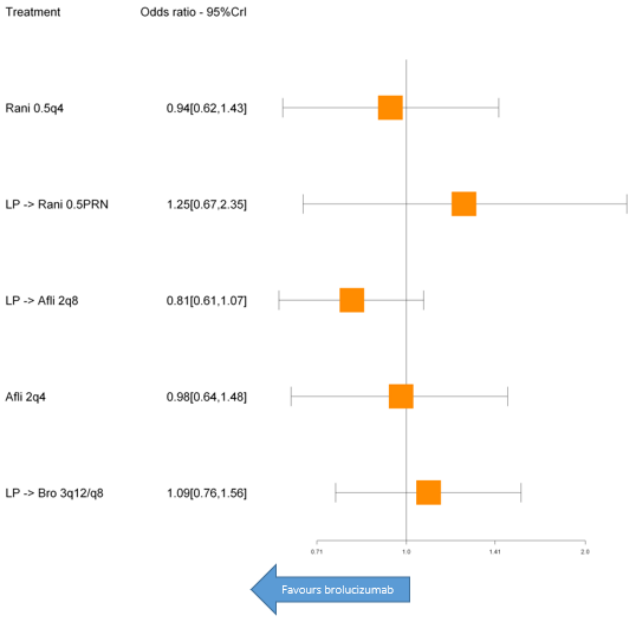


Abbreviations: Afli: aflibercept; Bro: brolucizumab; LP: loading phase; PRN: pro re nata; qXw: one injection every X weeks; Rani: ranibizumab.

The indirect comparisons obtained through the NMA are reported in Figure 3.20 (LP → Bro 6q12/q8w versus each comparator). Brolucizumab showed comparable efficacy to aflibercept

and ranibizumab for the odds of treatment discontinuation from Baseline to two years, with none of the treatment effects for this endpoint significant at a 95% credibility level.

Figure 3.20: Forest plot of the NMA results comparing the odds of treatment discontinuation from Baseline to two years between LP → Bro 6q12/q8w and each comparator (fixed-effects)



Abbreviations: Afli: aflibercept; Bro: brolucizumab; LP: loading phase; NMA: network meta-analysis; PRN: pro re nata; qXw: one injection every X weeks; Rani: ranibizumab.

B.3.9.4.6 Baseline pooling: Injection frequency (Baseline to one year)

For all baseline pooling results, the random-effects results were prioritised to take into account any between-trial heterogeneity.

Arm-based pooling demonstrated brolucizumab to have the second lowest injection frequency from Baseline to one year, when compared to aflibercept and ranibizumab regimens

The frequency of injections from Baseline to one year was assessed through arm-based pooling only. The absolute treatment effects for injection frequency at one year are presented in Table 3.17. When the treatment regimen included only one trial, the results are presented directly from that clinical trial. Among the included treatments, Afli 2q4w had the highest injection frequency, with a mean number of 11.9 injections. LP → Rani 0.5PRNX had the lowest injection frequency, with an average of 5.5 injections during the first year of follow-up. However, a PRNX regimen will be associated with high monitoring numbers (~10.3); therefore, LP → Bro 6q12/q8w will provide the lowest total injection and monitoring visits

Table 3.17: Absolute treatment effects for injection frequency from Baseline to one year, where baseline pooling is conducted for treatments with more than one trial

Intervention	No. of trials[a]	Fixed-effects		Random-effects		Pooled SD	Cochran Q Statistic	P-value Cochran Q	Between-trial variance
		Mean	SE	Mean	SE				
Afli 2q4w	1	11.90	0.13	11.90	0.13	3.13	0.00	.	0.00
LP → Afli 2TREX	1	9.70	0.22	9.70	0.22	2.55	0.00	.	0.00
LP → Afli 2q8w	3	7.23	0.04	7.14	0.15	1.90	26.72	0.00	0.06
LP → Bro 3q12/q8w	1	6.60	0.05	6.60	0.05	0.96	0.00	.	0.00
LP → Bro 6q12/q8w	2	6.66	0.04	6.66	0.05	1.03	1.64	0.20	0.00
LP → Rani 0.5PRN	2	7.52	0.12	7.08	0.65	2.17	14.17	0.00	0.79
LP → Rani 0.5PRNX	1	5.50	0.31	5.50	0.31	2.17	0.00	.	0.00
LP → Rani 0.5TREX	4	9.49	0.09	9.54	0.12	2.59	4.85	0.18	0.02
Rani 0.5PRN	1	6.90	0.18	6.90	0.18	3.00	0.00	.	0.00
Rani 0.5q4w	6	11.71	0.06	11.78	0.13	2.69	21.40	0.00	0.07

[a]When the treatment regimen included only one trial, the results are presented directly from that clinical trial. For treatments with more than one trial, baseline pooling was conducted to obtain an absolute treatment effect estimate.
Abbreviations: Afli: aflibercept; Bro: brolucizumab; LP: loading phase; NMA: network meta-analysis; PRN: pro re nata; qXw: one injection every X weeks; Rani: ranibizumab; SD: standard deviation; SE: standard error; TREX: treat and extend.

B.3.9.4.7 Baseline pooling: Injection frequency (one year to two years)

Arm-based pooling demonstrated that brolucizumab has the lowest injection frequencies from one year to two years, when compared to aflibercept and ranibizumab regimens

The frequency of injections from one year to two years was assessed through arm-based pooling only. The absolute treatment effects for injection frequency at one years are presented in Table 3.18. Rani 0.5q4w had the highest injection frequency, with a mean number of 11.16 injections for the random-effects model. LP → Bro 6q12/q8w had the lowest number of injections, with a mean number of 4.76 for the random-effects model.

Table 3.18: Absolute treatment effects for injection frequency from one year to two years, where baseline pooling is conducted for treatments with more than one trial

Intervention	No. of trials[a]	Fixed-effects		Random-effects		Pooled SD	Cochran Q Statistic	P-value Cochran Q	Between-trial variance
		Mean	SE	Mean	SE				
Afli 2q4w → PRN	1	4.80	0.08	4.80	0.08	1.95	0.00	.	0.00
LP → Afli 2TREX	1	7.30	0.54	7.30	0.54	6.28	0.00	.	0.00
LP → Afli 2q8w	2	5.55	0.09	5.47	0.25	2.60	6.10	0.01	0.10
LP → Afli 2q8w → PRN	1	5.00	0.07	5.00	0.07	1.84	0.00	.	0.00

LP → Bro 3q12/q8w	1	4.80	0.12	4.80	0.12	2.32	0.00	.	0.00
LP → Bro 6q12/q8w	2	4.83	0.09	4.76	0.35	2.35	15.46	0.00	0.23
LP → Rani 0.5PRN	1	5.60	0.23	5.60	0.23	3.86	0.00	.	0.00
LP → Rani 0.5TREX	2	8.22	0.40	8.22	0.40	5.88	0.38	0.54	0.00
Rani 0.5PRN	2	10.26	0.22	11.16	1.19	3.86	7.27	0.01	2.48
Rani 0.5q4w	1	5.60	0.10	5.60	0.10	2.38	0.00	.	0.00
Rani 0.5q4w → PRN	1	4.80	0.08	4.80	0.08	1.95	0.00	.	0.00

[a]When the treatment regimen included only one trial, the results are presented directly from that clinical trial. For treatments with more than one trial, baseline pooling was conducted to obtain an absolute treatment effect estimate.
Abbreviations: Afli: aflibercept; Bro: brolucizumab; LP: loading phase; NMA: network meta-analysis; PRN: pro re nata; qXw: one injection every X weeks; Rani: ranibizumab; SD: standard deviation; SE: standard error; TREX: treat and extend.

B.3.9.4.8 Baseline pooling: Treatment discontinuation

Molecule-based baseline pooling was conducted for treatment discontinuation, as discontinuation was not found to be statistically significantly affected by regimen characteristics in the NMA conducted by NICE in their clinical guideline for wAMD (NG82).[86] The results for aflibercept 2mg, brolucizumab 6mg, and ranibizumab 0.5mg are reported below in Table 3.19

Table 3.19: Baseline pooling results for treatment discontinuation at 2 years

Intervention	No. of trials	Fixed-effects		Random-effects		Pooled SD	Cochran Q Statistic	P-value Cochran Q	Between-trial variance
		Mean	SE	Mean	SE				
Aflibercept	5	0.164	0.008	0.171	0.015	0.371	12.954	0.012	0.001
Brolucizumab	2	0.144	0.013	0.151	0.036	0.355	7.421	0.006	0.002
Ranibizumab	6	0.152	0.010	0.152	0.010	0.359	1.780	0.619	0.000

Abbreviations: SD: standard deviation; SE: standard error.

B.3.9.4.9 Adverse events

Molecule-based baseline pooling was conducted for the frequency of serious AEs, as it is not anticipated that a dosing regimen would influence the incidence of serious AEs. The results for aflibercept 2mg, brolucizumab 6mg, and ranibizumab 0.5mg are reported below in Table 3.20.

Table 3.20: Two-year molecule-based baseline pooling results for the frequency of cataracts

Molecule	No. of trials	Mean (fixed-effects)	SE (fixed-effects)	Mean (random-effects)	SE (random-effects)	Pooled SD	Cochran Q Statistic	P-value of Cochran Q	Between-trial variance
2 years									
Aflibercept	4	0.0069	0.0002	0.0060	0.0007	0.0182	16.5145	0.0009	0.0000
Brolucizumab	2	0.0030	0.0001	0.0030	0.0001	0.0030	0.0000	1.0000	0.0000
Ranibizumab	1	0.002	0.0000818	0.002	0.0000818	0.001996	0.0000	0.0000	0.0000

Abbreviations: SD: standard deviation; SE: standard error.

Table 3.21: Two-year molecule-based baseline pooling results for the frequency of endophthalmitis

Molecule	No. of trials	Mean (fixed-effects)	SE (fixed-effects)	Mean (random-effects)	SE (random-effects)	Pooled SD	Cochran Q Statistic	P-value of Cochran Q	Between-trial variance
2 years									
Aflibercept	4	0.0039	0.0001	0.0033	0.0015	0.0186	164.0280	0.0000	0.0000
Brolucizumab	2	0.0036	0.0001	0.0055	0.0025	0.0054	125.5503	0.0000	0.0000
Ranibizumab	6	0.0092	0.0003	0.0100	0.0021	0.0215	85.2762	0.0000	0.0000
Sham	1	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	-	0.0000

Abbreviations: SD: standard deviation; SE: standard error.

Table 3.22: Two-year molecule-based baseline pooling results for the frequency of intraocular inflammation

Molecule	No. of trials	Mean (fixed-effects)	SE (fixed-effects)	Mean (random-effects)	SE (random-effects)	Pooled SD	Cochran Q Statistic	P-value of Cochran Q	Between-trial variance
2 years									
Aflibercept	2	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Brolucizumab	2	0.0091	0.0003	0.0095	0.0015	0.0094	18.1886	0.0000	0.0000
Ranibizumab	2	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000

Abbreviations: SD: standard deviation; SE: standard error.

Table 3.23: Two-year molecule-based baseline pooling results for the frequency of retinal detachment

Molecule	No. of trials	Mean (fixed-effects)	SE (fixed-effects)	Mean (random-effects)	SE (random-effects)	Pooled SD	Cochran Q Statistic	P-value of Cochran Q	Between-trial variance
2 years									
Aflibercept	4	0.0023	0.0001	0.0025	0.0004	0.0107	55.0041	0.0000	0.0000
Brolucizumab	2	0.0030	0.0001	0.0030	0.0001	0.0030	0.0000	1.0000	0.0000
Ranibizumab	4	0.0049	0.0002	0.0041	0.0009	0.0270	3.9504	0.2669	0.0049
Sham	1	0.0040	0.0003	0.0040	0.0003	0.0040	0.0000	-	0.0000

Abbreviations: SD: standard deviation; SE: standard error.

Table 3.24: Two-year molecule-based baseline pooling results for the frequency of retinal pigment epithelial tear

Molecule	No. of trials	Mean (fixed-effects)	SE (fixed-effects)	Mean (random-effects)	SE (random-effects)	Pooled SD	Cochran Q Statistic	P-value of Cochran Q	Between-trial variance
2 years									
Aflibercept	4	0.0048	0.0002	0.0024	0.0015	0.0243	19.1822	0.0003	0.0000
Brolucizumab	2	0.0035	0.0001	0.0040	0.0010	0.0040	43.5997	0.0000	0.0000
Ranibizumab	1	0.0020	0.0001	0.0020	0.0001	0.0020	0.0000	-	0.0000

Abbreviations: SD: standard deviation; SE: standard error.

Table 3.25: Two-year molecule-based baseline pooling results for the frequency of retinal tear

Molecule	No. of trials	Mean (fixed-effects)	SE (fixed-effects)	Mean (random-effects)	SE (random-effects)	Pooled SD	Cochran Q Statistic	P-value of Cochran Q	Between-trial variance
2 years									
Aflibercept	1	0.0030	0.0002	0.0030	0.0002	0.0030	0.0000	-	0.0000
Brolucizumab	1	0.0050	0.0003	0.0050	0.0003	0.0050	0.0000	-	0.0000
Ranibizumab	3	0.0040	0.0003	0.0040	0.0003	0.0309	1.4049	0.4954	0.0000
Sham	1	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	-	0.0000

Abbreviations: SD: standard deviation; SE: standard error.

Table 3.26: Two-year molecule-based baseline pooling results for the frequency of gastrointestinal events

Molecule	No. of trials	Mean (fixed-effects)	SE (fixed-effects)	Mean (random-effects)	SE (random-effects)	Pooled SD	Cochran Q Statistic	P-value of Cochran Q	Between-trial variance
2 years									
Ranibizumab	2	0.0060	0.0005	0.0060	0.0005	0.0304	0.4877	0.4849	0.0000

Abbreviations: SD: standard deviation; SE: standard error.

Table 3.27: Two-year molecule-based baseline pooling results for the frequency of stroke

Molecule	No. of trials	Mean (fixed-effects)	SE (fixed-effects)	Mean (random-effects)	SE (random-effects)	Pooled SD	Cochran Q Statistic	P-value of Cochran Q	Between-trial variance
2 years									
Aflibercept	4	0.0084	0.0002	0.0094	0.0009	0.0090	64.7270	0.0000	0.0000
Brolucizumab	2	0.0102	0.0005	0.0063	0.0048	0.0240	23.4139	0.0000	0.0000
Ranibizumab	4	0.0059	0.0002	0.0104	0.0018	0.0098	257.7988	0.0000	0.0000
Sham	1	0.0080	0.0005	0.0080	0.0005	0.0079	0.0000	-	0.0000

Abbreviations: SD: standard deviation; SE: standard error.

B.3.9.5 Uncertainties in the indirect and mixed treatment comparisons

The NMA was based on data from RCTs, which can be considered the gold standard in terms of evidence quality. The methodology employed for conducting the SLR and NMA was based on the guide to the methods of technology appraisal.[85] As such, the NMA was conducted in a Bayesian framework and the best model (fixed-effects versus random-effects) was chosen based on the deviance information criterion (DIC). The results from the NMA were generally similar to the results of the NMA in wAMD conducted by NICE in their clinical guideline (NG82) and, in the few cases where there were differences, the source of the difference was found to be due to the decisions made on which studies to include. Furthermore, the results of the NMA were supported by several sensitivity analyses conducted to assess the robustness of the base case results.

In addition, appropriate methods were used to impute missing data for the SD/SE in order to include as much relevant evidence as possible. Among the trials included in the NMA, the study populations were similar, as shown by the characteristics reported at baseline. Whilst heterogeneity was identified in the direct comparison between TREND, TREX-AMD and CAN-TREAT for mean change in BCVA at one year, this was likely due to the inherent variability of the follow-up treatment intervals in the TREX regimen. Furthermore, no inconsistency was identified in the closed loop containing the HAWK and HARRIER trials. The results from this NMA therefore provide a robust, up-to-date comparison of brolucizumab versus the relevant comparators to this appraisal: aflibercept and ranibizumab.

It is acknowledged that there are some limitations associated with the NMA. It was not possible to obtain meta-regression results adjusted on relevant covariates such as Baseline BCVA and treatment regimen. This was because the networks did not provide enough information to allow the models to converge.

Another limitation of the NMA was that time equivalence was assumed for one-year and two-year outcomes. In order to include all available evidence for treatments of interest, equivalence was assumed between 48 and 52 weeks for one-year outcomes and between 96 and 104 weeks for two-year outcomes. No publication was found to validate this hypothesis, but the results for HAWK and HARRIER at Week 52 were similar to those at Week 48. In addition, the results from sensitivity analyses that extrapolated endpoints that were published at 48 weeks and 104 weeks were similar to the base case. This demonstrated that there was no impact on the results with the equivalence assumption used.

In order to connect the networks, an assumption was made for VIEW 1&2. Whilst patients in VIEW 1&2 began a PRN treatment regimen at 52 weeks, these patients were still considered as remaining on continuous treatment arms (i.e. LP → Afli 2q8w, Afli 2q4w, and Rani 0.5q4w) in order to connect to the brolucizumab treatments. To assess the impact of this assumption, heterogeneity for Rani 0.5q4w was assessed for each endpoint at two years, and was only found for injection frequency. Since only baseline pooling was conducted for injection frequency, this switch to a PRN regimen was taken into account in these analyses. Furthermore CNV lesion size was considered as a treatment effect modifier in nAMD following feedback from a leading clinical expert who indicated that VIEW 1&2 seemed to be the biggest outlier. However, as described above, this trial was needed to connect the network and therefore this represents a limitation of the analysis.

A final limitation of the NMA was that Rani 0.5q4w versus LP → Rani 0.5TREX and LP → Bro 6q12/q8w versus LP → Afli 2q8w were the only comparisons for which multiple studies were included (as VIEW 1&2 were pooled in the analyses). The other comparisons were all connected by one trial only, making these arms of the network less robust.

Despite the above limitations the results of the NMA are still considered to be robust and represent the most recent analysis of comparative efficacy between brolucizumab and the relevant comparators aflibercept and ranibizumab. Results of the NMA demonstrated brolucizumab to be associated with comparable visual outcomes in terms of BCVA and superior anatomical outcomes in terms of decreasing retinal thickness with a lower injection frequency than current standard of care, enabling a cost-comparison analysis to be conducted.

B.3.10 Adverse reactions in HAWK and HARRIER

Summary

- The overall safety profile of brolucizumab observed across the HAWK and HARRIER trials was comparable to the safety profile of aflibercept
- Over 96 weeks, the mean number of active injections administered to patients in the brolucizumab treatment arms of HAWK and HARRIER was between 1 and 1.5 fewer than the number administered in the aflibercept arms
- The overall incidence of ocular and non-ocular AEs was balanced across all treatment arms in both HAWK and HARRIER and comparable to previous clinical trials of brolucizumab
  - The proportion of patients experiencing ≥1 ocular AE was 218 (60.9%), 220 (61.1%) and 201 (55.8%) patients in the brolucizumab 3 mg, brolucizumab 6 mg and aflibercept 2 mg arms, respectively in HAWK, and 174 (47.0%) and 176 (47.7%) patients in the brolucizumab 6 mg and aflibercept 2 mg arms, respectively in HARRIER
  - In HAWK, conjunctival haemorrhage was the most frequently reported ocular AE, occurring in 39 (10.9%), 29 (8.1%), and 32 (8.9%) patients in the brolucizumab 3 mg, brolucizumab 6 mg, and aflibercept 2 mg arms, respectively. In HARRIER, the most frequently reported ocular AE in the brolucizumab 6 mg arm was reduced VA, occurring in 32 (8.6%) patients; in the aflibercept 2 mg arm, cataract was the most frequently reported AE.
  - Non-ocular AEs were predominantly mild or moderate in severity. The most frequent non-ocular adverse events were typical of those reported in a nAMD population and there were no notable differences between arms. In HAWK up to Week 96, 60 patients (16.8%) in the brolucizumab 3 mg arm, 48 patients (13.3%) in the brolucizumab 6 mg arm, and 72 patients (20.0%) in the aflibercept 2 mg arm experienced at least 1 severe non-ocular AE. In HARRIER, up to Week 96, 37 patients (10.0%) in the brolucizumab 6 mg arm and 44 subjects (11.9%) in the aflibercept 2 mg arm experienced at least 1 severe non-ocular AE.
- Overall, no new, previously unreported types of AEs were identified compared with other anti-VEGF therapies.

B.3.10.1 Treatment exposure

Over 96 weeks, the mean number of active injections administered in the brolucizumab treatment arms of HAWK and HARRIER was between 1 and 1.5 fewer than the number administered in the aflibercept arms

The number of active injections administered overall from Baseline to Week 96 is presented in Table 3.28.

To account for premature treatment discontinuations, the number of active injections was adjusted by the number of days on the study (number of active injections expected during given study period versus number of active injections received during that study period). The mean number of active injections administered overall, weighted by the duration of study participation up to Week 96, was between 1 and 1.5 fewer for patients in the brolucizumab arms than the aflibercept arms in both HAWK (brolucizumab 3 mg: [redacted]; brolucizumab 6 mg: [redacted]; aflibercept 2 mg: [redacted]) and HARRIER (brolucizumab 6 mg: [redacted]; aflibercept 2 mg: [redacted]). The median number of injections received from Baseline to Week 96 was 11.0 for brolucizumab 3 mg, 10.0 for brolucizumab 6 mg and 13.0 for aflibercept 2 mg in HAWK, and 11.0 for brolucizumab 6 mg and 13.0 for aflibercept 2 mg in HARRIER. The differences in the number of active injections between the brolucizumab 6 mg and aflibercept 2 mg arms were driven by differences in the dosing intervals, with a majority of brolucizumab 6 mg subjects on a q12w dosing interval immediately following the loading dose phase.

Table 3.28: Extent of exposure to study treatment: number of active injections from Baseline to Week 96 (SAF)

Trial name	HAWK			HARRIER	
Extent of exposure	**Brolucizumab 3 mg, (N=358) n (%)**	**Brolucizumab 6 mg, (N=360) n (%)**	**Aflibercept 2 mg, (N=360) n (%)**	**Brolucizumab 6 mg, (N=370) n (%)**	**Aflibercept 2 mg, (N=369) n (%)**
Number of injections – n (%)					
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
11	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
13	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
14	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Descriptive statistics					
N	358	360	360	370	369
Mean (SD)	10.5 (2.55)	10.2 (2.74)	11.3 (3.21)	10.9 (2.38)	12.1 (2.32)
Median	10.0	10.0	13.0	11.0	13.0
Min, Max	2, 13	1, 13	1, 13	1, 13	1, 14

Abbreviations: SAF: safety analysis set; SD: standard deviation.
Source: HAWK CSR;[78] HARRIER CSR.[79]

B.3.10.2 Adverse events

B.3.10.2.1 Ocular adverse events

The number of patients with ≥1 AE in the study eye at Week 48 was similar across all treatment arms but higher in HAWK (brolucizumab 3 mg: 175 patients [48.9%]; brolucizumab 6 mg: 179 [49.7%]; aflibercept 2 mg: 170 [47.2%]) than HARRIER (brolucizumab 6 mg: 122 [33.0%]; aflibercept 2 mg: 119 [32.2%]). In HAWK, conjunctival haemorrhage was the most frequently ocular AE in the brolucizumab arms (brolucizumab 3 mg: 30 patients [8.4%]; brolucizumab 6 mg: 23 patients [6.4%]) and VA reduced was the most frequent in the aflibercept arm (24 patients [6.7%]). In HARRIER, VA reduced was the most frequently reported AE, which occurred in 20 subjects (5.4%) in each treatment arm.[76] These data are presented in Appendix F.

At Week 96, the number of patients with ≥1 AE in the study eye was higher than at Week 48 and remained similar across treatment arms and higher in HAWK (brolucizumab 3 mg: 218 patients [60.9%]; brolucizumab 6 mg: 220 [61.1%]; aflibercept 2 mg: 201 [55.8%]) than HARRIER (brolucizumab 6 mg: 174 [47.0%]; aflibercept 2 mg: 176 [47.7%]) (Table 3.29). Conjunctival haemorrhage remained the most frequent ocular AE across all treatment arms in HAWK, and in HARRIER, VA reduced and cataract were the most frequent AEs in the brolucizumab and aflibercept arms, respectively.[84] The majority of ocular AEs were of mild or moderate severity in HAWK (96.1%) and HARRIER (94.9%).

Data relating to ocular AEs in the study eye suspected to be related to the study drug can be found in the CSRs for HAWK and HARRIER.

Table 3.29: Ocular adverse events up to Week 96 (greater than or equal to 2% in any treatment group) by preferred term for the study eye (SAF)

Trial name	HAWK			HARRIER	
Preferred term	**Brolucizumab 3 mg, (N=358) n (%)**	**Brolucizumab 6 mg, (N=360) n (%)**	**Aflibercept 2 mg, (N=360) n (%)**	**Brolucizumab 6 mg, (N=370) n (%)**	**Aflibercept 2 mg, (N=369) n (%)**
Number of patients with at least one event	218 (60.9)	220 (61.1)	201 (55.8)	174 (47.0)	176 (47.7)
Conjunctival haemorrhage	39 (10.9)	29 (8.1)	32 (8.9)	17 (4.6)	19 (5.1)
VA reduced	34 (9.5)	22 (6.1)	29 (8.1)	32 (8.6)	26 (7.0)
Vitreous floaters	26 (7.3)	22 (6.1)	16 (4.4)	15 (4.1)	5 (1.4)
Retinal haemorrhage	14 (3.9)	21 (5.8)	20 (5.6)	12 (3.2)	4 (1.1)
Cataract	18 (5.0)	20 (5.6)	13 (3.6)	11 (3.0)	43 (11.7)
Vitreous detachment	24 (6.7)	19 (5.3)	19 (5.3)	10 (2.7)	8 (2.2)
Dry eye	20 (5.6)	19 (5.3)	26 (7.2)	10 (2.7)	11 (3.0)
Eye pain	28 (7.8)	18 (5.0)	21 (5.8)	13 (3.5)	19 (5.1)
Posterior capsule opacification	16 (4.5)	14 (3.9)	11 (3.1)	-	-
Intraocular pressure increased	16 (4.5)	13 (3.6)	15 (4.2)	14 (3.8)	15 (4.1)
Blepharitis	8 (2.2)	13 (3.6)	12 (3.3)	13 (3.5)	5 (1.4)
Retinal pigment epithelial tear	5 (1.4)	12 (3.3)	4 (1.1)	8 (2.2)	5 (1.4)
Vision blurred	16 (4.5)	11 (3.1)	10 (2.8)	-	-
Visual impairment	15 (4.2)	10 (2.8)	14 (3.9)	-	-
Eye irritation	10 (2.8)	10 (2.8)	11 (3.1)	-	-
Punctate keratitis	11 (3.1)	9 (2.5)	10 (2.8)	-	-
Conjunctivitis	3 (0.8)	9 (2.5)	3 (0.8)	15 (4.1)	8 (2.2)
Iritis	3 (0.8)	9 (2.5)	1 (0.3)	0 (0.0)	1 (0.3)

Uveitis	6 (1.7)	8 (2.2)	1 (0.3)	3 (0.8)	0 (0.0)
Visual field defect	9 (2.5)	7 (1.9)	5 (1.4)	-	-
Corneal abrasion	6 (1.7)	7 (1.9)	10 (2.8)	-	-
Macular fibrosis	10 (2.8)	5 (1.4)	4 (1.1)	-	-
Dry age-related macular degeneration	7 (2.0)	5 (1.4)	3 (0.8)	-	-
Foreign body sensation in eyes	8 (2.2)	4 (1.1)	9 (2.5)	-	-
Lacrimation increased	7 (2.0)	4 (1.1)	5 (1.4)	-	-
Lenticular opacities	7 (2.0)	1 (0.3)	4 (1.1)	13 (3.5)	12 (3.3)

Abbreviations: SAF: safety analysis set.
Source: HAWK CSR;[78] HARRIER CSR;[79] Singh et al. 2019.[84]

B.3.10.2.2 Non-ocular adverse events

The number of patients with ≥1 non-ocular AE at Week 48 was similar across all treatment arms in HAWK (brolucizumab 3 mg: 242 patients [67.6%]; brolucizumab 6 mg: 232 [64.5%]; aflibercept 2 mg: 258 [71.7%]) and HARRIER (brolucizumab 6 mg: 219 [59.2%]; aflibercept 2 mg: 211 [57.2%]). These data are presented in Appendix F.

At Week 96, the number of patients with ≥ 1 non-ocular AE was similar across all treatment arms in HAWK (brolucizumab 3 mg: 301 patients [84.1%]; brolucizumab 6 mg: 289 patients [80.3%]; aflibercept 2 mg: 303 patients [84.2%]) and across both treatment arms in HARRIER trial (brolucizumab 6 mg: 282 patients [76.2%]; aflibercept 2 mg: 272 patients [73.7%]) (Table 3.30).[84] In both trials, nasopharyngitis was the most frequently reported non-ocular AE across all treatment arms at Week 48 and Week 96. Across all treatment arms, the vast majority of ocular AEs up to Week 96 were of mild or moderate severity in HAWK (96.1%) and HARRIER (94.9%).

Additionally, at Week 96 the number of patients with ≥1 non-ocular AE in the study eye suspected to be related to the study drug was 11 in HAWK (brolucizumab 3 mg: 6 patients [1.7%]; brolucizumab 6 mg: 2 patients [0.6%]; aflibercept 2 mg: 3 patients [0.8%]) and 5 in HARRIER (brolucizumab 6 mg: 4 patients [1.1%]; aflibercept 2 mg: 1 patients [0.3%]).

Table 3.30: Non-ocular adverse events up to Week 96 (≥2% in any treatment group) by preferred term for the study eye (SAF)

Trial name	HAWK			HARRIER	
Preferred term	**Brolucizumab 3 mg, (N=358) n (%)**	**Brolucizumab 6 mg, (N=360) n (%)**	**Aflibercept 2 mg, (N=360) n (%)**	**Brolucizumab 6 mg, (N=370) n (%)**	**Aflibercept 2 mg, (N=369) n (%)**
Number of subjects with at least one event	301 (84.1)	289 (80.3)	303 (84.2)	282 (76.2)	272 (73.7)
Nasopharyngitis	44 (12.3)	38 (10.6)	44 (12.2)	43 (11.6)	31 (8.4)
Pneumonia	17 (4.7)	32 (8.9)	20 (5.6)	7 (1.9)	13 (3.5)
Urinary tract infection	41 (11.5)	27 (7.5)	41 (11.4)	16 (4.3)	19 (5.1)
Hypertension	33 (9.2)	25 (6.9)	24 (6.7)	28 (7.6)	25 (6.8)
Upper respiratory tract infection	17 (4.7)	18 (5.0)	16 (4.4)	6 (1.6)	14 (3.8)
Influenza	17 (4.7)	17 (4.7)	20 (5.6)	24 (6.5)	27 (7.3)
Arthralgia	19 (5.3)	15 (4.2)	21 (5.8)	14 (3.8)	13 (3.5)
Pain in extremity	14 (3.9)	15 (4.2)	10 (2.8)	9 (2.4)	4 (1.1)
Back pain	26 (7.3)	14 (3.9)	17 (4.7)	16 (4.3)	28 (7.6)
Diarrhoea	11 (3.1)	14 (3.9)	13 (3.6)	10 (2.7)	6 (1.6)
Cough	20 (5.6)	13 (3.6)	17 (4.7)	12 (3.2)	8 (2.2)
Bronchitis	13 (3.6)	13 (3.6)	22 (6.1)	23 (6.2)	21 (5.7)
Constipation	11 (3.1)	13 (3.6)	13 (3.6)	-	-
Nausea	17 (4.7)	12 (3.3)	12 (3.3)	-	-
Headache	10 (2.8)	12 (3.3)	13 (3.6)	12 (3.2)	8 (2.2)
Contusion	7 (2.0)	12 (3.3)	12 (3.3)	-	-
Chronic obstructive pulmonary disease	6 (1.7)	12 (3.3)	12 (3.3)	-	-
Arthritis	4 (1.1)	12 (3.3)	13 (3.6)	-	-
Sinusitis	17 (4.7)	11 (3.1)	14 (3.9)	-	-
Fall	18 (5.0)	10 (2.8)	7 (1.9)	-	-
Musculoskeletal pain	4 (1.1)	10 (2.8)	4 (1.1)	-	-

Seasonal allergy	3 (0.8)	10 (2.8)	9 (2.5)	-	-
Osteoarthritis	14 (3.9)	9 (2.5)	11 (3.1)	19 (5.1)	7 (1.9)
Blood pressure increased	9 (2.5)	9 (2.5)	9 (2.5)	2 (0.5)	11 (3.0)
Cardiac failure congestive	6 (1.7)	9 (2.5)	6 (1.7)	-	-
Atrial fibrillation	13 (3.6)	8 (2.2)	15 (4.2)	5 (1.4)	10 (2.7)
Dizziness	9 (2.5)	8 (2.2)	6 (1.7)	5 (1.4)	9 (2.4)
Gamma-glutamyltransferase increased	8 (2.2)	8 (2.2)	7 (1.9)	-	-
Herpes zoster	6 (1.7)	8 (2.2)	8 (2.2)	-	-
Dental caries	6 (1.7)	8 (2.2)	7 (1.9)	-	-
Basal cell carcinoma	5 (1.4)	8 (2.2)	6 (1.7)	-	-
Neck pain	2 (0.6)	8 (2.2)	3 (0.8)	-	-
Anaemia	12 (3.4)	7 (1.9)	15 (4.2)	5 (1.4)	8 (2.2)
Gastroesophageal reflux disease	11 (3.1)	7 (1.9)	3 (0.8)	-	-
Oedema peripheral	4 (1.1)	7 (1.9)	8 (2.2)	-	-
Dyspnoea	9 (2.5)	6 (1.7)	8 (2.2)	-	-
Vomiting	7 (2.0)	6 (1.7)	5 (1.4)	-	-
Anxiety	13 (3.6)	5 (1.4)	10 (2.8)	-	-
Insomnia	11 (3.1)	5 (1.4)	10 (2.8)	-	-
Laceration	9 (2.5)	5 (1.4)	6 (1.7)	-	-
Cystitis	9 (2.5)	5 (1.4)	4 (1.1)	17 (4.6)	5 (1.4)
Benign prostatic hyperplasia	8 (2.2)	5 (1.4)	5 (1.4)	-	-
Depression	7 (2.0)	5 (1.4)	7 (1.9)	-	-
Blood uric acid increased	7 (2.0)	4 (1.1)	4 (1.1)	-	-
Dehydration	4 (1.1)	4 (1.1)	8 (2.2)	-	-
Coronary artery disease	9 (2.5)	3 (0.8)	3 (0.8)	-	-
Asthenia	7 (2.0)	3 (0.8)	2 (0.6)	-	-
Blood urea increased	10 (2.8)	2 (0.6)	5 (1.4)	-	-

Haematoma	7 (2.0)	2 (0.6)	4 (1.1)	-	-
Muscle strain	4 (1.1)	1 (0.3)	10 (2.8)	-	-
Hypercholesterolaemia	-	-	-	13 (3.5)	8 (2.2)
Sciatica	-	-	-	9 (2.4)	8 (2.2)
Pharyngitis	-	-	-	2 (0.5)	12 (3.3)
Syncope	-	-	-	8 (2.2)	8 (2.2)

Abbreviations: SAF: safety analysis set.
Source: HAWK CSR;[78] HARRIER CSR.[79]

B.3.10.3 Serious adverse events

B.3.10.3.1 Serious ocular adverse events

At Week 48, a total of 19 patients experienced ≥1 ocular SAE in the study eye in HAWK (brolucizumab 3 mg: 5 patients [1.4%]; brolucizumab 6 mg: 11 patients [3.1%]; aflibercept 2 mg: 3 patients [0.8%]) and 13 patients in HARRIER (brolucizumab 6 mg: 9 patients [2.4%]; aflibercept 2 mg: 4 patients [1.1%]).[76] In HAWK, the most frequently reported ocular SAEs in the study eye were endophthalmitis and uveitis in the brolucizumab arms and VA reduced in the aflibercept arms. In HARRIER, the most frequently reported ocular SAEs in the study eye was uveitis in the brolucizumab arm; in the aflibercept arm none of the SAEs were reported in more than 1 patient each. These data are presented in Appendix F and are comparable to the safety profiles reported for anti-VEGF therapies in previous trials.

At Week 96, the number of patients who experienced ≥1 ocular SAE in the study eye increased to 24 patients experienced in HAWK (brolucizumab 3 mg: 7 patients [2.0%]; brolucizumab 6 mg: 12 patients [3.3%]; aflibercept 2 mg: 5 patients [1.4%]) and 19 patients in HARRIER (brolucizumab 6 mg: 13 patients [3.5%]; aflibercept 2 mg: 6 patients [1.6%]) (Table 3.31).[84] In HAWK, the most frequently reported ocular SAEs were endophthalmitis and VA reduced in the brolucizumab and aflibercept arms, respectively. In HARRIER, the most frequently reported ocular SAE in the brolucizumab arm was uveitis; none of the SAEs in the aflibercept arm were reported in more than 1 patient each.

Table 3.31: Serious ocular adverse events up to Week 96 by preferred term for the study eye (SAF)

Trial name	HAWK			HARRIER	
Preferred term	**Brolucizumab 3 mg, (N=358) n (%)**	**Brolucizumab 6 mg, (N=360) n (%)**	**Aflibercept 2 mg, (N=360) n (%)**	**Brolucizumab 6 mg, (N=370) n (%)**	**Aflibercept 2 mg, (N=369) n (%)**
Number of patients with at least one event	7 (2.0)	12 (3.3)	5 (1.4)	13 (3.5)	6 (1.6)

Endophthalmitis	3 (0.8)	3 (0.8)	0 (0.0)	1 (0.3)	1 (0.3)
Uveitis	1 (0.3)	2 (0.6)	0 (0.0)	3 (0.8)	0 (0.0)
Retinal detachment	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)
VA reduced	0 (0.0)	1 (0.3)	2 (0.6)	1 (0.3)	1 (0.3)
Macular hole	0 (0.0)	1 (0.3)	1 (0.3)	-	-
Cataract	0 (0.0)	1 (0.3)	0 (0.0)	-	-
Retinal artery thrombosis	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.3)	0 (0.0)
Retinal depigmentation	0 (0.0)	1 (0.3)	0 (0.0)	-	-
Retinopathy proliferative	0 (0.0)	1 (0.3)	0 (0.0)	-	-
Vitritis	0 (0.0)	1 (0.3)	0 (0.0)	-	-
Retinal artery occlusion	3 (0.8)	0 (0.0)	0 (0.0)	1 (0.0)	1 (0.3)
Glaucoma	1 (0.3)	0 (0.0)	0 (0.0)	-	-
Cataract subscapular	0 (0.0)	0 (0.0)	1 (0.3)	-	-
Retinal tear	-	-	-	2 (0.5)	1 (0.3)
Retinal pigment epithelial tear	-	-	-	2 (0.5)	0 (0.0)
Anterior chamber inflammation	-	-	-	1 (0.3)	0 (0.0)
Blindness	-	-	-	1 (0.3)	0 (0.0)
Cataract traumatic	-	-	-	1 (0.3)	0 (0.0)
Dacryocystitis	-	-	-	1 (0.3)	0 (0.0)
Retinal artery embolism	-	-	-	1 (0.3)	0 (0.0)
Dry age-related macular degeneration	-	-	-	0 (0.0)	1 (0.3)

Abbreviations: SAF: safety analysis set.
Source: HAWK CSR;[78] HARRIER CSR;[79] Singh et al. 2019.[84]

B.3.10.3.2 Serious non-ocular adverse events

At Week 48, a total of 162 patients experienced ≥1 non-ocular SAE in HAWK (brolucizumab 3 mg: 47 patients [13.1%]; brolucizumab 6 mg: 47 patients [13.1%]; aflibercept 2 mg: 68 patients [18.9%]) and 78 patients in HARRIER (brolucizumab 3 mg: 35 patients [9.5%]; aflibercept 2 mg: 43 patients [11.7%]).[76] In HAWK, the most frequently reported non-ocular SAEs in the study eye were pneumonia and cerebrovascular accident. In HARRIER, the most frequently reported non-ocular SAEs were rectal haemorrhage, cholecystitis acute, gastroenteritis, and pulmonary oedema in the brolucizumab arm and pneumonia in the aflibercept arm. These data are presented in Appendix F.

At Week 96, a total of 283 patients experienced ≥1 non-ocular SAE in HAWK (brolucizumab 3 mg: 88 patients [24.6%]; brolucizumab 6 mg: 85 patients [23.6%]; aflibercept 2 mg: 110 patients [30.6%]) and 154 patients in HARRIER (brolucizumab 6 mg: 69 patients [18.6%]; aflibercept 2 mg: 85 patients [23.0%]) (Table 3.32).[84] The most frequently reported non-ocular SAE was pneumonia across all treatment arms in HAWK. In HARRIER, the most frequently reported non-ocular SAEs were lower limb fracture and syncope in the brolucizumab 6 mg arm and pneumonia in the aflibercept 2 mg arm.

Table 3.32: Serious non-ocular adverse events up to Week 96 (≥3 patients in any treatment group) by preferred term (SAF)

Trial name	HAWK			HARRIER	
Preferred term	**Brolucizumab 3 mg, (N=358) n (%)**	**Brolucizumab 6 mg, (N=360) n (%)**	**Aflibercept 2 mg, (N=360) n (%)**	**Brolucizumab 6 mg, (N=370) n (%)**	**Aflibercept 2 mg, (N=369) n (%)**
Number of patients with at least one event	88 (24.6)	85 (23.6)	110 (30.6)	69 (18.6)	85 (23.0)
Pneumonia	7 (2.0)	10 (2.8)	9 (2.5)	2 (0.5)	8 (2.2)
Cardiac failure congestive	4 (1.1)	6 (1.7)	4 (1.1)	-	-
Chronic obstructive pulmonary disease	1 (0.3)	6 (1.7)	4 (1.1)	2 (0.5)	1 (0.3)
Atrial fibrillation	4 (1.1)	4 (1.1)	2 (0.6)	-	-
Cerebrovascular accident	3 (0.8)	4 (1.1)	3 (0.8)	0 (0.0)	4 (1.1)
Sepsis	3 (0.8)	4 (1.1)	1 (0.3)	-	-
Septic shock	0 (0.0)	3 (0.8)	0 (0.0)	-	-
Urinary tract infection	4 (1.1)	2 (0.6)	2 (0.6)	-	-
Hyponatraemia	4 (1.1)	2 (0.6)	1 (0.3)	-	-
Syncope	3 (0.8)	2 (0.6)	3 (0.8)	3 (0.8)	2 (0.5)

Myocardial infarction	1 (0.3)	2 (0.6)	3 (0.8)	2 (0.5)	0 (0.0)
Femur fracture	0 (0.0)	2 (0.6)	4 (1.1)	2 (0.5)	0 (0.0)
Coronary artery disease	6 (1.7)	1 (0.3)	3 (0.8)	-	-
Cholelithiasis	4 (1.1)	1 (0.3)	2 (0.6)	2 (0.5)	0 (0.0)
Transient ischaemic attack	3 (0.8)	1 (0.3)	2 (0.6)	1 (0.3)	2 (0.5)
Non-cardiac chest pain	1 (0.3)	1 (0.3)	3 (0.8)	-	-
Subdural haematoma	1 (0.3)	1 (0.3)	3 (0.8)	-	-
Influenza	3 (0.8)	0 (0.0)	1 (0.3)	-	-
Intestinal obstruction	1 (0.3)	0 (0.0)	3 (0.8)	-	-
Lower limb fracture	-	-	-	3 (0.8)	0 (0.0)
Cardiac failure	-	-	-	2 (0.5)	2 (0.5)
Ischaemic stroke	-	-	-	2 (0.5)	1 (0.3)
Prostate cancer	-	-	-	2 (0.5)	1 (0.3)
Rectal haemorrhage	-	-	-	2 (0.5)	1 (0.3)
Benign prostatic hyperplasia	-	-	-	2 (0.5)	0 (0.0)
Cholecystitis acute	-	-	-	2 (0.5)	0 (0.0)
Gastroenteritis	-	-	-	2 (0.5)	0 (0.0)
Inguinal hernia	-	-	-	2 (0.5)	0 (0.0)
Joint dislocation	-	-	-	2 (0.5)	0 (0.0)
Pulmonary oedema	-	-	-	2 (0.5)	0 (0.0)
Bronchitis	-	-	-	1 (0.3)	2 (0.5)
Femoral neck fracture	-	-	-	1 (0.3)	2 (0.5)
Osteoarthritis	-	-	-	1 (0.3)	2 (0.5)
Pulmonary embolism	-	-	-	1 (0.3)	2 (0.5)
Death	-	-	-	0 (0.0)	3 (0.8)
Arrhythmia	-	-	-	0 (0.0)	2 (0.5)
Cerebrovascular disorder	-	-	-	0 (0.0)	2 (0.5)

Fall	-	-	-	0 (0.0)	2 (0.5)
Humerus fracture	-	-	-	0 (0.0)	2 (0.5)

Abbreviations: SAF: safety analysis set.
Source: HAWK CSR;[78] HARRIER CSR;[79] Dugel et al. 2019;[76] Singh et al. 2019.[84]

B.3.10.4 Deaths, other serious adverse events, and other significant adverse events

At Week 48, 14 patients had died in HAWK (brolucizumab 3 mg: 4 patients [1.1%]; brolucizumab 6 mg: 4 patients [1.1%]; aflibercept 2 mg: 6 patients [1.7%]) and 7 patients in HARRIER (brolucizumab 6 mg: 3 patients [0.8%]; aflibercept 2 mg: 4 patients [1.1%]). No deaths were considered to be related to study treatment by the Investigator. In HAWK, 183 patients had experienced ≥1 SAE, and 40 led to premature study discontinuation (brolucizumab 3 mg: 11 patients [3.1%]; brolucizumab 6 mg: 12 patients [3.3%]; aflibercept 2 mg: 17 patients [4.7%]); the majority of these were related to ocular AEs in the study eye (72.5%). In HARRIER, 90 patients had experienced ≥1 SAE, and 16 led to premature study discontinuation (brolucizumab 6 mg: 12 patients [3.2%]; aflibercept 2 mg: 4 patients [1.1%]); the majority of these were also related to ocular AEs in the study eye (75.0%). 303 and 168 patients had experienced ≥1 SAE in HAWK and HARRIER respectively and 55 and 29 had led to premature study discontinuation. The majority of premature study discontinuations were related to ocular AEs in the study eye in both trials. These data are presented in Appendix F.

At Week 96, 29 patients had died in HAWK (brolucizumab 3 mg: 9 patients [2.5%]; brolucizumab 6 mg: 8 patients [2.2%]; aflibercept 2 mg: 12 patients [3.3%]) and 11 in HARRIER (brolucizumab 6 mg: 4 patients [1.1%]; aflibercept 2 mg: 7 patients [1.9%]) (Table 3.33).[84] No deaths were suspected to be related to study treatment by the Investigator in HARRIER. In HAWK, in the second year in the brolucizumab 3 mg treatment arm, one SAE with a fatal outcome (cerebrovascular accident) was considered to be related to the study treatment by the Investigator.

Table 3.33: Deaths, SAE or AE leading to permanent study treatment discontinuation up to Week 96 (SAF)

Trial name	**HAWK**			**HARRIER**	
Subjects with serious or significant AE	**Brolucizumab 3 mg, (N=358) n (%)**	**Brolucizumab 6 mg, (N=360) n (%)**	**Aflibercept 2 mg, (N=360) n (%)**	**Brolucizumab 6 mg, (N=370) n (%)**	**Aflibercept 2 mg, (N=369) n (%)**
Death	9 (2.5)	8 (2.2)	12 (3.3)	4 (1.1)	7 (1.9)
SAE	94 (26.3)	95 (26.4)	114 (31.7)	79 (21.4)	89 (24.1)
Study eye	7 (2.0)	12 (3.3)	5 (1.4)	13 (3.5)	6 (1.6)
Fellow eye	0 (0.0)	4 (1.1)	1 (0.3)	0 (0.0)	0 (0.0)
Non-ocular	88 (24.6)	85 (23.6)	110 (30.6)	69 (18.6)	85 (23.0)

AE leading to permanent study treatment discontinuation	17 (4.7)	16 (4.4)	22 (6.1)	20 (5.4)	9 (2.4)
Study eye	14 (3.9)	11 (3.1)	12 (3.3)	13 (3.5)	6 (1.6)
Fellow eye	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Non-ocular	3 (0.8)	5 (1.4)	10 (2.8)	8 (2.2)	3 (0.8)

Abbreviations: AE: adverse event; SAE: serious adverse event**;** SAF: safety analysis set.
Source: HAWK CSR;[78] HARRIER CSR;[79] Dugel et al. 2019;[76] Singh et al. 2019.[84]

B.3.11 Conclusions about comparable health benefits and safety

Evidence from the brolucizumab clinical trials

Evidence for the efficacy and safety of brolucizumab in wAMD derives from two pivotal phase III, head-to-head clinical trials versus aflibercept: HAWK and HARRIER.[76, 78, 79] Results from OSPREY, the phase II trial of brolucizumab in wAMD, also support the key primary and secondary outcomes from HAWK and HARRIER (see Appendix I).[77, 80]

Brolucizumab achieved clinically meaningful and consistent visual gains in the HAWK and HARRIER trials, demonstrating non-inferiority in terms of BCVA to aflibercept (see Section B.3.6). The primary endpoint of non-inferiority for brolucizumab versus aflibercept in terms of mean change in BCVA from Baseline to Week 48 was met in both the HAWK and HARRIER trials with highly significant p-values. At Week 48, the least squares (LS)-mean change in BCVA from Baseline was 6.6 versus 6.8 letters, and 6.9 versus 7.6 letters, for brolucizumab 6 mg versus aflibercept 2 mg in HAWK and HARRIER respectively ($p<0.0001$ for both comparisons, non-inferior 4-letter margin). The key secondary endpoint of non-inferiority to aflibercept in mean change in BCVA over the period of Week 36–48 was also met with highly significant p-values in both HAWK ($p\leq0.0001$, non-inferior 4-letter margin) and HARRIER ($p<0.0003$, non-inferior 4-letter margin). These results are supported by results from the phase II OSPREY trial, where brolucizumab met the key primary and secondary endpoints of non-inferiority to aflibercept for mean change in BCVA from Baseline to Weeks 12 and 16.

The visual outcomes for the key endpoints in HAWK and HARRIER were achieved with a majority of patients maintained on a q12w dosing interval immediately following the loading dose phase. More than 50% (56% in HAWK and 51% in HARRIER) of brolucizumab 6 mg patients were exclusively maintained on a q12w regimen immediately following the loading dose phase through to Week 48. Patients treated with brolucizumab therefore received fewer injections from Baseline through to Week 96 than patients treated with aflibercept. Over 96 weeks, the mean number of active injections administered to patients on the brolucizumab treatment arms was between 1 and 1.5 fewer injections than the number administered on the aflibercept arms. Brolucizumab therefore achieved comparable visual outcomes to aflibercept, at a lower injection frequency. The high-frequency dosing schedules of currently available anti-VEGF therapies represent a significant burden on patients, their carers, and ophthalmology clinics. This can result in patient under-treatment,[22, 58] due to the impact on patient adherence and clinic capacity constraints, risking symptom exacerbation and visual decline, and in some cases, vision loss. Brolucizumab therefore meets an unmet clinical need for a therapy which enables the administration of less frequent injections due to superior fluid reduction and better disease control, without reducing visual outcomes, with treatment and monitoring intervals based on an individual's anti-VEGF therapy need.

To enable the administration of less frequent injections, a treatment must suppress disease activity for longer than currently available anti-VEGF therapies, with retinal specialists determining the need for patient retreatment based on visual and anatomical parameters of disease activity.[38] The control of fluid accumulation is essential to the effective management of wAMD and major clinical guidelines (Europe-wide from the European Society of Retina Specialist [EURETINA] and NICE) recommend that treatment decisions are based around the presence of fluid.[32, 33] Results from HAWK and HARRIER showed that brolucizumab was superior to aflibercept in terms of reductions in retinal fluid (IRF and/or SRF) and CSFT. An increase in retinal fluid or CSFT is an important indicator of disease activity, as fluid accumulation and oedema may result in vision deterioration and, in some cases, vision loss. Significantly fewer

patients receiving brolucizumab had IRF and/or SRF at Week 16 and Week 48 compared with aflibercept, with differences maintained to Week 96.

At Week 16, the proportion of patients with IRF and/or SRF was 33.9% for brolucizumab 6 mg versus 52.2% for aflibercept 2 mg in HAWK (p<0.0001), and 29.4% versus 45.1% in HARRIER (p<0.0001). At Week 48, the proportion of patients with IRF and/or SRF was 31.2% for brolucizumab 6 mg versus 44.7% for aflibercept 2 mg in HAWK (p=0.0002), and 25.8% versus 43.9% in HARRIER (p<0.0001).[76] Brolucizumab 6 mg showed a superior reduction in CSFT compared with aflibercept 2 mg at Week 16 and Week 48 in HAWK (p=0.0008 and p=0.0012 respectively) and HARRIER (p<0.0001 for both time points). These differences were maintained at Week 96 (HAWK [p=0.0115] and HARRIER [p<0.0001]). Overall, brolucizumab was significantly superior to aflibercept in terms of anatomical outcomes and disease activity parameters; 30% fewer patients receiving brolucizumab had disease activity compared to those receiving aflibercept, at Week 16.

In addition, brolucizumab achieved a similar improvement in HRQoL compared with aflibercept. A comparable change from Baseline to Week 24 in VFQ-25 was observed for brolucizumab 6 mg and aflibercept 2 mg in both HAWK and HARRIER. The VFQ-25 analysis showed no relevant differences between treatment arms in the composite or any of the individual subscale scores.

The safety profile of brolucizumab was also comparable to the safety profile of aflibercept. The overall incidence of ocular and non-ocular AEs was balanced across all treatment groups in both HAWK and HARRIER trials. Overall, no new, previously unreported types of safety events were identified compared with other anti-VEGF therapies.

Indirect comparative evidence of brolucizumab versus the relevant comparators

In order to address the lack of head-to-head comparative evidence for brolucizumab versus ranibizumab, an NMA was performed comparing brolucizumab to aflibercept and ranibizumab. Results from the NMA demonstrated that brolucizumab is associated with comparable efficacy to aflibercept and ranibizumab in terms of change in BCVA from Baseline to one and two years. Additionally, in line with results from the phase II and III clinical trials, the NMA also demonstrated that brolucizumab is statistically significantly better than most aflibercept and ranibizumab regimens at decreasing retinal thickness from Baseline to one year. Visual and anatomical results were comparable for both LP → Bro 6q8w → q12w and LP → Bro 6q12/q8w regimens, where the latter regimen included over 50% of patients on a q12w brolucizumab dosing interval until Week 48. Results of the arm-based baseline pooling for injection frequency also demonstrated brolucizumab to be associated with the second lowest injection frequency across year one and the lowest injection frequency across year two versus most aflibercept and ranibizumab regimens. Brolucizumab therefore displays comparative visual acuity and superior anatomical outcomes with a lower injection frequency than current standard of care. With comparable efficacy in terms of BCVA outcomes shown between brolucizumab, aflibercept and ranibizumab, this therefore allows a cost-comparison case to be made.

Strengths and limitations of the clinical evidence base

The clinical evidence base presented within this submission has been primarily derived from two phase III, international, multicentre, randomised, double-masked, head-to-head trials, and one phase II multicentre, randomised, double-masked, two-arm trial. HAWK and HARRIER enrolled more than 1,800 patients, with OSPREY enrolling a further 89. As large, blinded and randomised trials, these studies present robust clinical evidence for the efficacy and safety of brolucizumab. Additionally, HARRIER included 36 patients across 16 trial sites within the UK. Therefore, the results presented here are considered to reflect standard UK clinical practice. Comparable

results for BCVA efficacy between aflibercept 2 mg arms in the VIEW studies and OSPREY further support the reliability of these results.[77] HAWK and HARRIER enrolled patients with a baseline BCVA between 23 and 78 letters. This represents a wider BCVA inclusion range than previous pivotal studies (ANCHOR, MARINA and VIEW I/II) and provides evidence for the efficacy of brolucizumab in patients with particularly good vision, including those still legally able to drive. Whilst differences in the magnitude of BCVA change between HAWK and HARRIER and previous trials can be seen (i.e. smaller BCVA gains in HAWK and HARRIER), this can be explained by the higher baseline BCVA value for HAWK and HARRIER with VA gain restricted due to the presence of a clinical expert defined "ceiling effect".[76, 87]

A limitation of the evidence base presented is that no head-to-head comparison is available between brolucizumab and ranibizumab. In order to overcome this limitation, an indirect treatment comparison was performed between aflibercept, ranibizumab and brolucizumab. The process for conducting the SLR and NMA was conducted in line with NICE guidelines,[85] conducted in a Bayesian framework and the best model (fixed-effects versus random-effects) was chosen based on the deviance information criterion (DIC). The results from the NMA were similar to the results of the NMA in wAMD conducted by NICE in their clinical guideline (NG82)[33] and, in the few cases where there were differences, the source of the difference was found to be due to the decisions made on which studies to include. The study populations of the trials included in the NMA were similar, with no heterogeneity identified in direct comparisons. Furthermore, the results of the NMA were supported by several sensitivity analyses conducted to assess the robustness of the base case results.

Overall, the clinical evidence presented in this submission supports the non-inferiority of brolucizumab versus aflibercept, and the comparative efficacy of brolucizumab to ranibizumab, for visual outcomes in terms of BCVA. The evidence also supports the clinical superiority of brolucizumab at improving anatomical outcomes, with increase in retinal fluid a key marker of disease activity. With the majority of brolucizumab-treated patients in the key phase III trials treated at a 12-week dosing interval immediately following the loading dose phase (56% in HAWK and 51% in HARRIER), it can be concluded that brolucizumab offers equivalent visual outcomes to current standard of care, at a reduced treatment and monitoring frequency. Brolucizumab therefore offers a solution to the current patient and healthcare system burdens associated with anti-VEGF therapies.

B.4 Cost-comparison analysis

Summary

- The relevant comparators to brolucizumab for the treatment of wAMD in the UK are the licensed anti-VEGF therapies aflibercept and ranibizumab
- The results of the HAWK and HARRIER trials demonstrate that brolucizumab to be associated with comparable BCVA outcomes that are achieved with a lower injection frequency versus aflibercept, as well as comparable safety and HRQoL
- The results of the NMA detailed in Section B.3.9.4 also demonstrate brolucizumab to be associated with comparable visual outcomes to aflibercept and ranibizumab in terms of BCVA and superior disease control in terms of decreasing retinal thickness, with a lower injection frequency. A cost-comparison analysis is therefore considered appropriate for decision making in this appraisal
- A cost-comparison analysis was conducted from a UK (England and Wales) healthcare system perspective with a lifetime time horizon to assess the difference in costs associated with the use of brolucizumab as a treatment for wAMD versus aflibercept and ranibizumab
- The costs considered within the analysis included drug acquisition and administration costs as well as monitoring costs and the cost of wAMD diagnosis
- Aflibercept was included in the analysis at the NHS list price; ranibizumab and brolucizumab were included at their confidential net prices to the NHS. All other costs were from appropriate sources including NHS reference costs and the PSSRU
- Rates of treatment discontinuation and the frequencies of injection and monitoring visits included within the analysis were estimated from the baseline pooling of data from relevant clinical trials, described in Section B.3.9.4
- Over a lifetime time horizon (and when brolucizumab and ranibizumab are provided at their net prices to the NHS), the use of brolucizumab was associated with cost savings of [redacted] versus aflibercept and [redacted] versus ranibizumab
- The results of a threshold analysis demonstrated that brolucizumab would remain cost saving over a lifetime time horizon provided the net price of aflibercept is not below [redacted]. This would represent a [redacted]. Any net price for aflibercept that is higher than [redacted] would result in brolucizumab being associated with cost savings versus aflibercept
- The assumptions adopted within the base case cost-comparison analysis were explored in several scenario analyses; brolucizumab remained cost saving versus both aflibercept and ranibizumab in all scenarios
- In deterministic sensitivity analysis (DSA), results were most sensitive to varying the rates of discontinuation for aflibercept and brolucizumab in the comparison versus aflibercept, the discontinuation rate for brolucizumab and the injection frequencies for brolucizumab and ranibizumab 0.5 mg q4w in the comparison versus ranibizumab
- With similar efficacy in terms of improvement in BCVA, similar impact on vision-related HRQoL, superior disease control and less frequent injections, brolucizumab is the most cost-effective treatment option for wAMD versus currently licensed anti-VEGF therapies and results in cost savings to the NHS over a lifetime time horizon

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 required.

The anticipated posology of brolucizumab is such that the majority of patients will receive brolucizumab q12w immediately after the loading dose phase. Baseline pooling results for injection frequencies demonstrated fewer injection and monitoring visits are required with brolucizumab versus aflibercept and ranibizumab. Details of the resource use associated with the use of brolucizumab are provided in Section B.4.2 below.

B.4.2 Cost-comparison analysis inputs and assumptions

The objective of this analysis was to evaluate the costs associated with brolucizumab versus aflibercept and ranibizumab for the treatment of wAMD from a UK (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 are presented in Table 4.1 below:

Table 4.1: Features of the cost-comparison analysis

Component	Approach
Population	Adults aged ≥50 years with wAMD (reflective of the populations included in the HAWK and HARRIER trials)
Intervention	Brolucizumab (6 LP→q12/q8w)
Comparator(s)	Aflibercept (weighted[a]) Ranibizumab (weighted[a])
Outcomes	Incremental per-patient costs and total per-patient costs
Perspective	NHS and personal social services (PSS) in England and Wales
Time horizon	Lifetime – 30 years (maximum age of 100 years)
Discounting	Costs discounted at 3.50%

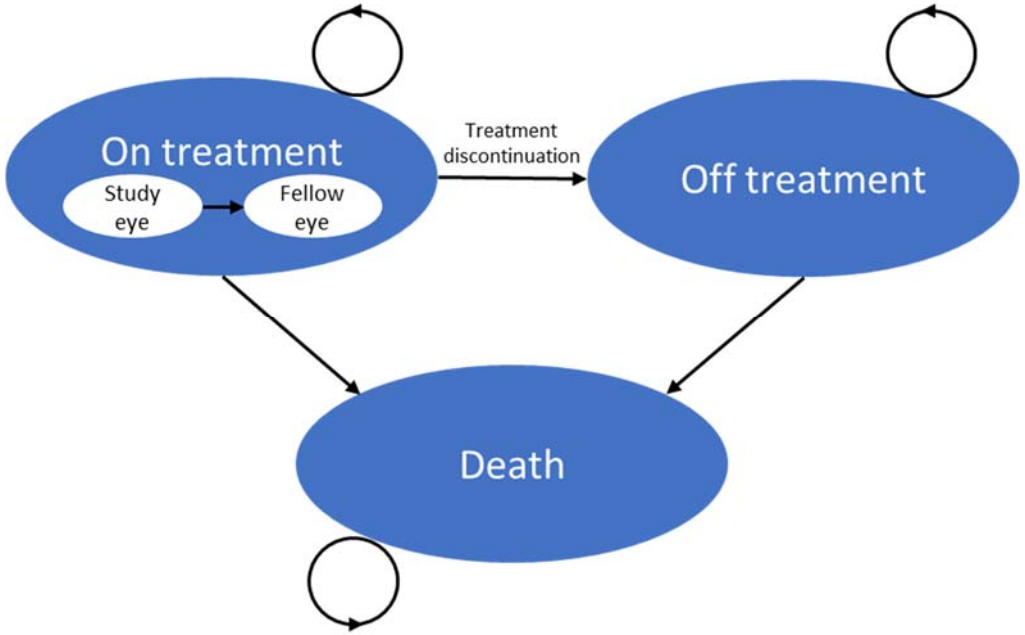
[a]In the base case analysis, a weighted average approach was adopted with regards to the treatment regimens for aflibercept and ranibizumab based on market share data on the use of each regimen. Scenario analyses for each individual regimen were also conducted.
Abbreviations: LP: loading phase; NHS: National Health Service; PSS: Personal Social Services; qXw: one injection every X weeks; wAMD: wet age-related macular degeneration.

Model structure

A cost-comparison model was developed in Microsoft Excel® 2016 using a Markov cohort approach to calculate the proportion of patients across three health states over time: On treatment (unilateral "study eye" or bilateral "fellow eye" treatment); Discontinued treatment (no treatment) and Death (Figure 4.1).

Patients could enter the model with either unilateral or bilateral disease. Patients with unilateral disease could develop bilateral disease over time according to an annual probability of neovascularisation. Once patients developed bilateral disease, they could not revert to having unilateral disease.

Figure 4.1: Cost-comparison model structure



A cycle length of one year was adopted, reflecting the relative rate of visual decline in this population. A half-cycle correction was also applied, assuming that state transitions occur, on average, half-way through each model cycle.

A lifetime time horizon (30 years) was adopted in line with the previous NICE appraisal for aflibercept in this indication (25 years). The time horizon was considered to be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.

Patient population

The patient population considered in the analysis was reflective of the anticipated marketing authorisation for brolucizumab and the populations evaluated in the HAWK and HARRIER trials: adults aged ≥50 years with active CNV lesions secondary to AMD that affect the subfield in the study eye and a VA of between 78−23 letters (inclusive).

In the base case analysis, the population baseline characteristics, including age, gender, and the proportion of patients with unilateral or bilateral wAMD at baseline, were based on pooled estimates from the brolucizumab 3 mg, brolucizumab 6 mg and aflibercept 2 mg arms of the HAWK and HARRIER trials to increase statistical power and reduce uncertainty (Table 4.2). Feedback from UK clinical experts agreed that the baseline characteristics of the model were generalisable to UK clinical practice.[88]

The baseline age and gender distribution were used to determine the cohort life expectancy, affecting the number of predicted treatment and monitoring visits.

Bilateral disease was assumed to require bilateral treatment. Patients with unilateral disease were also assumed to be at risk of developing wAMD in the fellow eye (bilateral disease) over time. In the base case analysis, the annual probability of developing wAMD in the fellow eye (16.60%) was based on data from the UK AMD database (Zarranz-Venture et al. 2014).[89] A scenario analysis was conducted to explore the impact of an alternative data source (Wong *et al.* 2008; 7.50%) for the annual probability of developing wAMD in the fellow eye.[90]

Table 4.2: Modelled population baseline characteristics

Characteristic	HAWK and HARRIER (pooled)	Source
Age, mean (SD, SE) at baseline	75.8 years (8.58, 0.22)	HAWK and HARRIER pooled analysis
Percentage of females	56.27%	HAWK and HARRIER pooled analysis
Percentage with bilateral disease at baseline	27.14%	HAWK and HARRIER pooled analysis
Annual probability of developing bilateral disease (developing wAMD in fellow eye)	16.60%	42.0% over 3 years (UK AMD database)[89]

Abbreviations: AMD: age-related macular degeneration; SD: standard deviation; SE: standard error; wAMD: wet age-related macular degeneration.

Mortality

Mortality was modelled by applying general population all-cause mortality data obtained from England and Wales National Life Tables published by the Office for National Statistics (2017) based on 2015−2017 mortality data. To reflect the patient population in the model, age- and gender-specific mortality rates were combined into a blended rate using the proportion of males and mean age set in the model to reflect the patient population in the HAWK and HARRIER trials.

B.4.2.2 Intervention and comparators' acquisition costs

A summary of the acquisition costs for brolucizumab, aflibercept and ranibizumab is presented in Table 4.3 below.

The drug acquisition cost for aflibercept was based on the list price stated in the British National Formulary.[91] Whilst a confidential PAS has been arranged with the Department of Health for aflibercept, this is unknown to Novartis and therefore the list price was used in the base case cost-comparison analysis.

Ranibizumab is also manufactured by Novartis; the confidential net price for this comparator is therefore known and was used in the base case cost-comparison analysis. Ranibizumab is available at a simple confidential discount PAS price of [redacted].

Brolucizumab is available at a simple confidential discount PAS price of [redacted] and this net price which has been used in the base case cost-comparison analysis. Hereafter the brolucizumab and ranibizumab prices used within the cost-comparison analysis will be referred to as net prices.

Table 4.3: Acquisition costs of the intervention and comparator technologies

	Brolucizumab	Aflibercept	Ranibizumab
Pharmaceutical formulation	120 mg/mL solution for injection in pre-filled syringe	2 mg/50 µL solution for injection vial	1.65 mg/0.165 mL solution for injection in pre-filled syringe
(Anticipated) care setting	Hospital	Hospital	Hospital
Acquisition cost used in the analysis (excluding VAT)	**Net price** [redacted]	**NHS list price[91]** £816.00	**Net price** [redacted]
Method of administration	Intravitreal injection	Intravitreal injection	Intravitreal injection
Dose	6 mg	2 mg	0.5 mg
Dosing regimen	LP→6q12/q8w	Weighted average of:[a] • Afli 2q4w[a]	Weighted average of:[a] • Rani 0.5q4w[a]

		• Afli 2 LP→q8w[a] • Afli 2 LP→q8w→PRN[a] • Afli 2 LP→TREX[a] • Afli 2q4w→PRN	• Rani 0.5q4w→PRN[a] • Rani 0.5 LP→PRN[a] • Rani 0.5TREX[a] • Rani 0.5 LP→PRNX • Rani 0.5PRN
No. of injections	**Year 1:** 6.66 **Year 2:** 4.76 **Year 3+:** 4.76	**Year 1:** 8.82 **Year 2:** 6.85 **Year 3+:** 6.85	**Year 1:** 9.16 **Year 2:** 7.91 **Year 3+:** 7.91
No. of monitoring visits (=total visits)	**Year 1:** 6.66 **Year 2:** 4.76 **Year 3+:** 4.76	**Year 1:** 8.82 **Year 2:** 8.17 **Year 3+:** 8.17	**Year 1:** 10.97 **Year 2:** 10.12 **Year 3+:** 10.12

[a]In the base case analyses, a weighted average approach was adopted with regards to the treatment regimens for aflibercept and ranibizumab based on market share data on the use of each regimen. Regimens marked with an [a] were included in the base case analysis. Scenario analyses for each of the individual regimens have also been conducted.
Abbreviations: PRN: pro re nata; PRNX: pro re nata and extend dosing regimen; qXw: one injection every X weeks; TREX: treat-and-extend dosing regimen; VAT: value-added tax.

Dosing regimens

For brolucizumab, a 6 mg LP→q12/q8w dosing regimen was included in the base case analysis, in line with the anticipated EMA licence. An explanation of the dosing regimen nomenclature is presented in Section B.3.9.2.

A range of dosing schedules are available for aflibercept and ranibizumab and feedback from clinical experts and market research indicated that UK clinicians routinely use a number of different treatment regimens for aflibercept and ranibizumab. The total number of injections a patient receives is a function of the regimen received and there is no standard regimen associated with each treatment. In order to more accurately capture the costs associated with the comparator therapies, a weighted average regimen was used for both aflibercept and ranibizumab in the base case cost-comparison analysis. This approach was also considered appropriate following feedback from UK clinical experts given the variation in clinical practice in the UK.[88]

This was informed using data from a UK market research study, which used computer aided web interviews to determine current practice in treating wAMD. A total of 50 UK-based retinal specialists were interviewed and asked the percentage of maintenance patients that were using each of the following regimens, after the initial loading dose phase:

- Fixed dosing: monthly (q4w)
- Fixed dosing: bi-monthly (q8w)
- Fixed dosing: quarterly (q12w)

- PRN
- TREX
- Other

The weights were then used to determine the number of injections and monitoring visits patients would receive each year in the base case cost-comparison analysis. The adoption of a weighted average approach was considered to be more reflective of real-world UK clinical practice than selecting, for example, the one most-commonly adopted treatment regimen for the base case analysis; however, results using single treatment regimens for each of the comparators were conducted in scenario analyses to test the impact of this approach.

Table 4.4 summarises the proportion of patients receiving each regimen. Quarterly dosing was excluded from the final weights, as data on injection frequency for these patients was not available from the trials identified in the SLR (Section B.3.9). 'Other' regimens were also excluded, as the survey did not record what regimens these patients would have used. Overall these regimens represent 6% and 7% of aflibercept and ranibizumab patients respectively, thus their exclusion from the model is not expected to substantially impact results.

Finally, the baseline pooling analysis of injection frequencies included data on two aflibercept PRN regimens (q4w→PRN and LP→q8w→PRN) and three ranibizumab PRN regimens (LP→PRN, PRN and q4w→PRN). For calculating PRN injection frequencies, it was assumed that aflibercept patients were treated with 2LP ->q8w-> PRN and ranibizumab patients were treatment with 0.5LP-> PRN, exclusively.

Table 4.4: Base case analysis weighted regimens

Dosing regimens	Data		Included?		Weight	
	Afli (n=44)	Rani (n=49)	Afli	Rani	Afli	Rani
q4w	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
q8w	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
q12w[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PRN	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TREX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a]q12w was not included in the overall weighted regimen as confirmed data are not currently available; [b]'Other' regimens were also excluded, as the market research survey did not record what regimens these patients would have followed.
Abbreviations: Afli: aflibercept; bro: brolucizumab; LP: loading phase; PRN: pro re nata; qXw: one injection every X weeks; rani: ranibizumab; TREX: treat-and-extend dosing regimen.

Treatment discontinuation

Treatment discontinuation was assumed to be constant over time hence an annual probability of treatment discontinuation was applied for the whole model time horizon. In the base case analysis, the annual probability of treatment discontinuation was estimated based on treatment arm pooling of data identified in the clinical SLR, using a random-effects model. Scenario analyses were conducted using estimates from the fixed-effects model and also based on the discontinuation rates adopted in NICE NG82.[86]

Discontinuation has been shown to be molecule-specific, therefore treatment arm-based pooling was conducted for each molecule, with other aspects of a treatment regimen not shown to have a significant effect on discontinuation.[86]

Bi-annual probabilities were derived from 2-year estimates and subsequently converted to an annual probability. The estimation of the annual probability of discontinuation and its standard error were based on the reported number of patients who discontinued prior to Week 96 assuming constant discontinuation rate as calculated in Equation 1.

Equation 1: Annual probability of discontinuation

$$Pr_{an} = 1 - (1 - \frac{N_{discontinued}}{N_{patients}})^{52/96}$$

The standard error for a probability (as it is applied directly in the simulation model, not the rate) is calculated using Equation 2.

Equation 2: Standard error for the probability

$$SE(pr) = \left(Pr * (1 - \mathrm{Pr})/N_{patients}\right)^{0.5}$$

Table 4.5: Annual treatment discontinuation rates applied in the base case analysis derived from baseline pooling analysis (random-effects model) – see Section B.3.9.4.8

Treatment	Bi-annual probability	Mean annual treatment discontinuation probability
Brolucizumab LP→6q12/q8w	15.10%	7.86%
Aflibercept weighted[a]	17.11%	8.95%
Ranibizumab weighted[a]	15.16%	7.89%

[a]In the base case analyses, a weighted average approach was adopted with regards to the treatment regimens for aflibercept and ranibizumab based on market share data on the use of each regimen. Scenario analyses for each individual regimen were also conducted.
Abbreviations: LP: loading phase; qXw: one injection every X weeks; SE: standard error.

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

Diagnosis

A one-off cost of FFA (£151.58) was assumed to be applied at the time of new diagnosis of wAMD in an eye prior to commencement of treatment. This cost was applied for any incident neovascularisation, thus was applied once at baseline and once for patients that later develop AMD in a second eye. The cost of an FFA was not applied at subsequent monitoring visits.

Table 4.6: Costs of diagnosis

Item	Unit cost	Source
FFA	£151.58	Fundus fluorescein angiography (FFA): Weighted average of Diagnostic Imaging codes for Contrast Fluoroscopy Procedures: RD30Z, RD31Z and RD32Z taken from NHS Reference Costs 2017/2018[92] based on the approach used in the economic evaluation of NG82[93]

Abbreviations: FFA: Fundus fluorescein angiography.

Injection administration and monitoring

In the base case analysis, the frequency of injection administration visits for each dosing regimen in years 1 and 2 was estimated based on treatment arm pooling of data identified in the clinical SLR, using a random-effects model to account for between-trial heterogeneity. A scenario analysis using the fixed-effects model was also tested. For aflibercept and ranibizumab, a weighted average approach was adopted, whereby the number of injection administration and monitoring visits was based on market share data on the use of each regimen (Table 4.4).

From Year 3 onwards it was assumed that the number of injections for each therapy would reflect the mean number of injections received in Year 2. Given the absence of RCT evidence beyond 2 years for brolucizumab and the relevant comparators, it is difficult to assume that a lower number of injections might be administered without assuming this could have a negative impact on VA. This is particularly relevant given the likely reduced follow up and injections in the long-term; long-term follow-up data for ranibizumab in the HORIZON study demonstrated that decreases in VA were most likely due to low monitoring and injection frequency during the open-label follow-up.[94] Similarly, in the VIEW1 open-label extension study, continuous injections were required throughout the follow up and were still associated with a small (3-letter) loss in VA.[95] This approach was also validated by UK clinical experts who agreed that that assuming that same injection numbers in Year 2 will be required in years 3+ was the best approach for the base case analysis.[88]

Taken together and in the absence of robust RCT evidence for the frequency of injection and monitoring visits, the base case cost comparison analysis assumed that the number of injections for each therapy would reflect the mean number of injections received in Year 2

In line with the economic assessment conducted in the NICE clinical guideline for AMD NG82,[86] it was assumed that for all continuous regimens, no additional monitoring visits would be required. Thus, in the base case analysis, the total number of injection administration and monitoring visits was considered to be fully represented by the frequency of injections for all continuous regimens.

For the PRN and PRNX regimens, the additional number of monitoring visits required was estimated from the SALUTE trial.[96] For PRN, the total number of visits required was estimated to be 12.7 in Year 1 and Year 2; for PRNX, the total number of required visits was estimated to be 10.1 in Year 1 and Year 2. For Year 3 onwards, as for other regimens, the number of treatment visits was assumed to be the same as Year 2. For PRN regimens with a loading phase, an additional 0.2 administration visits were estimated to be required in Year 1.[97] These assumptions are summarised in Table 4.7.

Table 4.7: Annual mean number of injections and total visits per dosing regimen (random-effects model)

Dosing regimen	Injections			Total visits		
	Year 0−1	Year 1−2	Year 3+	Year 0−1	Year 1−2	Year 3+
Bro 6 mg LP→q12/q8w	6.66	4.76	4.76	6.66	4.76	4.76
Afli weighted[a]	8.82	6.85	6.85	8.82	8.17	8.17
Rani weighted[a]	9.16	7.91	7.91	10.97	10.12	10.12

[a]In the base case analyses, a weighted average approach was adopted with regards to the treatment regimens for aflibercept and ranibizumab based on market share data on the use of each regimen. Scenario analyses for each individual regimen were also conducted.
Abbreviations: Afli: aflibercept; bro: brolucizumab; LP: loading phase; qXw: one injection every X weeks; rani: ranibizumab.

Table 4.8 Assumptions about total visits for selected treatment regimens defining additional monitoring frequency

Treatment regimen	Year 1	Year 2	Year 3 onwards	Source
Continuous regimens	NA	NA	NA	Assumption
PRN	12.7	12.7	12.7	(Eldem *et al.* 2015)[96] and NG82 assumption for Year 2
PRNX	10.1	10.1	10.1	(Eldem *et al.* 2015)[96] and NG82 assumption for Year 2
PRN/PRNX: additional for loading phase	0.20	0.00	0.00	(Barikian *et al.* 2015)[97]

Abbreviations: NA: not applicable; PRN: pro re nata; PRNX: pro re nata and extend dosing regimen.

Unit costs

The unit costs for injection administration and monitoring visits were obtained from NHS Reference Costs 2017/2018. Feedback from UK clinical experts agreed with the cost and resource assumptions adopted in the base case analysis.[88]

In the base case analysis, the cost of an injection administration visit was assumed to be associated with an outpatient consultant-led visit (£95.13). The proportion of outpatient versus day case visits were explored in scenario analyses.

The cost of monitoring was assumed to comprise one OCT procedure (£114.53), and was applied at every monitoring visit.

Table 4.9: Injection administration and monitoring costs

Item	Unit cost	Source
Consultant visit	£95.13	NHS Reference Costs 2017/2018[92], Consultant Led, Ophthalmology, Service code 130
OCT	£114.35	Optical coherence tomography (OCT): Outpatient Procedure code for Retinal Tomography: BZ88A (ophthalmology) taken from NHS Reference Costs 2017/2018[92] based on the approach used in the economic evaluation of NG82[93]
Scenario analysis only:		
Day case	£861.33	NHS Reference Costs 2017/2018[92], Minor Vitreous Retinal Procedure, Currency code BZ87A

Abbreviations: NHS: National Health Service; NICE: National Institute for Clinical Excellence; OCT: Optical coherence tomography.

Bilateral treatment multipliers

In the base case analysis, it was assumed that the treatment of bilateral wAMD comprises '1-stop' appointments, i.e. the cost of administration and monitoring is shared between eyes, in line with the approach adopted in the NICE clinical guideline for AMD NG82[86]. 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 4.10.

Table 4.10 Cost multipliers for bilateral treatment

Cost multiplier	Value	Assumptions	Source
Drug cost multiplier	2	Assumed use of two units	

Admin cost multiplier	1.5	Assumed that administration costs would only double in 50% of the cases	NICE clinical guideline for AMD NG82[86]
Monitoring cost multiplier	1	Assumed the monitoring costs are always shared	

Abbreviations: AMD: age-related macular degeneration; NICE: National Institute for Health and Care Excellence.

B.4.2.4 Adverse reaction unit costs and resource use

Given there were no statistically significant or clinically significant differences in safety observed between brolucizumab and aflibercept in the HAWK and HARRIER trials, AE costs were not incorporated in the base case analysis. The impact of considering the costs associated with AEs was explored in a scenario analysis.

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

Given the precedents available from the previous appraisal of aflibercept and ranibizumab in this indication, together with the recent NICE clinical guideline for AMD (NG82) which includes an economic evaluation, the majority of assumptions adopted in the base case analysis were based on the precedents from these appraisals.[2, 3, 93]

However, further clinical expert validation of the cost and resource use assumptions utilised in the base case cost-comparison analysis was sought from two leading UK clinical experts and a summary of the feedback is provided below:[88]

- Experts agreed with the baseline characteristics in the model which were derived from HAWK and HARRIER
- Experts agreed with the weighted average approach for aflibercept and ranibizumab
- Experts were supportive of the injections numbers for Year 1 and 2 for aflibercept and ranibizumab derived from the baseline pooling
- Experts agreed with assuming injections in Year 2 held for Years 3+ and were supportive of a scenario analysis to assess this i.e. a scenario based on the assumptions of TA294, where 4 injections are assumed for all anti-VEGF therapies
- Experts agreed with the cost and resource assumptions

B.4.2.7 Uncertainties in the inputs and assumptions

A summary of the assumptions adopted in the base case cost-comparison analysis is presented in Table 4.11.

Table 4.11: Assumptions adopted in the base case cost-comparison analysis

Assumption	Description
Equivalent efficacy across compounds and regimens	The cost-comparison model assumes that the different compounds have equivalent efficacy (BCVA) and safety, regardless of the treatment regimens or frequencies. This is assumed, though the compounds have different discontinuation probabilities. The HAWK and HARRIER trials demonstrate that brolucizumab is non-inferior to aflibercept in terms of BCVA outcomes and safety. Results from the NMA also demonstrated that brolucizumab is associated with comparable efficacy in terms of BCVA and safety versus both aflibercept and ranibizumab, and statistically superior efficacy in terms of reduction in retinal thickness.
General population mortality	The cohort followed the age- and gender-adjusted mortality probabilities from published England and Wales life tables. No increased mortality from bilateral disease, blindness or adverse events was observed, and mortality rates were the same regardless of wAMD treatment.
Discontinuation probability	The probability of treatment discontinuation was based on the compound and did not vary over time. The probability of treatment discontinuation was independent of treatment regimen, and whether the patient had unilateral or bilateral disease. In the base case analysis, the annual probability of treatment discontinuation was estimated based on treatment arm pooling of data identified in the clinical SLR, using a random-effects model.
No treatment switching	Patients were either on or off treatment and did not switch treatments.
Treatment frequency	The frequency of injection administration visits for each dosing regimen in Years 1 and 2 was estimated based on treatment arm-based baseline pooling of data identified in the clinical SLR, using a random-effects model to account for between-trial heterogeneity. A weighted average was applied to the injection data for aflibercept and ranibizumab in order to more accurately reflect UK clinical practice. It was assumed that the treatment frequency in Year 3 onwards would be equivalent to the number of injections observed in Year 2. Given the absence of RCT evidence beyond 2 years for brolucizumab and the relevant comparators, it is difficult to assume that a lower number of injections might be administered without also assuming this could have a negative impact on VA – data from the HORIZON and VIEW1 open-label

	extension demonstrate loss of VA despite continuous injections beyond Year 2.[94, 95]
Adverse event probability	The cost minimisation model assumes that the probability of adverse events was the same across all compounds and treatment regimens, thus safety is assumed to be equivalent. The probability of adverse events was independent of whether the patient was treated for unilateral or bilateral disease. The inclusion of costs for serious AEs were explored in a scenario analysis based on Week 96 molecule-based baseline pooling from the clinical data identified in the SLR (random-effects model).
Probability of developing bilateral disease	Patients with unilateral disease had a fixed annual probability of developing bilateral disease. The probability of developing bilateral disease was based on data from the UK AMD database (Zarranz-Venture et al. 2014).[89]
FFA	FFA was performed at the incidence of wAMD to confirm diagnosis. It was not performed in subsequent monitoring visits. The unit cost was £151.58 taken from NHS Reference Costs 2017/2018 (Weighted average of Diagnostic Imaging codes for Contrast Fluoroscopy Procedures: RD30Z, RD31Z and RD32Z).[92]
OCT	OCT was performed at each monitoring visit. The unit cost was £114.35 based on the Outpatient Procedure code for Retinal Tomography: BZ88A (ophthalmology) taken from NHS Reference Costs 2017/2018[92].
Costs for bilateral disease	Patients with bilateral disease incurred twice the treatment costs, one and a half times the administration costs, and had the same monitoring costs as a patient with unilateral disease. This assumption is in line with the approach adopted in the NICE clinical guideline for AMD NG82.[86]

Abbreviations: CMM: cost minimisation model; FFA: fundas fluorescein angiography; NICE: National Institute of Health and Care Excellence; OCT: optical coherence tomography; wAMD: wet age-related macular degeneration.

B.4.3 Base case results

The results of the base case cost-comparison analysis are presented in Table 4.12. These results assume that aflibercept is provided at list price whilst brolucizumab and ranibizumab are provided at their confidential net prices.

Assuming equal efficacy in terms of BCVA outcomes and safety, the use of brolucizumab is estimated to result in per-patient cost savings of [redacted] versus aflibercept and [redacted] versus ranibizumab over a lifetime time horizon.

Whilst a confidential PAS discount has been arranged with the Department of Health for aflibercept, this is unknown to Novartis. As such, a threshold analysis was conducted to ascertain the discount to the list price of aflibercept that would be required to make aflibercept cost saving when compared with brolucizumab. When adopting the base case cost-comparison assumptions, the results of this threshold analysis demonstrate that brolucizumab would remain cost saving over a lifetime time horizon provided the net price of aflibercept is not below [redacted]. This would represent a [redacted]. Any net price for aflibercept that is higher than [redacted] would result in brolucizumab being associated with cost savings versus aflibercept.

With similar efficacy in terms of improvement in BCVA, similar impact on vision-related HRQoL, superior disease control and less frequent injections, brolucizumab is the most cost-effective treatment option for wAMD versus currently licensed anti-VEGF therapies and results in cost savings to the NHS over a lifetime time horizon.

Table 4.12: Base case cost-comparison results (with brolucizumab and ranibizumab provided at their net prices; aflibercept at list price)

	Brolucizumab 6 mg LP→q12/q8w	Aflibercept weighted[a]	Ranibizumab weighted[a]
Drug costs	[redacted]	£53,515	[redacted]
Admin costs	[redacted]	£5,060	[redacted]
OCT costs	[redacted]	£5,383	[redacted]
FFA costs	[redacted]	£207	[redacted]
AE costs	[redacted]	£0.00	[redacted]
Total costs	[redacted]	£64,164	[redacted]
Incremental costs	-	[redacted]	[redacted]

[a]In the base case analyses, a weighted average approach was adopted with regards to the treatment regimens for aflibercept and ranibizumab based on market share data on the use of each regimen. Scenario analyses for each individual regimen were also conducted.
Abbreviations: AE: adverse events; FFA: fundus fluorescein angiography; LP: loading phase; OCT: ocular coherence tomography; qXw: one injection every X weeks.

B.4.4 Sensitivity and scenario analyses

B.4.4.1 Deterministic sensitivity analysis

Deterministic sensitivity analysis (DSA) was conducted by varying all input parameters in the model. Whenever available, values were varied using confidence intervals obtained directly from the same data source that informed the mean value. In the absence of data on the variability around a particular value, it was varied by ±20%.

Versus aflibercept, the results of the DSA demonstrate that the rates of discontinuation for aflibercept and brolucizumab as well as the treatment cost multiplier included for the treatment of bilateral disease, have the greatest impact on the incremental cost (Figure 4.2). Versus ranibizumab, the results of the DSA demonstrate that the discontinuation rate for brolucizumab and the injection frequencies for brolucizumab and ranibizumab 0.5 mg q4w, have the greatest impact on the incremental cost (

Figure 4.3).

Figure 4.2: Tornado diagram of the top ten most influential parameters in the cost-comparison versus aflibercept (with brolucizumab and ranibizumab provided at their net prices; aflibercept at list price)

Abbreviations: FE: fixed-effects; FFA: fundus fluorescein angiography; LP: loading phase; RE: random-effects; OCT: ocular coherence tomography.

The results of the DSA versus ranibizumab demonstrate the monitoring costs for ranibizumab and brolucizumab, followed by the requirement to administer and monitor bilateral treatment in the long term (year 3+) to have the greatest impact on the incremental cost. The results were also sensitive to the frequency of injections for ranibizumab and brolucizumab (

Figure 4.3).

Figure 4.3: Tornado diagram of the top ten most influential parameters in the cost-comparison versus ranibizumab (with brolucizumab and ranibizumab provided at their net prices; aflibercept at list price)

Abbreviations: FE: fixed-effects; FFA: fundus fluorescein angiography; LP: loading phase; OCT: ocular coherence tomography; RE: random-effects.

B.4.4.2 Scenario analyses

Various scenario analyses were conducted to explore the impact of assumptions that were included in the base case analysis. The results of the scenario analyses are presented in Table 4.13 below. Across all of the scenarios conducted, brolucizumab remained cost saving versus both aflibercept and ranibizumab.

Table 4.13: Scenario analyses results (with brolucizumab and ranibizumab provided at their net prices; aflibercept at list price)

	Scenario	Incremental cost versus aflibercept	% change from base case incremental cost	Incremental cost versus ranibizumab	% change from base case incremental cost
Base case		[redacted]	[redacted]	[redacted]	[redacted]
Demographics					
1.	Baseline age: 65 years	[redacted]	[redacted]	[redacted]	[redacted]
2.	Proportion of female patients: 50%	[redacted]	[redacted]	[redacted]	[redacted]
Discount rate					
3.	Discount rate: 0%	[redacted]	[redacted]	[redacted]	[redacted]
Incidence of bilateral disease					
4.	Probability of developing wAMD in fellow eye: 7.50%	[redacted]	[redacted]	[redacted]	[redacted]
Bilateral treatment multiplier for drug costs					
5.	4 times	[redacted]	[redacted]	[redacted]	[redacted]
Dosing regimens					
6.	Aflibercept 2 mg q4w	[redacted]	[redacted]	-	-
7.	Aflibercept 2 mg q4w→PRN	[redacted]	[redacted]	-	-
8.	Aflibercept 2 mg LP→q8w	[redacted]	[redacted]	-	-
9.	Aflibercept 2 mg LP→q8w→PRN	[redacted]	[redacted]	-	-
10.	Aflibercept 2 mg LP→TREX	[redacted]	[redacted]	-	-
11.	Ranibizumab 0.5 mg LP→PRN	-	-	[redacted]	[redacted]
12.	Ranibizumab 0.5 mg LP→PRNX	-	-	[redacted]	[redacted]
13.	Ranibizumab 0.5 mg PRN	-	-	[redacted]	[redacted]
14.	Ranibizumab 0.5 mg TREX	-	-	[redacted]	[redacted]
15.	Ranibizumab 0.5 mg q4w	-	-	[redacted]	[redacted]
16.	Ranibizumab 0.5 mg q4w→PRN	-	-	[redacted]	[redacted]
Treatment discontinuation					
17.	NMA baseline pooling, fixed-effects	[redacted]	[redacted]	[redacted]	[redacted]
18.	NICE NG82 Appendix J	[redacted]	[redacted]	[redacted]	[redacted]

Injection and monitoring frequency					
19.	NMA baseline pooling, fixed-effects	[redacted]	[redacted]	[redacted]	[redacted]
20.	Alternative Year 3+ injection frequency, piecewise NMA	[redacted]	[redacted]	[redacted]	[redacted]
21.	Additional monitoring in Year 1 for brolucizumab included	[redacted]	[redacted]	[redacted]	[redacted]
22.	Alternative year 3+ injection and monitoring frequencies: UK expert opinion	[redacted]	[redacted]	[redacted]	[redacted]
Injection administration setting					
23.	36.8% day case administration (as per NG82)	[redacted]	[redacted]	[redacted]	[redacted]
Aflibercept appraisal assumptions					
24.	TA294 assumptions	[redacted]	[redacted]	[redacted]	[redacted]
25.	TA294 costs and assumptions	[redacted]	[redacted]	[redacted]	[redacted]
Adverse events					
26.	Inclusion of adverse events (based on 96-week baseline pooling [random-effects])	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: LP: loading phase; PRN: pro re nata; PRNX: pro re nata and extend dosing regimen; qXw: one injection every X weeks; RE: random-effects; TREX: treat-and-extend dosing regimen; w: weeks.

Scenarios 1–2: Demographics

In scenario 1, a baseline age of 65 years was adopted (versus 75.8 years in the base case analysis); in scenario 2, the proportion of females was set to 50% (versus 56.27% in the base case analysis). Scenario 1 results in brolucizumab being more cost saving versus both aflibercept and ranibizumab. Scenario 2 had a very minimal impact on the base case cost-comparison results.

Scenario 3: Discount rate

A scenario adopting a discount rate of 0% for costs was conducted; this resulted in brolucizumab being more cost saving versus both aflibercept and ranibizumab.

Scenario 4: Probability of developing bilateral disease

A scenario was conducted whereby the probability of developing bilateral disease was set to 7.50% based on (Wong *et al.* 2008)[90] (versus 16.6% in the base case analysis). This scenario resulted in reduced incremental costs between brolucizumab and both aflibercept and ranibizumab, though brolucizumab remained cost saving across both scenarios.

Scenario 5: Bilateral treatment multiplier

The base case assumed that patients with bilateral disease incurred 2x the treatment costs of those with unilateral disease. This assumption was explored by increasing the bilateral treatment

multiplier to 4x. This results in brolucizumab being more cost saving versus both aflibercept and ranibizumab.

Scenarios 6–16: Alternative dosing regimens

The base case analysis adopted a weighted average approach to the number of injection and monitoring visits for aflibercept and ranibizumab based on UK market share data on the use of each regimen. Several scenario analyses were therefore conducted to investigate the costs of brolucizumab versus alternative individual aflibercept and ranibizumab dosing regimens.

Table 4.14 presents the annual mean number of injections and visits estimated per dosing regimen, based on treatment arm-based baseline pooling of data identified in the clinical SLR, using a random-effects model to account for between-trial heterogeneity.

Brolucizumab remained cost saving versus both aflibercept and ranibizumab across all alternative dosing regimen scenarios conducted. Brolucizumab LP→6q12/q8w was found to be most cost-saving regimen versus the 2 mg q4w regimen for aflibercept, and a 0.5 q4w regimen for ranibizumab. The cost savings for brolucizumab were smallest versus the ranibizumab PRN and PRNX regimens; however, brolucizumab was still found to be cost saving versus these regimens.

Table 4.14: Annual mean number of injections and total visits per dosing regimen (random-effects)

Dosing regimen	Injections			Total visits		
	Year 0−1	Year 1−2	Year 3+	Year 0−1	Year 1−2	Year 3+
Afli 2 q4w	11.90	11.90	11.90	11.90	11.90	11.90
Afli 2q4w→PRN	7.14	5.00	5.00	7.14	12.70	12.70
Afli 2 LP→q8w	7.14	5.47	5.47	7.14	5.47	5.47
Afli 2 LP→q8w→PRN	7.14	5.00	5.00	7.14	12.70	12.70
Afli 2 LP→TREX	9.70	7.30	7.30	9.70	7.30	7.30
Rani 0.5 LP→PRN	7.08	5.60	5.60	12.90	12.70	12.70
Rani 0.5 LP→PRNX	5.50	5.50	5.50	10.30	10.10	10.10
Rani 0.5PRN	6.90	5.60	5.60	12.70	12.70	12.70
Rani 0.5TREX	9.54	8.22	8.22	9.54	8.22	8.22
Rani 0.5q4w	11.78	11.16	11.16	11.78	11.16	11.16
Ranibizumab 0.5q4w →PRN	11.78	5.60	5.60	11.78	12.70	12.70

Abbreviations: Afli: aflibercept; bro: brolucizumab; LP: loading phase; PRN: pro re nata; PRNX: pro re nata and extend dosing regimen; qXw: one injection every X weeks; rani: ranibizumab; TREX: treat-and-extend dosing regimen.

Scenarios 17–18: Treatment discontinuation

Two scenarios were conducted whereby treatment discontinuation values from the random-effects model based on pooled analysis of HAWK and HARRIER (Table 4.15), and values from NICE NG82 Appendix J (Table 4.16) were utilised. The use of treatment discontinuation rates from the fixed-effects model had a very minimal impact on the base case results. The use of the treatment discontinuation rates from NICE NG82 results in further cost savings versus aflibercept and reduced cost savings versus ranibizumab, but brolucizumab remained cost saving overall.

Table 4.15: Annual treatment discontinuation rates applied in the base case analysis derived from baseline pooling analysis (fixed-effects model)

Treatment	Bi-annual probability	Mean annual treatment discontinuation probability
Brolucizumab 6 mg LP→q12/q8w	14.44%	7.50%
Aflibercept weighted[a]	16.36%	8.55%
Ranibizumab weighted[a]	15.16%	7.89%

[a]In the base case analyses, a weighted average approach was adopted with regards to the treatment regimens for aflibercept and ranibizumab based on market share data on the use of each regimen. Scenario analyses for each individual regimen were also conducted.
Abbreviations: qXw: one injection every X week; SE: standard error.

Table 4.16: Treatment discontinuation (based on NICE NG82 Appendix J)

	Brolucizumab 6 mg LP→q12/q8w	Aflibercept weighted[a]	Ranibizumab weighted[a]
Baseline log (odds)	-	-	-2.3310
Log odds ratio versus Rani 0.5 mg	-0.6080	-0.6080	-
Odds ratio versus Rani 0.5 mg	0.5444	0.5444	-
Odds of discontinuation	0.0529	0.0529	0.0972
Annual probability	5.03%	5.03%	8.86%

[a]In the base case analyses, a weighted average approach was adopted with regards to the treatment regimens for aflibercept and ranibizumab based on market share data on the use of each regimen. Scenario analyses for each individual regimen were also conducted.
Abbreviations: qXw: one injection every X weeks.

Scenarios 19–22: Alternative injection frequencies

A scenario analysis using the fixed-effects model (versus the random-effects in the base case) to estimate the number of injection and monitoring visits was adopted (assuming the base case weighted average approach for the dosing regimens of the comparators) (Table 4.17).

Table 4.17: Annual mean number of injections and total visits per dosing regimen (fixed-effects model)

Dosing regimen	Injections			Total visits		
	Year 0−1	Year 1−2	Year 3+	Year 0−1	Year 1−2	Year 3+
Bro 6 mg LP→q12/q8w	6.66	4.83	4.83	6.66	4.83	4.83
Afli weighted[a]	8.85	6.87	6.87	8.85	8.19	8.19
Rani weighted[a]	9.26	7.76	7.76	10.93	9.96	9.96

[a]In the base case analyses, a weighted average approach was adopted with regards to the treatment regimens for aflibercept and ranibizumab based on market share data on the use of each regimen. Scenario analyses for each individual regimen were also conducted.
Abbreviations: Afli: aflibercept; bro: brolucizumab; LP: loading phase; qXw: one injection every X weeks; rani: ranibizumab.

A scenario analysis was conducted to test the assumption that the frequency of injection and monitoring visits in Year 3 onwards reflects the frequency of injection and monitoring visits required in Year 2. A piecewise analysis was conducted, in line with the approach adopted in NG82.

For continuous regimens (monthly, bi-monthly and quarterly), imperfect adherence was taken into account by multiplying each predicted number of annual injections by the adherence found in the IVAN study.[98] The IVAN study, that evaluated ranibizumab versus bevacizumab, was selected as it is a UK study and is therefore more likely to reflect adherence to injections in the NHS than other studies. The same adherence was applied to both aflibercept and ranibizumab.

For discontinuous regimens (PRN, TREX, PRNX), a piecewise network was used to estimate long-term injection numbers. Rani 0.5PRN was used as a reference based on the ARMD database.[99] The number of injections relative to Rani 0.5 PRN were then calculated based on the clinical trial data that provided data from Baseline to two years or from one to two years. Full details of the methodology undertaken for this scenario analysis are presented in Appendix D.

Whilst this scenario resulted in reduced incremental costs for brolucizumab versus aflibercept and ranibizumab, brolucizumab remained cost saving versus both comparators.

Table 4.18: Estimation of injection visits in Year 3+ using the piecewise analysis

Dosing regimen	Year 3+
Bro 6 mg LP→q12/q8w	4.80
Afli weighted[a]	4.87
Rani weighted[a]	5.34

Abbreviations: Afli: aflibercept; bro: brolucizumab; LP: loading phase; qXw: one injection every X weeks; rani: ranibizumab.

Finally, two further scenarios were conducted to test the injection frequency assumptions. In the first scenario, additional monitoring in Year 1 was included for brolucizumab, given the additional wording anticipated in the SmPC for brolucizumab, whereby patients may require a disease activity assessment at Week 16.[1]

In the second scenario, alternative injection and monitoring frequencies were adopted in Year 3+ based on feedback from UK clinical experts – the number of injection and monitoring visits is assumed to be the same for all three anti-VEGF therapies: 4 in Year 3+.[88]

In both of these scenarios, brolucizumab remained cost saving versus both aflibercept and ranibizumab.

Scenario 23: Administration setting

A scenario analysis was carried out to investigate the impact of conducting 36.8% of wAMD treatment visits as day cases, and the rest in an outpatient clinic setting, as per the assumptions adopted by NICE in NG82. Whilst this scenario resulted in reduced incremental costs for brolucizumab versus aflibercept and ranibizumab, brolucizumab remained cost saving versus both comparators.

Scenario 24–25: Aflibercept TA294 costs/resource use assumptions

Scenario analyses were conducted to include the cost/resource use assumptions from TA294 (

Table 4.19) – one scenario with solely the resource use assumptions (percentage of outpatient administrations) and one with both the cost/resource use assumptions. Whilst this scenario resulted in reduced incremental costs for brolucizumab versus aflibercept and ranibizumab, brolucizumab remained cost saving versus both comparators.

Table 4.19: TA294 cost/resource use assumptions

Item	Cost/assumption
FFA diagnosis costs	117.26
OCT monitoring costs	117.26
Consultant visit administration cost	79.74
Day case administration cost	402.08
Percent of administration as outpatient (versus day case)	44.87%

Abbreviations: FFA: FFA: fundas fluorescein angiography; OCT: optical coherence tomography.

Scenario 26: Inclusion of adverse events

The impact of including the costs and resource use associated with AEs was explored in a scenario analysis. For this scenario analysis, patients were assumed to be subject to the risk of experiencing AEs whilst on treatment only. The risk of experiencing AEs was dependent on being on treatment in any eye, and was not increased for bilateral treatment, consistent with the approach to modelling AEs in the NICE clinical guideline for AMD NG82.[86] Additionally, the probability of AEs was assumed to be the same across all compounds and treatment regimens.

Only serious ocular AEs were considered relevant for inclusion within the analysis. Additionally, stroke was deemed an important complication associated with anti-VEGF treatment by the NICE guideline committee, and hence was also included within the model. Both overall and serious AEs were considered for stroke given the severity of this AE; this approach is consistent with NG82. For this scenario analysis, the incidence of serious ocular AEs was based on Week 96 molecule-based baseline pooling from the clinical data identified in the SLR (random-effects model) (Table 4.20).

The inclusion of the costs for serious ocular AEs had a minimal impact on the base case results, given the comparable safety profiles between all three therapies.

Table 4.20: Annual AE incidence rates applied in the scenario analysis

AE	Brolucizumab 6 mg LP→q12/q8w	Aflibercept weighted[a]	Ranibizumab weighted[a]
Cataract	0.30%	0.60%	0.20%
Endophthalmitis	0.55%	0.33%	1.00%
Gastrointestinal event	0.00%	0.00%	0.00%
Intraocular inflammation	0.95%	0.00%	0.00%
Retinal detachment	0.30%	0.25%	0.41%
Retinal pigment epithelial tear	0.40%	0.24%	0.20%
Retinal tear	0.50%	0.30%	0.40%
Stroke	0.63%	0.94%	1.04%

[a]In the base case analyses, a weighted average approach was adopted with regards to the treatment regimens for aflibercept and ranibizumab based on market share data on the use of each regimen. Scenario analyses for each individual regimen were also conducted.
Abbreviations: AE: adverse event; LP: loading phase; qXw: one injection every X weeks.

The unit costs of AEs were taken from the NICE clinical guideline for AMD NG82.[86] Resource use associated with AEs was assumed to reflect the healthcare required to treat that event on a

one-off basis except in the case of stroke, which has an ongoing resource requirement. Despite equal annual AE probabilities between treatments, the total AE costs are different across the anti-VEGF therapies due to different discontinuation rates.

Table 4.21: Unit costs of AEs

AE	Unit cost	Source
Cataract	£913.42	Weighted average of non-elective short-stay and day-case codes for Phacoemulsification Cataract Extraction and Lens Implant: BZ34A, B and C, NHS Reference Costs 2017/18[92]
Endophthalmitis	£1,643.71	NG82[93] prices inflated to 2018 prices using Office for National Statistics (ONS) [100] inflation indices: Table 23 D7FC (06.3 Hospital services). 2014/15: 97.1, 2018: 113.1. Based on resource use in NG82[86]
Gastrointestinal event	£441.43	Weighted average of non-elective short-stay and day-case codes for Abdominal Pain (FD05A and B) and for Non-Malignant Gastrointestinal Tract Disorders (FD10A to M), NHS Reference Costs 2017/2018[92]
Intraocular inflammation[a]	£0	Assumption
Retinal detachment	£1,649.30	Followed methodology in the economic evaluation in NG82[93]: 75% requiring non-elective vitrectomy, 2 outpatient visits required, outpatient attendance is £95.13 per visit. Costs sheet of NHS Reference Costs 2017/18[92] Vitrectomy cost is weighted average of day-case procedures: BZ84A, BZ84B.[92] Urgent vitrectomy (non-elective) cost is weighted average of non-elective short-stay and non-elective inpatients BZ84A, BZ84B[92]
RPE tear	£0	Assumption
Retinal tear	£656.70	Weighted average of non-elective short-stay and day-case codes for Phacoemulsification Cataract Extraction and Lens Implant: BZ34A, B and C, NHS Reference Costs 2017/18[92]
Stroke[b]	£4,215.94	NG82[86] prices inflated to 2018 prices using Office for National Statistics (ONS) [100] inflation indices: Table 23 D7FC (06.3 Hospital services). 2014/15: 97.1, 2018: 113.1. Based on resource use in NG82[86]
Stroke – recurrent annual cost	£159.69	Weighted average of non-elective short-stay and day-case codes for Phacoemulsification Cataract Extraction and Lens Implant: BZ34A, B and C, NHS Reference Costs 2017/18[92]

[a]Uveitis and vitritis; [b]Stroke related recurrent annual cost, considered as ongoing event.
Abbreviations: AE: adverse event; ONS: Office for National Statistics; NHS: National Health Service; NICE: National Institute for Health and Care Excellence

B.4.5 Subgroup analysis

No economic subgroup analyses have been conducted for the purposes of this appraisal. Results of the subgroup analyses up to Week 48 in the HAWK and HARRIER trials (discussed in further detail in Section B.3.7) showed a relevant benefit in terms of BCVA improvement from Baseline for brolucizumab patients regardless of lesion type and was not suggestive of subgroup-specific differences.

B.4.6 Interpretation and conclusions of the evidence

wAMD is a debilitating, chronic, rapidly progressing disease characterised by the leaking of fluid from the formation of abnormal blood vessels underneath the macula occurring in response to abnormally high levels of VEGF.[24, 27, 28] Unresolved fluid accumulation leads to an increase in CSFT and generalised disruption to the anatomical architecture of the retina which ultimately results in severe and irreversible vision loss.[32, 41] The control of fluid accumulation is therefore essential to the effective management of wAMD and improving and maintaining vision.

The anti-VEGF therapies aflibercept and ranibizumab are the current standard of care of wAMD, with several studies demonstrating that both therapies have equal efficacy and similar safety profiles.[53-55] Both therapies have been assessed and recommended for reimbursement for the treatment of wAMD by NICE.[2, 3, 33]

The current management of wAMD is associated with a distinct treatment burden relating to the high monitoring and injection frequency of these therapies. Real-world evidence demonstrates that visual outcomes with current anti-VEGF therapies are related to injection frequency; however, the high treatment burden impacts both patient adherence (due to factors such as injection fear, anxiety and the inconvenience of attending clinic appointments) as well as ophthalmology clinic capacity, which can lead to delayed follow-up of wAMD patients, placing these patients at risk of symptom exacerbation and vision loss.[58-60] There remains a clear unmet need for a therapy that suppresses disease activity (fluid accumulation and CSFT) for longer than currently available anti-VEGF therapies, enabling the administration of less frequent injections immediately following the loading dose phase without reducing visual outcomes. Furthermore, the earlier identification of patients who are able to be maintained on a longer treatment interval is critical, to enable ophthalmology clinics to plan ahead with regards to clinic capacity. In turn, this may lead to better patient adherence and a reduced risk of undertreatment, leading to improved visual outcomes, patient independence and HRQoL.

Brolucizumab is anticipated to be used in clinical practice in accordance with its full licensed indication, for the treatment of wAMD. Therefore, the relevant comparators to brolucizumab in this position are aflibercept and ranibizumab. The efficacy of brolucizumab as a treatment for wAMD has been demonstrated in three large randomised head-to-head trials versus aflibercept; comprising two phase III trials (HAWK and HARRIER) and one phase II trial (OSPREY).

The clinical evidence demonstrated that treatment with brolucizumab required fewer injections to achieve a similar improvement in BCVA versus aflibercept, with a majority of patients maintained on a q12w dosing interval immediately following the loading dose phase. Brolucizumab was also statistically superior to aflibercept in terms of improvements in CSFT, retinal fluid (IRF and SRF) and disease activity. The safety profile of brolucizumab is also comparable to the safety profile of aflibercept; the overall incidence of ocular and non-ocular AEs was balanced across all treatment groups in both HAWK and HARRIER trials and no new, previously unreported types of AEs were identified compared with other anti-VEGF therapies.

The results of an NMA also demonstrated brolucizumab to be associated with comparable efficacy versus aflibercept and ranibizumab in terms of change in BCVA from Baseline to one and two years. The NMA also demonstrated brolucizumab (LP → Bro 6q12/q8w) to be statistically significantly better than all aflibercept and ranibizumab regimens at decreasing retinal thickness from Baseline to one year. Results of the arm-based baseline pooling for injection frequency also demonstrated brolucizumab to be associated with the second lowest injection frequency across year one and the lowest injection frequency in year two versus all aflibercept and ranibizumab regimens.

The results of the cost-comparison analysis indicate that brolucizumab is a cost-saving alternative to aflibercept and ranibizumab. Over a lifetime time horizon (and when [redacted]), the use of brolucizumab was associated with cost savings of [redacted] versus aflibercept and [redacted] versus ranibizumab.

The key strength of the evidence supporting this submission is that it is based on two large international RCTs, which demonstrate the equivalence of brolucizumab to a key comparator aflibercept, and the results of a robust NMA of RCTs that demonstrate brolucizumab to be associated with comparable efficacy in terms of BCVA and safety, and statistically significantly superior in terms of reduction in retinal thickness, versus both aflibercept and ranibizumab. The results are generalisable to clinical practice in England as the model utilises weighted average treatment regimens for aflibercept and ranibizumab based on the results from a survey of UK retinal specialists. The primary limitation of the cost-comparison analysis is that aflibercept has a confidential PAS, therefore the results of the cost-comparison model do not reflect the true cost of aflibercept, however a threshold analysis indicates that brolucizumab would remain cost saving over a lifetime time horizon provided the net price of aflibercept is not below [redacted]. This would represent a [redacted] and any net price for aflibercept that is higher than [redacted] would result in brolucizumab being associated with cost savings versus aflibercept.

The assumptions adopted within the base case cost-comparison analysis were explored in extensive scenario analyses; the results of which demonstrated brolucizumab remains cost saving across all scenarios versus both aflibercept and ranibizumab. In addition, the key cost and resource use assumptions were validated by two leading UK clinical experts.[88]

With similar efficacy in terms of improvement in BCVA, similar impact on vision-related HRQoL, superior disease control and less frequent injections, the results of the economic analysis indicate that brolucizumab is the most cost-effective treatment option for wAMD versus currently licensed anti-VEGF therapies and results in cost savings to the NHS over a lifetime time horizon.

As the first anti-VEGF therapy to have a licensed q12w maintenance dose immediately following the loading phase, brolucizumab addresses the unmet need associated with currently available anti-VEGF therapies, by providing patients with a therapy with superior fluid reduction that suppresses disease activity for longer than currently available anti-VEGF therapies. In turn, this allows for an earlier extension in the treatment interval immediately following the loading dose phase based on lasting disease control, and the earlier identification of patients who are able to be maintained on a longer treatment interval may help with clinic capacity constraints.[62]

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B.6 Appendices

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

Appendix D: Identification, selection and synthesis of clinical evidence

Appendix E: Adverse reactions

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

Appendix G: Checklist of confidential information

Appendix H: OSPREY Trial

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Fast track appraisal

Brolucizumab for treating wet age-related macular degeneration [ID1254]

Clarification questions

November 2019

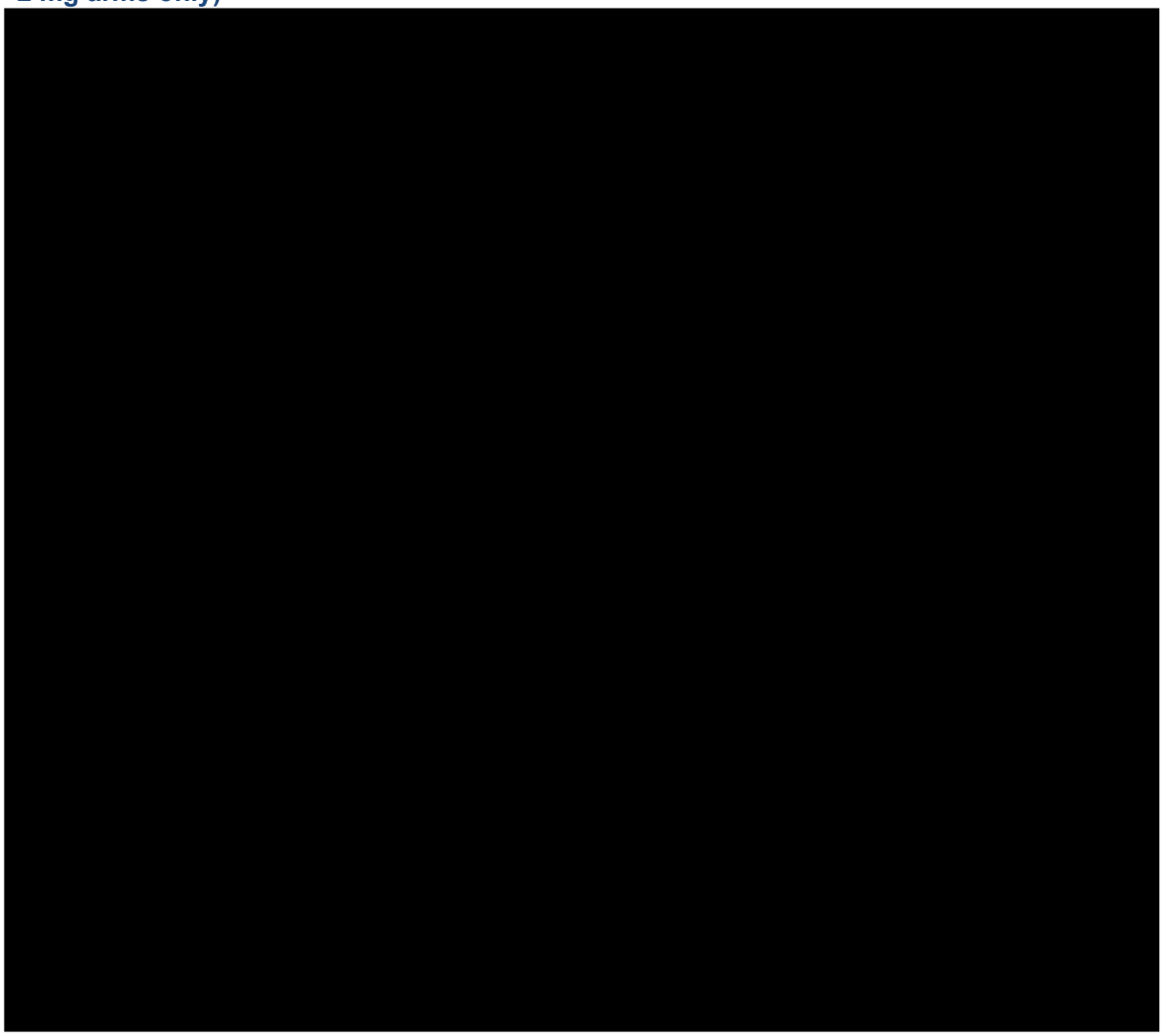
File name	Version	Contains confidential information	Date
ID1254 Brolucizumab for wAMD Clarification Questions Response [ACIC]	**2**	**Yes**	**29 November 2019**

Section A: Clarification on effectiveness data

A1. Please provide CONSORT diagrams of patient flow for the brolucizumab 6mg arm and aflibercept 2mg arm to study end at 96 weeks. Please provide separate diagrams for HAWK and HARRIER (2 diagrams).

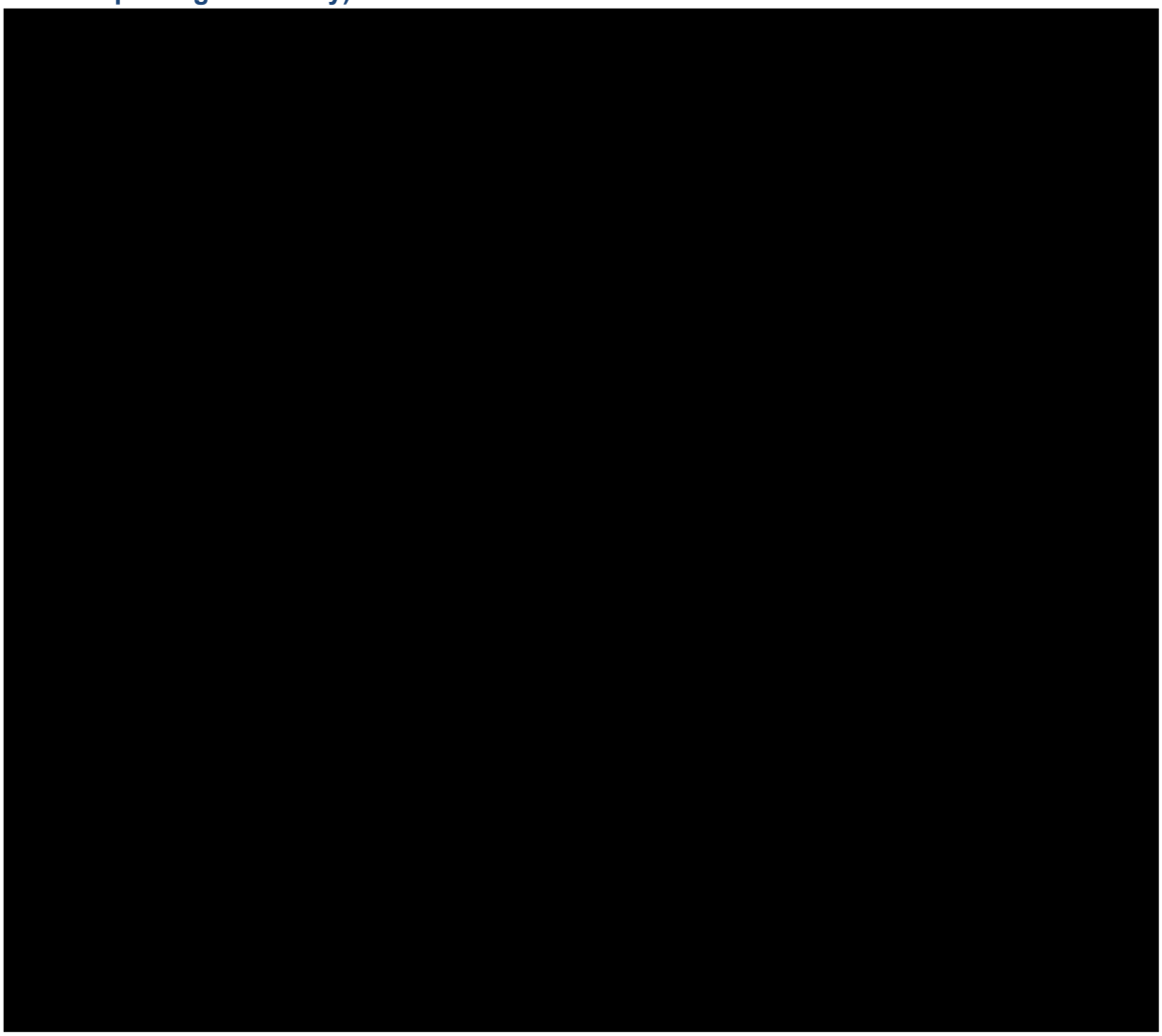
The CONSORT diagrams of patient flow for the brolucizumab 6 mg arm and aflibercept 2 mg arms to study end at 96 weeks for both HAWK and HARRIER are presented below in Figure 1 and Figure 2 respectively.

Figure 1: CONSORT diagram for HAWK up to Week 96 (brolucizumab 6 mg and aflibercept 2 mg arms only)



Source: HAWK CSR (Table 10-2).[1]

Figure 2: CONSORT diagram for HARRIER up to Week 96 (brolucizumab 6 mg and aflibercept 2 mg arms only)



Source: HARRIER CSR (Table 10-2).[2]

A2. In HAWK and HARRIER dosing schedules differ between the brolucizumab arm and the aflibercept arm and some patients in the brolucizumab arm(s) transfer from 1 injection every 12 weeks (q12w) to 1 injection every 8 weeks (q8w). Please explain how;

1. physicians performing anatomical, fluid retention and best-corrected visual acuity (BCVA) assessments
2. treating physicians, and
3. patients

were blinded to treatment allocation and how this blinding was maintained during the course of the trials. Please make particular reference to patients with changing dosing frequency in the brolucizumab arm.

At Baseline, all eligible patients were randomised centrally using an Interactive Response Technology (IRT) system in a 1:1 ratio to receive either brolucizumab or aflibercept. The IRT

assigned a randomisation number to the patient, which was used to link the patient to a treatment arm and specified a unique medication number for the first package of study treatment to be administered to the patient. The randomisation number was not communicated to unmasked staff. Answers to parts 1, 2 and 3 of this question are presented below:

1. Best-corrected visual acuity (BCVA) assessments were undertaken by a masked Investigator, who was not allowed to perform any tasks that could have unmasked him/her to the patient's treatment. In addition to the BCVA testing, the masked Investigator assessed wAMD disease activity in order to identify patients in the brolucizumab arm with a q8w treatment need. The masked Investigator was also responsible for capturing data in the electronic data capture system. Disease activity was also assessed in the aflibercept arm to allow for respective comparative analyses, with no impact on treatment frequency. The IRT system was utilised to implement the outcome of the disease activity assessments (DAAs) at the appropriate visits. If disease activity was identified by the masked Investigator, the appropriate information was recorded in the IRT and the system made the necessary changes to the dosing regimen, i.e. assignment of the respective patient to q8w regimen. The masked Investigator maintained the same role throughout the study.[3]

2. All study treatments (brolucizumab, aflibercept, or sham) were administered by an unmasked treating physician. The unmasked treating physician also completed the post-injection assessment to ensure that the injection procedure and/or study medication did not endanger the health of the eye. The unmasked treating physician maintained the same role throughout the study.[3]

3. Following the three loading doses, each patient was injected every 12 weeks (q12w) up to Week 96, unless there was disease activity assessed according to the guidance provided at disease assessment visits, after which patients would be converted to a q8w dosing regimen. If patients were converted to a q8w dosing regimen, they were not able to return to a q12w dosing regimen, even if disease activity was not detected for the rest of the study.[3] From Week 16, patients who did not receive an active injection due to differences in treatment regimen (q8w versus q12w) were administered a sham injection to maintain masking. [redacted].[1, 2]

[redacted].[1, 2]

A3. In 2 tables, please tabulate the values (mean, standard error [s.e.], 95% confidence interval [CI]) that underlie figure 3.5 and 3.8 in the company submission. In these tables, please include:

- values for the subset of people receiving brolucizumab (6 mg) who remained q12w to week 48
- values for the subset of people receiving brolucizumab (6 mg) who remained q12w to week 96, and

- values treating lost to follow-up as missing data, rather than last observation carried forward (LOCF).

The results requested have been tabulated in Appendix A.

Table 20 presents the data that underlies Figure 3.5, the change in BCVA from Baseline through to Week 96 in HAWK and HARRIER. The mean change is presented as a least-squares mean (LS-mean) as a result of an analysis of variance (ANOVA) pairwise analysis. Table 21 presents the same information where missing data are treated as lost to follow-up, by only presenting the observed population (FAS-observed). As no ANOVA pairwise analysis was conducted between the arms for this population, descriptive mean values and confidence intervals are presented only.

Table 22 presents the data underlying Figure 3.8, the change in CSFT from Baseline through to Week 96 by time point. The mean change is presented as a LS-mean as a result of an ANOVA pairwise analysis. For the HAWK trial, both comparisons (brolucizumab 3 mg and brolucizumab 6 mg versus aflibercept) are presented. Table 23 presents the same information treating missing data as lost to follow-up, rather than carrying the last observation forward. No ANOVA pairwise analysis was conducted in the FAS-observed population, and therefore descriptive mean values and confidence intervals are presented only.

With regards to the ERG's request to provide:

- Values for the subset of people receiving brolucizumab (6 mg) who remained q12w to week 48 and
- Values for the subset of people receiving brolucizumab (6 mg) who remained q12w to week 96

Please see Table 24 which presents the mean BCVA change from Baseline for patients receiving brolucizumab (6 mg) who remained q12w to Week 48. Table 25 presents the same data for patients who remained on q12w to Week 96, and the corresponding data for patients who received q8w dosing up to Week 96. These data are presented as LS-means resulting from ANOVA pairwise analyses.

It has not been possible to provide the following datasets due to time constraints as these data are not readily available:

- Change in CSFT for the subset of patients remaining q12w up to Week 48
- Change in CSFT for the subset of patients remaining q12 up to Week 96

The corresponding data for BCVA (Table 24 and Table 25) was available in a shorter timeframe because they formed part of a regulatory agency request previously.[4] We are liaising with the NICE project team to follow up with this response.

A4. Please state which, if any, of the mean values in table 3.19 (company submission) are statistically significantly different from one another at the 5% level.

Table 3.19 of the company submission contains the baseline pooling results to obtain absolute treatment effects for the discontinuation of brolucizumab, aflibercept, and ranibizumab. The values that NICE has requested to be compared have been pooled from multiple trials. For example, the discontinuation rate identified for aflibercept is a weighted average of the discontinuation rates published in each aflibercept trial. Comparing these pooled values would not be the same as conducting a simple comparison of means, and it would not be appropriate to conduct a statistical test to identify significant differences between the treatments without adjusting for study differences. In order to obtain statistical differences on the relative efficacy, an NMA would be the most appropriate approach.

As documented, a regimen-based NMA was conducted to determine relative treatment effects for discontinuation, however, a molecule-based NMA would not be appropriate to determine relative treatment effects as it would pool multiple regimens of the same treatment and result in heterogeneity among the trials being pooled.

A5. The mean and standard deviation values of central susbfield thickness (CSFT) total reported in table 3.4 of the company submission seem to be out of range compared with the reported median and range, and those of the HARRIER trial. Please confirm accuracy of the data.

Please accept our apologies, the mean (SD) CSFT total (µm) data were reported incorrectly for the HAWK trial. This discrepancy has been corrected in the table below.

Table 1: Baseline characteristics of patients in the HAWK and HARRIER trials (FAS) Week 48 analysis

Trial name	HAWK			HARRIER	
Characteristic	**Brolucizumab 3 mg (n=358)**	**Brolucizumab 6 mg (n=360)**	**Aflibercept 2 mg (n=360)**	**Brolucizumab 6 mg (n=370)**	**Aflibercept 2 mg (n=369)**
CSFT total (µm)					
Mean (SD)	466.6 (167.42)	463.1 (166.62)	457.9 (146.37)	473.6 (171.39)	465.3 (151.21)
Median (range)	427 (168–1392)	417 (217–1204)	425 (215–1082)	434 (200–1192)	442 (206–1319)
Min–Max	168–1392	217–1204	215–1082	200–1192	206–1319

Abbreviations: CSFT: central subfield thickness; FAS: full analysis set; SD: standard deviation.
Source: HAWK CSR (Table 14.1-4.5);[78] HARRIER CSR (Table 14.1-4.1);[79] Dugel et al. 2019.[76]

A6. Page 57 of the company submission states, “Results from both HAWK and HARRIER showed brolucizumab 6 mg in the HAWK trial to be advantageous compared to aflibercept (2 mg) at both the 48- and 96-week time point, in terms of the proportion of patients gaining ≥15 BCVA letters or reaching a BCVA of ≥84

letters (Table 3.11).” However, data in table 3.11 show mean changes rather than proportions. Please clarify.

Please note that the statement “Results from both HAWK and HARRIER showed brolucizumab 6 mg in the HAWK trial to be advantageous compared to aflibercept (2 mg) at both the 48- and 96-week time points, in terms of the proportion of patients gaining ≥15 BCVA letters or reaching a BCVA of ≥84 letters” relates only to the statistically significant results within the analysis of secondary BCVA endpoints (highlighted in green in Table 2 below), which correspond to the results for the *difference in the proportion of patients* gaining ≥15 BCVA letters or reaching a BCVA of ≥84 letters in the HAWK trial at both Week 48 and Week 96. This has been made clearer within Table 2 below.

Table 2: Selected secondary endpoints related to BCVA at, and up to, Week 48 and Week 96 (FAS-LOCF)

Trial name	**HAWK**
Secondary BCVA endpoint	**Brolucizumab 6 mg – aflibercept 2 mg difference (95% CI), p value**
Analysis at Week 48	
Mean change from Baseline (Week 4 – Week 48)	0.0 (-1.5, 1.6), p=0.9647
Mean change from Baseline (Week 12 – Week 48)	0.1 (-1.6, 1.8), p=0.9235
Proportion of patients with ≥15 letters gained from Baseline/BCVA of ≥84 letters at Week 48	8.2 (2.2, 15.0), p=0.0136
Proportion of patients with ≥15 letters loss from Baseline at Week 48	0.9 (-2.7, 4.3), p=0.6198
Proportion of patients with BCVA of ≥73 letters at Week 48	-2.4 (-8.6, 3.6), p=0.4442
Analysis at Week 96	
Mean change from Baseline at Week 96	0.5 (-1.6, 2.7), p=0.6326
Mean change from Baseline (Week 84 – Week 96)	0.4 (-1.7, 2.5), p=0.7289
Mean change from Baseline (Week 4 – Week 96)	0.0 (-1.7, 1.8), p=0.9554
Mean change from Baseline (Week 12 – Week 96)	0.1 (-1.7, 1.9), p=0.9379
Proportion of patients with ≥15 letters gained from Baseline/BCVA of ≥84 letters at Week 96	7.2 (1.4, 13.8), p=0.0313
Proportion of patients with ≥15 letters loss from Baseline at Week 96	0.7 (-3.6, 4.6), p=0.7210
Proportion of patients with BCVA of ≥73 letters at Week 96	2.3 (-3.8, 9.0), p=0.4820

Abbreviations: BCVA: best-corrected visual acuity; CI: confidence interval; FAS: full analysis set; LOCF: last observation carried forward.
Source: HAWK CSR (Table 14.2-25.1.1_y2);[78] Dugel et al. 2019.[76]

A7. What is the number/proportion of patients from UK centres in the HAWK and HARRIER trials, by treatment arms?

Details of the number of patients from UK centres in the HAWK and HARRIER trials are provided below.

HAWK

[redacted]

HARRIER

[redacted]

A8. Please provided forest plots for analyses shown in table 25 of the appendices (page 65) with an I^2 value of over 70%.

Please find below forest plots for the analyses shown in Table 25 of the company submission appendices with an I^2 value of >70%:

Figure 3: Forest plot of the NMA results directly comparing the difference in mean change in BCVA from Baseline to one year between Rani 0.5q4w and Afli 2q8w

[redacted]

Abbreviations: Afli: aflibercept; BCVA: best-corrected visual acuity; CI: confidence interval; Diff: difference; FE: fixed effects; NMA: network meta-analysis; qXw: one injection every X weeks; Rani: ranibizumab; RE: random effects; vs: versus.

Figure 4: Forest plot of the NMA results directly comparing the difference in mean change in BCVA from Baseline to one year between Rani 0.5q4w and LP→Rani 0.5TREX

Abbreviations: AMD: age-related macular degeneration; BCVA: best-corrected visual acuity; CI: confidence interval; FE: fixed effects; LP: loading phase; NMA: network meta-analysis; Rani: ranibizumab; RE: random effects; TREX: treat-and extend dosing regimen; vs: versus.

Figure 5: Forest plot of the NMA results directly comparing the difference in mean change in BCVA from Baseline to one year between LP→Afli 2q8w and Afli 2q4w

Abbreviations: Afli: aflibercept; BCVA: best-corrected visual acuity; CI: confidence interval; Diff: difference; FE: fixed effects; NMA: network meta-analysis; qXw: one injection every X weeks; RE: random effects; vs: versus.

A9. Using data from tables 35 to 40 of the appendices, please provide forest plots showing data of individual trial arms for which baseline pooling was carried out.

Please find below forest plots showing data of individual trial arms for which baseline pooling was carried out:

Figure 6: Forest plot of the NMA results of the individual treatment data and baseline pooling results for treatment discontinuation of aflibercept 2 mg from Baseline to one year

Abbreviations: Afli: aflibercept; CI: confidence interval; FE: fixed effects; LP: loading phase; prop: proportion; qXw: one injection every X weeks; RE: random effects; TREX: treat-and extend dosing regimen.

Figure 7: Forest plot of the NMA results of individual treatment data and baseline pooling results for treatment discontinuation of brolucizumab 6 mg from Baseline to one year

Abbreviations: Bro: brolucizumab; CI: confidence interval; FE: fixed effects; LP: loading phase; prop: proportion; qXw: one injection every X weeks; RE: random effects.

Figure 8: Forest plot of the NMA results of individual treatment data and baseline pooling results for treatment discontinuation of ranibizumab 6 mg from Baseline to one year

Abbreviations: CI: confidence interval; FE: fixed effects; LP: loading phase; PRN: pro re nata dosing regimen; prop: proportion; qXw: one injection every X weeks; Rani: ranibizumab; RE: random effects; TREX: treat-and extend dosing regimen.

Figure 9: Forest plot of the NMA results of individual treatment data and baseline pooling results for treatment discontinuation from Baseline to two years

Abbreviations: Afli: aflibercept; CI: confidence interval; FE: fixed effects; LP: loading phase; PRN: pro re nata dosing regimen; prop: proportion; qXw: one injection every X weeks; Rani: ranibizumab; RE: random effects; TREX: treat-and extend dosing regimen.

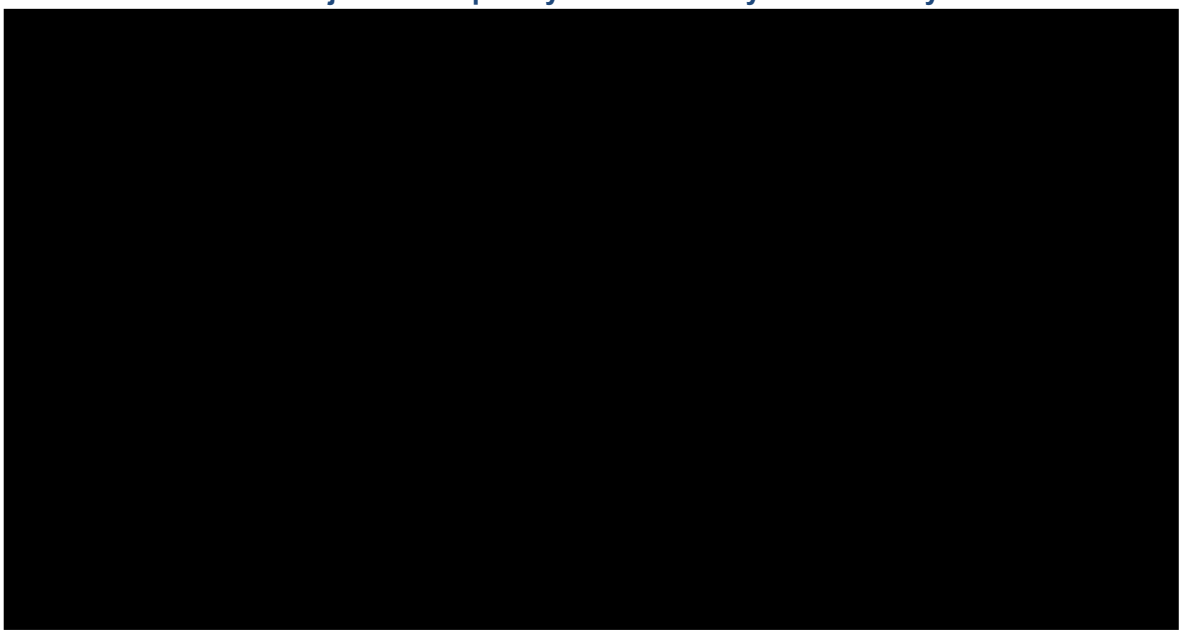
Figure 10: Forest plot of the NMA results of individual treatment data and baseline pooling results for annualised injection frequency from Baseline to one year[a]

[a]Injection frequencies represent the annualised number of injections from Baseline to one year; for HAWK and HARRIER the values have been extrapolated from 48 weeks to 52 weeks.
Abbreviations: Afli: aflibercept; AMD: age-related macular degeneration; CI: confidence interval; FE: fixed effects; LP: loading phase; NMA: network meta-analysis; PRN: pro re nata; qXw: one injection every X weeks; Rani: ranibizumab; RE: random effects; TREX: treat-and extend dosing regimen.

Figure 11: Forest plot of the NMA results of individual treatment data and baseline pooling results for annualised injection frequency from Baseline to two years[a]

[a]Injection frequencies represent the annualised number of injections between baseline and Year 2; for HAWK, HARRIER, and VIEW 1&2 (not pictured above, as values were not pooled) the values have been extrapolated from 96 weeks to 104 weeks.
Abbreviations: Afli: aflibercept; AMD: age-related macular degeneration; CI: confidence interval; FE: fixed effects; LP: loading phase; NMA: network meta-analysis; PRN: pro re nata; qXw: one injection every X weeks; Rani: ranibizumab; RE: random effects; TREX: treat-and extend dosing regimen.

Figure 12: Forest plot of the NMA results of individual treatment data and baseline pooling results for annualised injection frequency between one year and two years[a]



[a]Injection frequencies were calculated as the difference in annualised number of injections between Year 1 and Year 2.
Abbreviations: Afli: aflibercept; AMD: age-related macular degeneration; CI: confidence interval; FE: fixed effects; LP: loading phase; NMA: network meta-analysis; qXw: one injection every X weeks; Rani: ranibizumab; RE: random effects; TREX: treat-and extend dosing regimen.

A10. Please clarify why surface under the cumulative ranking line (SUCRA) was presented only for sensitivity analyses (in the appendices document), but not the base case analyses.

The SUCRA is a numeric presentation of ranking, and presents a single number associated with the rank of each treatment regimen.[5] There are limitations associated with SUCRA analyses and, given these limitations, it was not considered appropriate to include these within the main submission. For transparency, the SUCRA results for all base case analyses have been provided in response to this question.

However, please note that these results should be interpreted with caution, due to the limitations associated with the SUCRA analyses detailed below:

1. As a single ranking value, SUCRA does not capture the magnitude of differences in effects between treatments. Subsequently, the differences in ranks between treatment regimens presented by SUCRA may imply a statistically relevant difference for a relevant outcome, even if there is none
2. SUCRA does not reflect the quality of the evidence on which the rankings are based, as the same ratings may be obtained from a small, low-quality or large, high-quality body of evidence

Consequently, the apparently clear hierarchy offered by SUCRA may be open to misinterpretation.

Table 3: SUCRA for mean change in BCVA from Baseline to one year

Treatment	SUCRA
Afli 2q4w	[redacted]
LP → Rani 0.5PRNX	[redacted]

LP → Rani 0.5TREX	[redacted]
Rani 0.5q4w	[redacted]
LP → Afli 2q8w	[redacted]
LP → Bro 6q12/q8w	[redacted]
LP → Rani 0.5q12w	[redacted]
LP → Bro 6q8w → q12w	[redacted]
LP → Bro 3q12/q8w	[redacted]
Rani 0.5PRN	[redacted]
LP → Rani 0.5PRN	[redacted]
LP → Afli 2TREX	[redacted]
Sham IVT	[redacted]

Abbreviations: BCVA: best-corrected visual acuity; IVT: intravitreal; LP: loading phase; PRN: pro re nata dosing regimen; PRNX: pro re nata and extend dosing regimen; qXw: one injection every X weeks; SUCRA: surface under the cumulative ranking curve; TREX: treat-and-extend dosing regimen.

Table 4: SUCRA for mean change in BCVA from Baseline to two years

Treatment	SUCRA
Rani 0.5q4w	[redacted]
Afli 2q4w	[redacted]
LP → Bro 6q12/q8w	[redacted]
LP → Afli 2q8w	[redacted]
LP → Bro 3q12/q8w	[redacted]
LP → Rani 0.5PRN	[redacted]
Rani 0.5PRN	[redacted]
LP → Rani 0.5TREX	[redacted]
LP → Afli 2TREX	[redacted]
Sham IVT	[redacted]

Abbreviations: BCVA: best-corrected visual acuity; IVT: intravitreal; LP: loading phase; PRN: pro re nata dosing regimen; PRNX: pro re nata and extend dosing regimen; qXw: one injection every X weeks; SUCRA: surface under the cumulative ranking curve; TREX: treat-and-extend dosing regimen.

Table 5: SUCRA for mean change in BCVA from one year to two years

Treatment	SUCRA
LP → Bro 3q12/q8w	[redacted]
LP → Rani 0.5PRN	[redacted]
LP → Bro 6q12/q8w	[redacted]
Rani 0.5q4w	[redacted]
LP → Afli 2q8w	[redacted]
Afli 2q4w	[redacted]
LP → Rani 0.5TREX	[redacted]
Sham IVT	[redacted]

Abbreviations: BCVA: best-corrected visual acuity; IVT: intravitreal; LP: loading phase; PRN: pro re nata dosing regimen; PRNX: pro re nata and extend dosing regimen;qXw: one injection every X weeks; SUCRA: surface under the cumulative ranking curve; TREX: treat-and-extend dosing regimen.

Table 6: SUCRA for mean change in retinal thickness from Baseline to one year

Treatment	SUCRA
LP → Bro 6q12/q8w	[redacted]
LP → Bro 3q12/q8w	[redacted]
LP → Bro 6q8w → q12w	[redacted]
LP → Afli 2q8w	[redacted]
Afli 2q4w	[redacted]
Rani 0.5q4w	[redacted]

LP → Rani 0.5TREX	[redacted]
LP → Rani 0.5PRN	[redacted]
Rani 0.5PRN	[redacted]

Abbreviations: IVT: intravitreal; LP: loading phase; PRN: pro re nata dosing regimen; qXw: one injection every X weeks; SUCRA: surface under the cumulative ranking curve; TREX: treat-and-extend dosing regimen.

Table 7: SUCRA for mean change in retinal thickness from Baseline to two years

Treatment	SUCRA
LP → Bro 3q12/q8w	[redacted]
LP → Bro 6q12/q8w	[redacted]
LP → Afli 2TREX	[redacted]
LP → Rani 0.5TREX	[redacted]
LP → Afli 2q8w	[redacted]
Afli 2q4w	[redacted]
Rani 0.5q4w	[redacted]
LP → Rani 0.5PRN	[redacted]
Rani 0.5PRN	[redacted]

Abbreviations: IVT: intravitreal; LP: loading phase; PRN: pro re nata dosing regimen; qXw: one injection every X weeks; SUCRA: surface under the cumulative ranking curve; TREX: treat-and-extend dosing regimen.

Table 8: SUCRA for odds of losing at least 15 letters from Baseline to one year

Treatment	SUCRA
LP → Bro 3q12/q8w	[redacted]
LP → Bro 6q12/q8w	[redacted]
Rani 0.5PRN	[redacted]
Afli 2q4w	[redacted]
LP → Afli 2q8w	[redacted]
Rani 0.5q4w	[redacted]
LP → Rani 0.5q12w	[redacted]
LP → Rani 0.5TREX	[redacted]
LP → Afli 2TREX	[redacted]
LP → Rani 0.5PRNX	[redacted]
LP → Rani 0.5PRN	[redacted]
LP → Rani 0.5q8w	[redacted]
Sham IVT	[redacted]

Abbreviations: IVT: intravitreal; LP: loading phase; PRN: pro re nata dosing regimen; qXw: one injection every X weeks; SUCRA: surface under the cumulative ranking curve; TREX: treat-and-extend dosing regimen.

Table 9: SUCRA for odds of losing at least 15 letters from Baseline to two years

Treatment	SUCRA
LP → Afli 2q8w	[redacted]
LP → Bro 6q12/q8w	[redacted]
Afli 2q4w	[redacted]
Rani 0.5q4w	[redacted]
LP → Bro 3q12/q8w	[redacted]
Rani 0.5PRN	[redacted]
LP → Rani 0.5PRN	[redacted]
LP → Rani 0.5TREX	[redacted]
Sham IVT	[redacted]

Abbreviations: IVT: intravitreal; LP: loading phase; PRN: pro re nata dosing regimen; qXw: one injection every X weeks; SUCRA: surface under the cumulative ranking curve; TREX: treat-and-extend dosing regimen.

Table 10: SUCRA values for odds of gaining at least 15 letters from Baseline to one year

Treatment	SUCRA
LP → Rani 0.5TREX	[redacted]
LP → Rani 0.5PRNX	[redacted]
LP → Bro 6q12/q8	[redacted]
Afli 2q4	[redacted]
LP → Afli 2TREX	[redacted]
Rani 0.5q4	[redacted]
LP → Afli 2q8	[redacted]
LP → Rani 0.5PRN	[redacted]
LP → Bro 3q12/q8	[redacted]
LP → Rani 0.5q8	[redacted]
Rani 0.5PRN	[redacted]
LP → Rani 0.5q12	[redacted]
Sham IVT	[redacted]

Abbreviations: IVT: intravitreal; LP: loading phase; PRN: pro re nata dosing regimen; PRNX: pro re nata and extend dosing regimen; qXw: one injection every X weeks; SUCRA: surface under the cumulative ranking curve; TREX: treat-and-extend dosing regimen.

Table 11: SUCRA for odds of gaining at least 15 letters from Baseline to two years

Treatment	SUCRA
LP → Rani 0.5TREX	[redacted]
LP → Bro 3q12/q8w	[redacted]
LP → Bro 6q12/q8w	[redacted]
LP → Afli 2q8w	[redacted]
Rani 0.5q4w	[redacted]
Afli 2q4w	[redacted]
LP → Rani 0.5PRN	[redacted]
Rani 0.5PRN	[redacted]
Sham IVT	[redacted]

Abbreviations: IVT: intravitreal; LP: loading phase; PRN: pro re nata dosing regimen; qXw: one injection every X weeks; SUCRA: surface under the cumulative ranking curve; TREX: treat-and-extend dosing regimen.

Table 12: SUCRA for treatment discontinuation from Baseline to one year

Treatment	SUCRA
LP → Rani 0.5q8w	[redacted]
LP → Rani 0.5PRN	[redacted]
LP → Bro 3q12/q8w	[redacted]
LP → Rani 0.5TREX	[redacted]
Afli 2q4w	[redacted]
LP → Bro 6q8w → q12w	[redacted]
LP → Afli 2TREX	[redacted]
LP → Bro 6q12/q8w	[redacted]
Rani 0.5q4w	[redacted]
LP → Afli 2q8w	[redacted]

Abbreviations: IVT: intravitreal; LP: loading phase; PRN: pro re nata dosing regimen; qXw: one injection every X weeks; SUCRA: surface under the cumulative ranking curve; TREX: treat-and-extend dosing regimen.

Table 13: SUCRA for treatment discontinuation from Baseline to one years

Treatment	SUCRA
LP → Rani 0.5PRN	[redacted]
LP → Bro 3q12/q8w	[redacted]
LP → Bro 6q12/q8w	[redacted]
Afli 2q4w	[redacted]
Rani 0.5q4w	[redacted]

LP → Afli 2q8w		[redacted]

Abbreviations: IVT: intravitreal; LP: loading phase; PRN: pro re nata dosing regimen; qXw: one injection every X weeks; SUCRA: surface under the cumulative ranking curve.

A11. Given that both closed loops in the evidence network are formed by data from only two trials (HAWK and HARRIER, and VIEW1 and VIEW2, respectively), the direct evidence and indirect evidence in these loops appear to be based on the same datasets. Please clarify whether this results in 'double counting' of the same data.

The data from each trial are only included once in any analysis and therefore this would not result in double counting. As NMAs combine both direct and indirect evidence together, studies forming closed loops can provide both types of evidence, which can strengthen the analysis compared to indirect evidence alone.

Section B: Clarification on cost-effectiveness data

B1 PRIORITY QUESTION: Please provide the monthly market share data for bevacizumab up to the latest currently available date. Please provide data in a table formatted in line with the example below, with n for bevacizumab, N for the market as a whole and the %=n/N market share. Please clarify the nature of the values for bevacizumab (n) and the total market (N) (for example, patient numbers, numbers of administrations, etc.) Please also clarify how the total market N is defined and calculated. Please clarify the source of this data and whether it is specific to the NHS.

Month	Bevacizumab	Market	Market share
Jan 2018	n=???	N=???	%=n/N
Feb 2018	n=???	N=???	%=n/N
Mar 2018	n=???	N=???	%=n/N
… etc.	n=???	N=???	%=n/N

[redacted]

1. [redacted]
2. [redacted]

- [redacted]

[redacted]

[redacted]

14 [redacted]

Table 14: Bevacizumab market share data

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: VEGF: vascular endothelial growth factor; wAMD: wet age-related macular degeneration.
Source: Novartis Data on File, 2019.[6]

B2 PRIORITY QUESTION. The submission states (page 11) that HAWK and HARRIER demonstrate similar benefits between the scope specified lesion defined subgroups (classic or occult neovascularisation in nature). For each trial please provide evidence about the similarity of dosing between the scope specified lesion defined subgroups.

At a minimum, please include the extent of exposure for both the brolucizumab 6mg arm(s) and the aflibercept arms.

For the brolucizumab arm, please include the proportions changing from q12w dosing to q8w dosing at 48 weeks and at 96 weeks.

The extent of exposure for the brolucizumab 6 mg and aflibercept 2 mg arms by scope-specified lesion defined subgroups is presented up to Week 44 and Week 92 in Table 15 and Table 16 respectively.

Table 15: Extent of exposure to study treatment: number of active injections from Baseline to Week 44 by lesion defined subgroup (SAF)

Trial name	HAWK		HARRIER	
	Brolucizumab 6 mg	Aflibercept 2 mg	Brolucizumab 6 mg	Aflibercept 2 mg
Predominantly classic				
Number of injections – n (%)	[redacted]	[redacted]	[redacted]	[redacted]

0	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]	[redacted]
Descriptive Statistics				
N	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]	[redacted]
Minimally classic				
Number of injections – n (%)	[redacted]	[redacted]	[redacted]	[redacted]
0	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]	[redacted]
Descriptive Statistics				
N	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]	[redacted]
Occult				
Number of injections – n (%)	[redacted]	[redacted]	[redacted]	[redacted]
0	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]

Descriptive Statistics				
N	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: SAF: safety analysis set; SD: standard deviation.
Source: HAWK CSR;[1] HARRIER CSR.[2]

Table 16: Extent of exposure to study treatment: number of active injections from Baseline to Week 92 by lesion defined subgroup (SAF)

Trial name	HAWK		HARRIER	
	Brolucizumab 6 mg	Aflibercept 2 mg	Brolucizumab 6 mg	Aflibercept 2 mg
Predominantly classic				
Number of injections – n (%)	[redacted]	[redacted]	[redacted]	[redacted]
0	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]
11	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]
13	[redacted]	[redacted]	[redacted]	[redacted]
Descriptive Statistics				
N	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]	[redacted]
Minimally classic				
Number of injections – n (%)	[redacted]	[redacted]	[redacted]	[redacted]
0	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]

5	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]
11	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]
13	[redacted]	[redacted]	[redacted]	[redacted]
Descriptive Statistics				
N	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]	[redacted]
Occult				
Number of injections – n (%)	[redacted]	[redacted]	[redacted]	[redacted]
0	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]
11	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]
13	[redacted]	[redacted]	[redacted]	[redacted]
14			[redacted]	[redacted]
Descriptive Statistics				
N	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: SAF: safety analysis set; SD: standard deviation.
Source: Novartis data on file, 2019.

The proportions of patients in the brolucizumab 6 mg arm changing from q12w to q8w dosing up to Week 44 and Week 92 by scope-specified lesion defined subgroups are presented in Table 17 for HAWK and HARRIER. Please note that the analyses were carried out at Week 48 and Week 96, but as data was taken at disease activity assessment visits, these fall on Week 44 and Week 92.

Table 17: Proportion of patients changing from q12w to q8w intervals up to Week 44 and Week 92 in HAWK and HARRIER by lesion defined subgroup (FAS "Efficacy/Safety approach")[a]

Trial name	HAWK	HARRIER
	Brolucizumab 6 mg (n=360)	Brolucizumab 6 mg (n=370)
Week 44[a]		
Predominantly classic	45.52	47.11
Minimally classic	46.58	53.13
Occult	43.26	49.68
Week 92[a]		
Predominantly classic	52.83	57.98
Minimally classic	59.94	66.25
Occult	54.66	63.48

[a]Note analyses carried out at Week 48 and Week 96, but as data was taken at disease activity assessment visits, these fall on Week 44 and Week 92.
Abbreviations: FAS: full analysis set; qXw; one injection every X weeks.
Source: HAWK CSR (Table 14.2-6.5);[1] HARRIER CSR (Table 14.2-6.5).[2]

B3 PRIORITY QUESTION. Please present the 4 weekly dosing separately for HAWK and HARRIER for the brolucizumab 6mg arm and for the aflibercept 2mg arm to study end (week 96). Please complete the table below including the number of injections (n) and the number of patients remaining in trial and eligible for treatment (N).

Week	brolucizumab q12w		brolucizumab q8w		aflibercept q8w	
0	n=???	N=???	n=???	N=???	n=???	N=???
4	n=???	N=???	n=???	N=???	n=???	N=???
8	n=???	N=???	n=???	N=???	n=???	N=???
12	n=???	N=???	n=???	N=???	n=???	N=???
… etc….	n=???	N=???	n=???	N=???	n=???	N=???
96	n=???	N=???	n=???	N=???	n=???	N=???

The 4-weekly dosing for the brolucizumab 6 mg (q8w and q12w dosing) and aflibercept 2 mg arms, including the number of patients receiving active injections (n) and the number of patients remaining in the trial and eligible for treatment (N), for HAWK and HARRIER are presented in Table 18 and Table 19, respectively.

Table 18: 4-weekly dosing by visit from Baseline to Week 96 in HAWK (FAS [number of patients receiving active injection] and all randomised analysis set [number of patients participating])

Trial name	HAWK						
	Brolucizumab 6 mg					Aflibercept 2 mg	
	q12w (n)	Total q12w number eligible (N)	q8w (n)	Total q8w number eligible (N)	Total number eligible (N)	q8w (n)	Total number eligible (N)
Week							
0					[redacted]	[redacted]	[redacted]
4					[redacted]	[redacted]	[redacted]
8					[redacted]	[redacted]	[redacted]
12					[redacted]	[redacted]	[redacted]
16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
28	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
32	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
40	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
44	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
48	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
52	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
56	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
60	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
64	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
68	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
72	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
76	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
80	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
84	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
88	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
92	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
96	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

n represents the number of patients receiving active injections by visit. Values are based on patients receiving active injections according to or deviating from protocol.
N (q8w) represents the total number of patients with at least one identified q8w need by the investigator up to Week 96. This data is only available for visits were a DAAs were carried out.
N (q12w) represents the total number of patients with no identified q8w need by the investigator up to Week 96. This data is only available for visits were a DAAs were carried out.
N (total) represents the total number of patients participating by visit.
Data on the number of patients receiving active injections are available up to Week 92 only.
*The q12/q8w status of a patient at the start of the visit is defined from Week 16 onwards.
Abbreviations: FAS: full analysis set; qXw; one injection every X weeks.
Source: HAWK CSR (Table 14.1-1.1.3, 14.1-1.3 and 14.2-5.14).[1]

Table 19: 4-weekly dosing by visit from Baseline to Week 96 in HARRIER (FAS [number of patients receiving active injection] and all randomised analysis set [number of patients participating])

Trial name	HARRIER						
	Brolucizumab 6 mg					Aflibercept 2 mg	
	q12w (n)	Total q12w number eligible (N)	q8w (n)	Total q8w number eligible (N)	Total number eligible (N)	q8w (n)	Total number eligible (N)
Week							
0							
4							
8							
12							
16							
20							
24							
28							
32							
36							
40							
44							
48							
52							
56							
60							
64							
68							
72							
76							
80							
84							
88							
92							
96							

n represents the number of patients receiving active injections by visit. Values are based on patients receiving active injections according to or deviating from protocol.
N (q8w) represents the total number of patients with at least one identified q8w need by the investigator up to Week 96. This data is only available for visits where DAAs were carried out.
N (q12w) represents the total number of patients with no identified q8w need by the investigator up to Week 96. This data is only available for visits where DAAs were carried out.
N (total) represents the total number of patients participating by visit.
Data on the number of patients receiving active injections are available up to Week 92 only.
*The q12/q8w status of a patient at the start of the visit is defined from Week 16 onwards.
Abbreviations: FAS: full analysis set; qXw; one injection every X weeks.
Source: HARRIER CSR (Table 14.1-1.1.3, 14.1-1.3 and 14.2-5.14).[2]

B4 PRIORITY QUESTION. Please provide the individual respondent data that underlies:

1. **the proportions reported in table 4.4**
2. **and the number of injections and number of monitoring visits reported in table 4.3, and**
3. **the number of injections reported in table 4.14.**

Please also provide a copy of the questionnaire(s) used to elicit these values.

Responses to parts 1, 2 and 3 of this question are provided below.

1. The anti-VEGF dosing regimen proportions reported in Table 4.4 of the company submission were derived from internal Novartis market research. This was an independent market research study so Novartis does not have access to individual respondent level data to protect respondents anonymity and confidentiality. The questions used to elicit the responses were:
   - [redacted]
   - [redacted]

The responses are presented in Figure 13 below:

Figure 13: Anti-VEGF dosing regimen proportions - internal Novartis market research

[redacted]

Abbreviations: PRN: pro re nata dosing regimen.

2. The number of injections and number of monitoring visits reported in Table 4.3 of the company submission has been calculated from market share data on the use of each dosing regimen (reported in Table 4.4) and each dosing regimen's respective number of injections and number of monitoring visits (reported in Table 4.14). As a result, individual respondent data was not required to estimate the numbers in Table 4.3.

3. The injection numbers reported in Table 4.14 of the company submission are from the baseline pooling meta-analyses described in Table 3.17 and Table 3.18 in Sections B.3.9.4.6 and B.3.9.4.7 of the submission. As no evidence was found for injections received beyond year two of treatment, the data for Year 3+ injections are assumed to be the same as Year 2. Monitoring visits are assumed to be the same as injection visits, except for PRN and PRNX regimens which use the data described in Table 4.8. For regimens with missing data points, the following assumptions about injection frequencies were made:
    - Aflibercept 2q4w→PRN is equivalent to aflibercept 2 q4w in Year 1
    - Aflibercept 2q4w in Year 2 is equivalent to aflibercept 2 q4w in Year 1
    - Aflibercept 2 LP→q8w→PRN is equivalent to aflibercept 2 LP→q8w in Year 1
    - Ranibizumab 0.5q4w→PRN is equivalent to ranibizumab 0.5 q4w in Year 1
    - Ranibizumab 0.5 LP→PRNX in Year 2 is equivalent to ranibizumab 0.5 LP→PRNX in Year 1
    - Ranibizumab 0.5 PRN is equivalent to ranibizumab 0.5 LP→PRN in Year 2

Individual respondent data and questionnaire(s) are therefore inapplicable for the data in Table 4.14.

Section C: Textual clarification and additional points

C1. The draft SmPC suggests [redacted]. What is the company's interpretation of this? With the exception of any treatment holidays due to of adverse events, can routine brolucizumab dosing fall outside the q12w to q8w range?

Please note that the referenced SmPC is a draft SmPC and is therefore subject to change based on ongoing consultation with the EMA.

In terms of Novartis' interpretation of the draft SmPC wording "[redacted]", we hope that the following response provides further clarification.

The recommended dose is 6 mg (0.05 mL) administered every four weeks (monthly) for the first three doses (loading dose phase). 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, a q12w dosing regimen should be considered. In patients with disease activity, a q8w dosing regimen should be considered. Physicians may further individualise treatment intervals based on disease activity.[7]

[redacted] In the HAWK and HARRIER trials, more than 50% (56% in HAWK and 51% in HARRIER) of brolucizumab 6 mg

patients were exclusively maintained on a q12w regimen immediately after the loading dose phase from Baseline through to Week 48.[3]

It should be noted that the study design of the HAWK and HARRIER trials meant that when patients were allocated to a q8w regimen due to disease activity, they were not able to return to a q12w regimen even if disease activity was not detected for the remainder of the study[3]; it is not considered that this approach is reflective of real-world clinical practice where clinicians will reassess patients on an ongoing basis and individualise treatment maintenance intervals based on disease activity.

In summary, routine brolucizumab dosing is not expected to fall outside the q12w to q8w range.

C2. Two of the 'Data on File' documents referenced in the company submission appear to be missing from the reference pack:

- 8. Novartis Data on File. UK Clinical Expert Feedback. 2019 (referred to on page 10)
- 87. Novartis Data on File. Clinical Expert Feedback Received at a Recent Advisory Board. 2019 (referred to on page 103)

Please provide these documents in full, to enable interpretation of comments in the context in which they were quoted.

Reference 8

Reference 8 supports the following content within the company submission: "The comparators considered relevant to this appraisal were also confirmed by feedback from UK clinical experts experienced in the management of wAMD".

Feedback from 1:1 interviews with four UK clinical experts experienced in the treatment of wAMD (2 consultant ophthalmologists; 1 consultant ophthalmic surgeon; 1 consultant ophthalmology/vitreo-retinal surgeon) confirmed that ranibizumab and aflibercept represent the current standard of care for people with wAMD.[8]

Reference 87

Reference 87 supports the following content within the company submission: "Whilst differences in the magnitude of BCVA change between HAWK and HARRIER and previous trials can be seen (i.e. smaller BCVA gains in HAWK and HARRIER), this can be explained by the higher baseline BCVA value for HAWK and HARRIER with VA gain restricted due to the presence of a clinical expert defined "ceiling effect".

Please note that this content was previously incorrectly referenced, and should have been referenced to the Dugel *et al.* (2019) manuscript.[3] This manuscript has been included in the reference pack with the relevant content highlighted. Whilst the topic of differences in magnitude of BCVA change due to differences in baseline BCVA ("ceiling effect") has been informally discussed with clinical experts, the published Dugel *et al.* (2019) manuscript is the correct reference for the submission.

References

1. Novartis Data on File. RTH258-C001 (HAWK) Clinical Study Report.
2. Novartis Data on File. RTH258-C002 (HARRIER) Clinical Study Report.
3. Dugel PU, Koh A, Ogura Y, et al. HAWK and HARRIER: phase 3, multicenter, randomized, double-masked trials of brolucizumab for neovascular age-related macular degeneration. Ophthalmology 2019.
4. Food and Drug Administration - Center for Drug Evaluation and Research. Brolucizumab Statistical Review and Evaluation 2019.
5. Mbuagbaw L, Rochwerg B, Jaeschke R, et al. Approaches to interpreting and choosing the best treatments in network meta-analyses. Systematic Reviews 2017;6:79.
6. Novartis Data on File. Bevacizumab Market Share in England for wAMD.
7. Novartis Data on File. Draft Brolucizumab Summary of Product Characteristics.
8. Novartis Data on File. UK Clinical Expert Feedback on Comparators. 2019.

Appendix A

Table 20: Change in BCVA from Baseline to Week 96 (FAS-LOCF)

Trial name	HAWK			HARRIER	
Characteristic	**Brolucizumab 3 mg (n=358)**	**Brolucizumab 6 mg (n=360)**	**Aflibercept 2 mg (n=360)**	**Brolucizumab 6 mg (n=370)**	**Aflibercept 2 mg (n=369)**
Week 4					
n					
LS mean difference from Baseline (SE)[a]					
95% CI					
LS mean difference from Baseline (SE)[b]					
95% CI					
LS mean difference from Baseline versus aflibercept (SE)					
95% CI					
Week 8					
n					
LS mean difference from Baseline (SE)[a]					
95% CI					
LS mean difference from Baseline (SE)[b]					
95% CI					
LS mean difference from Baseline versus aflibercept (SE)					
95% CI					
Week 12					
n					
LS mean difference from Baseline (SE)[a]					
95% CI					
LS mean difference from Baseline (SE)[b]					
95% CI					
LS mean difference from Baseline versus aflibercept (SE)					
95% CI					
Week 16					
n					
LS mean difference from Baseline (SE)[a]					
95% CI					
LS mean difference from Baseline (SE)[b]					
95% CI					

Trial name	HAWK			HARRIER	
Characteristic	**Brolucizumab 3 mg (n=358)**	**Brolucizumab 6 mg (n=360)**	**Aflibercept 2 mg (n=360)**	**Brolucizumab 6 mg (n=370)**	**Aflibercept 2 mg (n=369)**
LS mean difference from Baseline versus aflibercept (SE)	[redacted]	[redacted]		[redacted]	
95% CI	[redacted]	[redacted]		[redacted]	
Week 20					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference from Baseline (SE)[a]	[redacted]		[redacted]		
95% CI	[redacted]		[redacted]		
LS mean difference from Baseline (SE)[b]		[redacted]	[redacted]	[redacted]	[redacted]
95% CI		[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference from Baseline versus aflibercept (SE)	[redacted]	[redacted]		[redacted]	
95% CI	[redacted]	[redacted]		[redacted]	
Week 24					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference from Baseline (SE)[a]	[redacted]		[redacted]		
95% CI	[redacted]		[redacted]		
LS mean difference from Baseline (SE)[b]		[redacted]	[redacted]	[redacted]	[redacted]
95% CI		[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference from Baseline versus aflibercept (SE)	[redacted]	[redacted]		[redacted]	
95% CI	[redacted]	[redacted]		[redacted]	
Week 28					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference from Baseline (SE)[a]	[redacted]		[redacted]		
95% CI	[redacted]		[redacted]		
LS mean difference from Baseline (SE)[b]		[redacted]	[redacted]	[redacted]	[redacted]
95% CI		[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference from Baseline versus aflibercept (SE)	[redacted]	[redacted]		[redacted]	
95% CI	[redacted]	[redacted]		[redacted]	
Week 32					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference from Baseline (SE)[a]	[redacted]		[redacted]		
95% CI	[redacted]		[redacted]		
LS mean difference from Baseline (SE)[b]		[redacted]	[redacted]	[redacted]	[redacted]
95% CI		[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference from Baseline versus aflibercept (SE)	[redacted]	[redacted]		[redacted]	
95% CI	[redacted]	[redacted]		[redacted]	

Trial name	HAWK			HARRIER	
Characteristic	**Brolucizumab 3 mg (n=358)**	**Brolucizumab 6 mg (n=360)**	**Aflibercept 2 mg (n=360)**	**Brolucizumab 6 mg (n=370)**	**Aflibercept 2 mg (n=369)**
Week 36					
n					
LS mean difference from Baseline (SE)[a]					
95% CI					
LS mean difference from Baseline (SE)[b]					
95% CI					
LS mean difference from Baseline versus aflibercept (SE)					
95% CI					
Week 40					
n					
LS mean difference from Baseline (SE)[a]					
95% CI					
LS mean difference from Baseline (SE)[b]					
95% CI					
LS mean difference from Baseline versus aflibercept (SE)					
95% CI					
Week 44					
n					
LS mean difference from Baseline (SE)[a]					
95% CI					
LS mean difference from Baseline (SE)[b]					
95% CI					
LS mean difference from Baseline versus aflibercept (SE)					
95% CI					
Week 48					
n					
LS mean difference from Baseline (SE)[a]					
95% CI					
LS mean difference from Baseline (SE)[b]					
95% CI					
LS mean difference from Baseline versus aflibercept (SE)					
95% CI					
Week 52					
n					

Trial name	HAWK			HARRIER	
Characteristic	**Brolucizumab 3 mg (n=358)**	**Brolucizumab 6 mg (n=360)**	**Aflibercept 2 mg (n=360)**	**Brolucizumab 6 mg (n=370)**	**Aflibercept 2 mg (n=369)**
LS mean difference from Baseline (SE)[a]	[redacted]		[redacted]		
95% CI	[redacted]		[redacted]		
LS mean difference from Baseline (SE)[b]		[redacted]	[redacted]	[redacted]	[redacted]
95% CI		[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference from Baseline versus aflibercept (SE)	[redacted]	[redacted]		[redacted]	
95% CI	[redacted]	[redacted]		[redacted]	
Week 56					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference from Baseline (SE)[a]	[redacted]		[redacted]		
95% CI	[redacted]		[redacted]		
LS mean difference from Baseline (SE)[b]		[redacted]	[redacted]	[redacted]	[redacted]
95% CI		[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference from Baseline versus aflibercept (SE)	[redacted]	[redacted]		[redacted]	
95% CI	[redacted]	[redacted]		[redacted]	
Week 60					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference from Baseline (SE)[a]	[redacted]		[redacted]		
95% CI	[redacted]		[redacted]		
LS mean difference from Baseline (SE)[b]		[redacted]	[redacted]	[redacted]	[redacted]
95% CI		[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference from Baseline versus aflibercept (SE)	[redacted]	[redacted]		[redacted]	
95% CI	[redacted]	[redacted]		[redacted]	
Week 64					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference from Baseline (SE)[a]	[redacted]		[redacted]		
95% CI	[redacted]		[redacted]		
LS mean difference from Baseline (SE)[b]		[redacted]	[redacted]	[redacted]	[redacted]
95% CI		[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference from Baseline versus aflibercept (SE)	[redacted]	[redacted]		[redacted]	
95% CI	[redacted]	[redacted]		[redacted]	
Week 68					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference from Baseline (SE)[a]	[redacted]		[redacted]		
95% CI	[redacted]		[redacted]		

Trial name	HAWK			HARRIER	
Characteristic	**Brolucizumab 3 mg (n=358)**	**Brolucizumab 6 mg (n=360)**	**Aflibercept 2 mg (n=360)**	**Brolucizumab 6 mg (n=370)**	**Aflibercept 2 mg (n=369)**
LS mean difference from Baseline (SE)[b]					
95% CI					
LS mean difference from Baseline versus aflibercept (SE)					
95% CI					
Week 72					
n					
LS mean difference from Baseline (SE)[a]					
95% CI					
LS mean difference from Baseline (SE)[b]					
95% CI					
LS mean difference from Baseline versus aflibercept (SE)					
95% CI					
Week 76					
n					
LS mean difference from Baseline (SE)[a]					
95% CI					
LS mean difference from Baseline (SE)[b]					
95% CI					
LS mean difference from Baseline versus aflibercept (SE)					
95% CI					
Week 80					
n					
LS mean difference from Baseline (SE)[a]					
95% CI					
LS mean difference from Baseline (SE)[b]					
95% CI					
LS mean difference from Baseline versus aflibercept (SE)					
95% CI					
Week 84					
n					
LS mean difference from Baseline (SE)[a]					
95% CI					
LS mean difference from Baseline (SE)[b]					
95% CI					

Trial name	HAWK			HARRIER	
Characteristic	**Brolucizumab 3 mg (n=358)**	**Brolucizumab 6 mg (n=360)**	**Aflibercept 2 mg (n=360)**	**Brolucizumab 6 mg (n=370)**	**Aflibercept 2 mg (n=369)**
LS mean difference from Baseline versus aflibercept (SE)	[redacted]	[redacted]		[redacted]	
95% CI	[redacted]	[redacted]		[redacted]	
Week 88					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference from Baseline (SE)[a]	[redacted]		[redacted]		
95% CI	[redacted]		[redacted]		
LS mean difference from Baseline (SE)[b]		[redacted]	[redacted]	[redacted]	[redacted]
95% CI		[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference from Baseline versus aflibercept (SE)	[redacted]	[redacted]		[redacted]	
95% CI	[redacted]	[redacted]		[redacted]	
Week 92					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference from Baseline (SE)[a]	[redacted]		[redacted]		
95% CI	[redacted]		[redacted]		
LS mean difference from Baseline (SE)[b]		[redacted]	[redacted]	[redacted]	[redacted]
95% CI		[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference from Baseline versus aflibercept (SE)	[redacted]	[redacted]		[redacted]	
95% CI	[redacted]	[redacted]		[redacted]	
Week 96					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference from Baseline (SE)[a]	[redacted]		[redacted]		
95% CI	[redacted]		[redacted]		
LS mean difference from Baseline (SE)[b]		[redacted]	[redacted]	[redacted]	[redacted]
95% CI		[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference from Baseline versus aflibercept (SE)	[redacted]	[redacted]		[redacted]	
95% CI	[redacted]	[redacted]		[redacted]	

[a]ANOVA pairwise analysis between brolucizumab 3mg and aflibercept; [b]ANOVA pairwise analysis between brolucizumab 6mg and aflibercept.
Abbreviations: ANOVA: analysis of variance; BCVA: best-corrected visual acuity; CI: confidence interval; FAS: full analysis set; LOCF: last observation carried forward; LS; least squares; SE: standard error.
Source: Table 14.2-9.1_y2 HAWK CSR;[1] Table 14.2-9.1_y2 HARRIER CSR.[2]

Table 21: Change in BCVA from Baseline to Week 96 (FAS-Observed)

Trial name	HAWK			HARRIER	
Characteristic	**Brolucizumab 3 mg (n=358)**	**Brolucizumab 6 mg (n=360)**	**Aflibercept 2 mg (n=360)**	**Brolucizumab 6 mg (n=370)**	**Aflibercept 2 mg (n=369)**
Week 4					
n					
Mean change from Baseline (SE)					
95% CI					
Week 8					
n					
Mean change from Baseline (SE)					
95% CI					
Week 12					
n					
Mean change from Baseline (SE)					
95% CI					
Week 16					
n					
Mean change from Baseline (SE)					
95% CI					
Week 20					
n					
Mean change from Baseline (SE)					
95% CI					
Week 24					
n				359	
Mean change from Baseline (SE)					
95% CI					
Week 28					
n					
Mean change from Baseline (SE)					
95% CI					
Week 32					
n					
Mean change from Baseline (SE)					
95% CI					

Trial name	HAWK			HARRIER	
Characteristic	**Brolucizumab 3 mg (n=358)**	**Brolucizumab 6 mg (n=360)**	**Aflibercept 2 mg (n=360)**	**Brolucizumab 6 mg (n=370)**	**Aflibercept 2 mg (n=369)**
Week 36					
n					
Mean change from Baseline (SE)					
95% CI					
Week 40					
n					
Mean change from Baseline (SE)					
95% CI					
Week 44					
n					
Mean change from Baseline (SE)					
95% CI					
Week 48					
n					
Mean change from Baseline (SE)					
95% CI					
Week 52					
n					
Mean change from baseline (SE)					
95% CI					
Week 56					
n					
Mean change from baseline (SE)					
95% CI					
Week 60					
n					
Mean change from baseline (SE)					
95% CI					
Week 64					
n					
Mean change from baseline (SE)					
95% CI					
Week 68					
n					

Trial name	HAWK			HARRIER	
Characteristic	**Brolucizumab 3 mg (n=358)**	**Brolucizumab 6 mg (n=360)**	**Aflibercept 2 mg (n=360)**	**Brolucizumab 6 mg (n=370)**	**Aflibercept 2 mg (n=369)**
Mean change from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 72					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean change from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 76					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean change from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 80					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean change from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 84					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean change from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 88					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean change from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 92					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean change from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 96					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean change from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ANOVA pairwise analyses were not conducted for the FAS-observed population, therefore descriptive means and confidence intervals are presented.
Abbreviations: ANOVA: analysis of variance; BCVA: best-corrected visual acuity; CI: confidence interval; FAS: full analysis set; SE: standard error.
Source: Table 4.2-9.3_y2 HAWK CSR;[1] Table 14.2-9.3_y2 HARRIER CSR;[2]

Table 22: Change in CSFT (total, µm) from Baseline to Week 96 (FAS-LOCF)

Trial name	HAWK			HARRIER	
Characteristic	Brolucizumab 3 mg (n=358)	Brolucizumab 6 mg (n=360)	Aflibercept 2 mg (n=360)	Brolucizumab 6 mg (n=370)	Aflibercept 2 mg (n=369)
Week 4					
n					
LS mean difference from Baseline (SE)[a]					
95% CI					
LS mean difference from Baseline (SE)[b]					
95% CI					
LS mean difference from Baseline versus aflibercept (SE)					
95% CI					
Week 8					
n					
LS mean difference from Baseline (SE)[a]					
95% CI					
LS mean difference from Baseline (SE)[b]					
95% CI					
LS mean difference from Baseline versus aflibercept (SE)					
95% CI					
Week 12					
n					
LS mean difference from Baseline (SE)[a]					
95% CI					
LS mean difference from Baseline (SE)[b]					
95% CI					
LS mean difference from Baseline versus aflibercept (SE)					
95% CI					
Week 16					
n					
LS mean difference from Baseline (SE)[a]					
95% CI					
LS mean difference from Baseline (SE)[b]					
95% CI					
LS mean difference from Baseline versus aflibercept (SE)					
95% CI					

Trial name	HAWK			HARRIER	
Characteristic	**Brolucizumab 3 mg (n=358)**	**Brolucizumab 6 mg (n=360)**	**Aflibercept 2 mg (n=360)**	**Brolucizumab 6 mg (n=370)**	**Aflibercept 2 mg (n=369)**
Week 20					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference from Baseline (SE)[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference from Baseline (SE)[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference from Baseline versus aflibercept (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 24					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference from Baseline (SE)[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference from Baseline (SE)[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference from Baseline versus aflibercept (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 28					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference from Baseline (SE)[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference from Baseline (SE)[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference from Baseline versus aflibercept (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 32					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference from Baseline (SE)[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference from Baseline (SE)[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference from Baseline versus aflibercept (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 36					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Trial name	HAWK			HARRIER	
Characteristic	**Brolucizumab 3 mg (n=358)**	**Brolucizumab 6 mg (n=360)**	**Aflibercept 2 mg (n=360)**	**Brolucizumab 6 mg (n=370)**	**Aflibercept 2 mg (n=369)**
LS mean difference from Baseline (SE)[a]	[redacted]		[redacted]		
95% CI	[redacted]		[redacted]		
LS mean difference from Baseline (SE)[b]		[redacted]	[redacted]	[redacted]	[redacted]
95% CI		[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference from Baseline versus aflibercept (SE)	[redacted]	[redacted]		[redacted]	
95% CI	[redacted]	[redacted]		[redacted]	
Week 40					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference from Baseline (SE)[a]	[redacted]		[redacted]		
95% CI	[redacted]		[redacted]		
LS mean difference from Baseline (SE)[b]		[redacted]	[redacted]	[redacted]	[redacted]
95% CI		[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference from Baseline versus aflibercept (SE)	[redacted]	[redacted]		[redacted]	
95% CI	[redacted]	[redacted]		[redacted]	
Week 44					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference from Baseline (SE)[a]	[redacted]		[redacted]		
95% CI	[redacted]		[redacted]		
LS mean difference from Baseline (SE)[b]		[redacted]	[redacted]	[redacted]	[redacted]
95% CI		[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference from Baseline versus aflibercept (SE)	[redacted]	[redacted]		[redacted]	
95% CI	[redacted]	[redacted]		[redacted]	
Week 48					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference from Baseline (SE)[a]	[redacted]		[redacted]		
95% CI	[redacted]		[redacted]		
LS mean difference from Baseline (SE)[b]		[redacted]	[redacted]	[redacted]	[redacted]
95% CI		[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference from Baseline versus aflibercept (SE)	[redacted]	[redacted]		[redacted]	
95% CI	[redacted]	[redacted]		[redacted]	
Week 52					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference from Baseline (SE)[a]	[redacted]		[redacted]		
95% CI	[redacted]		[redacted]		

Trial name	HAWK			HARRIER	
Characteristic	**Brolucizumab 3 mg (n=358)**	**Brolucizumab 6 mg (n=360)**	**Aflibercept 2 mg (n=360)**	**Brolucizumab 6 mg (n=370)**	**Aflibercept 2 mg (n=369)**
LS mean difference from Baseline (SE)[b]		[redacted]	[redacted]	[redacted]	[redacted]
95% CI		[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference from Baseline versus aflibercept (SE)	[redacted]	[redacted]		[redacted]	
95% CI	[redacted]	[redacted]		[redacted]	
Week 56					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference from Baseline (SE)[a]	[redacted]		[redacted]		
95% CI	[redacted]		[redacted]		
LS mean difference from Baseline (SE)[b]		[redacted]	[redacted]	[redacted]	[redacted]
95% CI		[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference from Baseline versus aflibercept (SE)	[redacted]	[redacted]		[redacted]	
95% CI	[redacted]	[redacted]		[redacted]	
Week 60					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference from Baseline (SE)[a]	[redacted]		[redacted]		
95% CI	[redacted]		[redacted]		
LS mean difference from Baseline (SE)[b]		[redacted]	[redacted]	[redacted]	[redacted]
95% CI		[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference from Baseline versus aflibercept (SE)	[redacted]	[redacted]		[redacted]	
95% CI	[redacted]	[redacted]		[redacted]	
Week 64					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference from Baseline (SE)[a]	[redacted]		[redacted]		
95% CI	[redacted]		[redacted]		
LS mean difference from Baseline (SE)[b]		[redacted]	[redacted]	[redacted]	[redacted]
95% CI		[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference from Baseline versus aflibercept (SE)	[redacted]	[redacted]		[redacted]	
95% CI	[redacted]	[redacted]		[redacted]	
Week 68					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference from Baseline (SE)[a]	[redacted]		[redacted]		
95% CI	[redacted]		[redacted]		
LS mean difference from Baseline (SE)[b]		[redacted]	[redacted]	[redacted]	[redacted]
95% CI		[redacted]	[redacted]	[redacted]	[redacted]

Trial name	HAWK			HARRIER	
Characteristic	**Brolucizumab 3 mg (n=358)**	**Brolucizumab 6 mg (n=360)**	**Aflibercept 2 mg (n=360)**	**Brolucizumab 6 mg (n=370)**	**Aflibercept 2 mg (n=369)**
LS mean difference from Baseline versus aflibercept (SE)	[redacted]	[redacted]			
95% CI	[redacted]	[redacted]			
Week 72					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference from Baseline (SE)[a]	[redacted]		[redacted]		
95% CI	[redacted]		[redacted]		
LS mean difference from Baseline (SE)[b]		[redacted]	[redacted]	[redacted]	[redacted]
95% CI		[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference from Baseline versus aflibercept (SE)	[redacted]	[redacted]		[redacted]	
95% CI	[redacted]	[redacted]		[redacted]	
Week 76					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference from Baseline (SE)[a]	[redacted]		[redacted]		
95% CI	[redacted]		[redacted]		
LS mean difference from Baseline (SE)[b]		[redacted]	[redacted]	[redacted]	[redacted]
95% CI		[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference from Baseline versus aflibercept (SE)	[redacted]	[redacted]		[redacted]	
95% CI	[redacted]	[redacted]		[redacted]	
Week 80					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference from Baseline (SE)[a]	[redacted]		[redacted]		
95% CI	[redacted]		[redacted]		
LS mean difference from Baseline (SE)[b]		[redacted]	[redacted]	[redacted]	[redacted]
95% CI		[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference from Baseline versus aflibercept (SE)	[redacted]	[redacted]		[redacted]	
95% CI	[redacted]	[redacted]		[redacted]	
Week 84					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference from Baseline (SE)[a]	[redacted]		[redacted]		
95% CI	[redacted]		[redacted]		
LS mean difference from Baseline (SE)[b]		[redacted]	[redacted]	[redacted]	[redacted]
95% CI		[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference from Baseline versus aflibercept (SE)	[redacted]	[redacted]		[redacted]	
95% CI	[redacted]	[redacted]		[redacted]	

Trial name	HAWK			HARRIER	
Characteristic	**Brolucizumab 3 mg (n=358)**	**Brolucizumab 6 mg (n=360)**	**Aflibercept 2 mg (n=360)**	**Brolucizumab 6 mg (n=370)**	**Aflibercept 2 mg (n=369)**
Week 88					
n					
LS mean difference from Baseline (SE)[a]					
95% CI					
LS mean difference from Baseline (SE)[b]					
95% CI					
LS mean difference from Baseline versus aflibercept (SE)					
95% CI					
Week 92					
n					
LS mean difference from Baseline (SE)[a]					
95% CI					
LS mean difference from Baseline (SE)[b]					
95% CI					
LS mean difference from Baseline versus aflibercept (SE)					
95% CI					
Week 96					
n					
LS mean difference from Baseline (SE)[a]					
95% CI					
LS mean difference from Baseline (SE)[b]					
95% CI					
LS mean difference from Baseline versus aflibercept (SE)					
95% CI					

[a]ANOVA pairwise analysis between brolucizumab 3mg and aflibercept; [b]ANOVA pairwise analysis between brolucizumab 6mg and aflibercept.
Abbreviations: ANOVA: analysis of variance; CI: confidence interval; CST: central subfield thickness; FAS: full analysis set; LOCF: last observation carried forward; LS: least-squares; SE: standard error
Source: Table 14.2-15.1_y2 HAWK CSR;[1] Table 14.2-15.1_y2 HARRIER CSR;[2]

Table 23: Change in CSFT (total, µm) from Baseline to Week 96 (FAS-Observed)

Trial name		HAWK			HARRIER	
Characteristic		Brolucizumab 3 mg (n=358)	Brolucizumab 6 mg (n=360)	Aflibercept 2 mg (n=360)	Brolucizumab 6 mg (n=370)	Aflibercept 2 mg (n=369)
Baseline						
	n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean					
	95% CI					
Week 4						
	n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean change from Baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 8						
	n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean change from Baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 12						
	n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean change from Baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 16						
	n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean change from Baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 20						
	n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean change from Baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 24						
	n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean change from Baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 28						
	n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean change from Baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Trial name	HAWK			HARRIER	
Characteristic	**Brolucizumab 3 mg (n=358)**	**Brolucizumab 6 mg (n=360)**	**Aflibercept 2 mg (n=360)**	**Brolucizumab 6 mg (n=370)**	**Aflibercept 2 mg (n=369)**
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 32					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean change from Baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 36					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean change from Baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 40					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean change from Baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 44					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean change from Baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 48					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean change from Baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 52					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean change from Baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 56					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean change from Baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 60					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean change from Baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Trial name	HAWK			HARRIER	
Characteristic	**Brolucizumab 3 mg (n=358)**	**Brolucizumab 6 mg (n=360)**	**Aflibercept 2 mg (n=360)**	**Brolucizumab 6 mg (n=370)**	**Aflibercept 2 mg (n=369)**
Week 64					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean change from Baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 68					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean change from Baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 72					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean change from Baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 76					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean change from Baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 80					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean change from Baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 84					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean change from Baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 88					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean change from Baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 92					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean change from Baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 96					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Trial name	HAWK			HARRIER	
Characteristic	**Brolucizumab 3 mg (n=358)**	**Brolucizumab 6 mg (n=360)**	**Aflibercept 2 mg (n=360)**	**Brolucizumab 6 mg (n=370)**	**Aflibercept 2 mg (n=369)**
Mean change from Baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ANOVA pairwise analyses were not conducted for the FAS-observed population, therefore descriptive means and confidence intervals are presented.
Abbreviations: ANOVA: analysis of variance; BCVA: best-corrected visual acuity; CI: confidence interval; FAS: full analysis set; SE: standard error.
Source: HAWK CSR[1]; HARRIER CSR.[2]

Table 24: Change in BCVA for patients receiving brolucizumab (6 mg) by dosing regimen up to Week 48

Trial name	HAWK		HARRIER	
Characteristics	**Patients remaining q12w (n=199)**	**Patients receiving q8w (n=147)**	**Patients remaining q12w (n=193)**	**Patients receiving q8w (n=168)**
Week 4				
LS mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]
Week 8				
LS mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]
Week 12				
LS mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]
Week 16				
LS mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]
Week 20				
LS mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]
Week 24				
LS mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]
Week 28				
LS mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]
Week 32				
LS mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]
Week 36				
LS mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]
Week 40				
LS mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]

Clarification questions

Week 44				
LS mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]
Week 48				
LS mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference versus aflibercept	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BCVA: best-corrected visual acuity; CI: confidence interval; LS: least squares; SE: standard error; qXw: one injection every X weeks.
Source: Novartis data on file, 2019.

Table 25: Change in BCVA for patients receiving brolucizumab (6 mg) by dosing regimen up to Week 96

Trial name	HAWK		HARRIER	
Characteristics	Patients remaining q12w (n=176)	Patients receiving q8w (n=170)	Patients remaining q12w (n=152)	Patients receiving q8w (n=209)
Week 4				
LS mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]
Week 8				
LS mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]
Week 12				
LS mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]

Clarification questions

95% CIs	[redacted]	[redacted]	[redacted]	[redacted]
Week 16				
LS mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]
Week 20				
LS mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]
Week 24				
LS mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]
Week 28				
LS mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]
Week 32				
LS mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]
Week 36				

Clarification questions

LS mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]
Week 40				
LS mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]
Week 44				
LS mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]
Week 48				
LS mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]
Week 52				
LS mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]
Week 56				
LS mean difference	[redacted]	[redacted]	[redacted]	[redacted]

Clarification questions

from baseline (SE)				
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]
Week 60				
LS mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]
Week 64				
LS mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]
Week 68				
LS mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]
Week 72				
LS mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]
Week 76				
LS mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]

Clarification questions

95% CIs	[redacted]	[redacted]	[redacted]	[redacted]
Week 80				
LS mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]
Week 84				
LS mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]
Week 88				
LS mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]
Week 92				
LS mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]
Week 96				
LS mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]
LS mean	[redacted]	[redacted]	[redacted]	[redacted]

Clarification questions

difference versus aflibercept				
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BCVA: best-corrected visual acuity; CI: confidence interval; LS: least squares; SE: standard error; qXw: one injection every X weeks.
Source: Novartis data on file, 2019.

Clarification questions

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Fast track appraisal

Brolucizumab for treating wet age-related macular degeneration [ID1254]

Clarification questions – Addendum for Question A3

December 2019

File name	Version	Contains confidential information	Date
ID1254 Brolucizumab for wAMD Clarification Questions Response – Addendum for Question A3 [ACIC]	**2**	**Yes**	**20 December 2019**

Section A: Clarification on effectiveness data

A3. In 2 tables, please tabulate the values (mean, standard error [s.e.], 95% confidence interval [CI]) that underlie figure 3.5 and 3.8 in the company submission. In these tables, please include:

- values for the subset of people receiving brolucizumab (6 mg) who remained q12w to week 48
- values for the subset of people receiving brolucizumab (6 mg) who remained q12w to week 96, and
- values treating lost to follow-up as missing data, rather than last observation carried forward (LOCF).

Table 1 presents the data that underlie Figure 3.5, the mean BCVA change from Baseline for patients receiving brolucizumab (6 mg) who remained q12w to Week 48 or switched to a q8w regimen, and Table 2 presents the corresponding data for patients who remained on a q12w dosing regimen or switched to a q8w regimen up to Week 96.

These tables were previously included in the original ERG response document; however, for completeness, these tables have been updated and now include both the LS mean difference from baseline (resulting from ANOVA pairwise analyses), in addition to the descriptive mean difference from baseline and the associated 95% confidence intervals.

Table 3 and Table 4 present the same data for the mean CSFT change from Baseline up to Week 48 (Table 3) and Week 96 (Table 4). In both HAWK and HARRIER, CSFT values at Baseline for patients in the brolucizumab 6 mg arm who switched to q8w by both Week 48 and Week 96

[redacted]

[redacted]

Table 1: Change in BCVA for patients receiving brolucizumab (6 mg) by dosing regimen up to Week 48

Trial name	HAWK		HARRIER	
Characteristics	**Patients remaining q12w (n=199)**	**Patients receiving q8w (n=147)**	**Patients remaining q12w (n=193)**	**Patients receiving q8w (n=168)**
Baseline				
Mean BCVA (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
Week 4				
LS mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]
Week 8				
LS mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]
Week 12				
LS mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]
Week 16				
LS mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]
Week 20				
LS mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]
Week 24				
LS mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]

Week 28				
LS mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]
Week 32				
LS mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]
Week 36				
LS mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]
Week 40				
LS mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]
Week 44				
LS mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]
Week 48				
LS mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference versus aflibercept	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BCVA: best-corrected visual acuity; CI: confidence interval; LS: least squares; SE: standard error; qXw: one injection every X weeks.
Source: Novartis data on file, 2019.

Table 2: Change in BCVA for patients receiving brolucizumab (6 mg) by dosing regimen up to Week 96

Trial name	HAWK		HARRIER	
Characteristics	Patients remaining q12w (n=170)	Patients receiving q8w (n=176)	Patients remaining q12w (n=152)	Patients receiving q8w (n=209)
Baseline				
Mean BCVA (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
Week 4				
LS mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]
Week 8				
LS mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]
Week 12				
LS mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]
Week 16				
LS mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]

95% CIs	[redacted]	[redacted]	[redacted]	[redacted]
Week 20				
LS mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]
Week 24				
LS mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]
Week 28				
LS mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]
Week 32				
LS mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]
Week 36				
LS mean difference from	[redacted]	[redacted]	[redacted]	[redacted]

baseline (SE)				
Mean difference from baseline (SE)				
95% CIs				
Week 40				
LS mean difference from baseline (SE)				
Mean difference from baseline (SE)				
95% CIs				
Week 44				
LS mean difference from baseline (SE)				
Mean difference from baseline (SE)				
95% CIs				
Week 48				
LS mean difference from baseline (SE)				
Mean difference from baseline (SE)				
95% CIs				
Week 52				
LS mean difference from baseline (SE)				
Mean difference from baseline (SE)				

95% CIs	[redacted]	[redacted]	[redacted]	[redacted]
Week 56				
LS mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]
Week 60				
LS mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]
Week 64				
LS mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]
Week 68				
LS mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]
Week 72				
LS mean difference from	[redacted]	[redacted]	[redacted]	[redacted]

baseline (SE)				
Mean difference from baseline (SE)				
95% CIs				
Week 76				
LS mean difference from baseline (SE)				
Mean difference from baseline (SE)				
95% CIs				
Week 80				
LS mean difference from baseline (SE)				
Mean difference from baseline (SE)				
95% CIs				
Week 84				
LS mean difference from baseline (SE)				
Mean difference from baseline (SE)				
95% CIs				
Week 88				
LS mean difference from baseline (SE)				
Mean difference from baseline (SE)				

95% CIs	[redacted]	[redacted]	[redacted]	[redacted]
Week 92				
LS mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]
Week 96				
LS mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference versus aflibercept	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BCVA: best-corrected visual acuity; CI: confidence interval; LS: least squares; SE: standard error; qXw: one injection every X weeks.
Source: Novartis data on file, 2019.

Table 3: Change in CSFT for patients receiving brolucizumab (6 mg) by dosing regimen up to Week 48

Trial name	HAWK		HARRIER	
Characteristics	**Patients remaining q12w (n=199)**	**Patients receiving q8w (n=147)**	**Patients remaining q12w (n=193)**	**Patients receiving q8w (n=168)**
Baseline				
Mean CSFT (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
Week 4				
LS mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]

Week 8				
LS mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]
Week 12				
LS mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]
Week 16				
LS mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]
Week 20				
LS mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]
Week 24				
LS mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]
Week 28				
LS mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]
Week 32				
LS mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]
Week 36				
LS mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]
Week 40				
LS mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]
Week 44				
LS mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]

Mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]
Week 48				
LS mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI: confidence interval; CSFT: central subfield thickness; LS: least squares; SE: standard error; qXw: one injection every X weeks.
Source: Novartis data on file, 2019.

Table 4: Change in CSFT for patients receiving brolucizumab (6 mg) by dosing regimen up to Week 96

Trial name	HAWK		HARRIER	
Characteristics	**Patients remaining q12w (n=170)**	**Patients receiving q8w (n=176)**	**Patients remaining q12w (n=152)**	**Patients receiving q8w (n=209)**
Baseline				
Mean CSFT (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]
Week 4				
LS mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]
Week 8				
LS mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]
Week 12				
LS mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]
Week 16				
LS mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]
Week 20				

LS mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]
Week 24				
LS mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]
Week 28				
LS mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]
Week 32				
LS mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]
Week 36				
LS mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]
Week 40				
LS mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]
Week 44				
LS mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]
Week 48				
LS mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]

Mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]
Week 52				
LS mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]
Week 56				
LS mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]
Week 60				
LS mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]
Week 64				
LS mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]
Week 68				
LS mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]
Week 72				
LS mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]
Week 76				
LS mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]

Mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]
Week 80				
LS mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]
Week 84				
LS mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]
Week 88				
LS mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]
Week 92				
LS mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]
Week 96				
LS mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Mean difference from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI: confidence interval; CSFT: central subfield thickness; LS: least squares; SE: standard error; qXw: one injection every X weeks.
Source: Novartis data on file, 2019.

NICE National Institute for Health and Care Excellence

Patient organisation submission

Brolucizumab for treating wet age-related macular degeneration [ID1254]

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.

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- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Macular Society
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	The Macular Society is the leading national charity fighting to end sight loss caused by macular disease. Every day over 300 people in the UK face the shock of a diagnosis of macular disease. This sight loss can rob people of their independence, leaving them unable to drive, read or recognise their family. Our members tell us what a profoundly isolating condition it is. People with macular disease are seven times more likely to feel distressed or depressed. We help people adapt to life with sight loss, regain their confidence and independence and take back control of their lives. We are one of the few sight loss charities that actively fund and support medical research into macular disease. With the exception of the details in the answer to 4b, all our income is fundraised from legacies, grants, donations from individuals and fundraising activities such as our lottery, raffle, appeals and community and challenge events. We have 28,000 members who we communicate with on a regular basis, 370,000 website visitors a year and our Advice & Information (A&I) Service responds to over 16,000 queries a year.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant	Novartis Feb 2020 - £2,995.15 – payment for the Macular Society's attendance and support of a patient advisory meeting.

manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	Apr 2020 - £16,669 – part payment (20%) for the Macular Society's consultancy support of Novartis' campaign to support people with wet AMD. (The campaign aims to increase awareness and education of the disease for the benefit of a variety of stakeholders and the wider public.) May 2020 - £23,636 – part payment for the Macular Society's support of Novartis' campaign to support people with wet AMD.
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	**Wet AMD survey** A survey was conducted by the Macular Society in early 2020 to understand the burden that frequent anti-VEGF injections and ophthalmology appointments has on wet AMD patients and their carers or family. A total of 449 responses were received from across the UK. A full report will be published in August but key highlights are included in the submission to support specific points. **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?	We offer free counselling for people affected by macular disease and sometimes counselling sessions are focused fully on the distress caused to patients facing the eye injection treatment. We also offer a 'buddy' service, putting people who have had injections in touch with people concerned about having injections. This is to offer reassurance and insight into what the experience is like, with the hope of offering some comfort. Quotes from people who took part in our wet AMD survey: 1. My poor vision means we are likely to need to sell our house in the country and move to one closer to public transport and other amenities. I also struggle to continue to play competitive golf which is my main pastime. My husband who works full time in his own business takes me to my clinic appointments which means he loses a morning or afternoon's work regularly. 2. As I am a carer for an adult son with Down's syndrome, with no other family, I rely on friends to take me to appointments & take/collect him from day centres whilst I have treatment. Living in a rural area without public transport means the worry of deterioration of my sight & being unable to drive is constant.

	3. I feel incredibly fortunate. I have had a total of 66 injections in my left eye (initially Lucentis and now Eylea) and am still having them. This has improved and maintained the level of sight. Because of having both eyes monitored on each visit wet AMD was spotted in my right eye and treatment began very early. 4. It has been difficult to come to terms with the need to rely on others to get routine things done. The injections are horrible but the alternative is worse!
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Responses from callers to the Advice & Information Service overwhelmingly report how wonderful the NHS is. Many agree their treatment maintains their sight and can be anxious when treatment intervals are extended or stopped. However, personal experiences of cancelled appointments, frustration over communication with clinics, many hours spent waiting around in clinic, are all common themes. Injections are not available in local health care settings, meaning many patients travel a good distance to attend injection clinics and need a driver to accompany them. Quotes from people who took part in our wet AMD survey: 1. My daughters both live a distance from me so a whole day is needed plus an overnight stay for every appointment. So this impacts considerably on family life for them as well as me. 2. Have had to travel by public transport over a fair distance to the hospital over the last 5 years. Especially after the injection, which can be over a two hour journey, when all you want to do is get home.

8. Is there an unmet need for patients with this condition?	Yes, many people when diagnosed are not given detailed information or are unable to take in the details at their diagnosis appointment. This leaves them unable to properly manage their treatment or even fully understand there is a treatment. Our A&I service takes numerous enquiries from people who do not fully understand what macular disease is and have been left baffled and confused. Our A&I service frequently provides advocacy to help people who have been diagnosed onto the right treatment path. However, many people who have been diagnosed are not aware that we are here to help.
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, 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. Due to the COVID-19 pandemic, since March eye clinics have only been seeing patients who need injections to save their sight. A return to operating eye clinics as they were before March seems unlikely given the on-going requirements for social distancing. There will be a continuing need to protect this vulnerable set of elderly people and many have been very nervous to attends appointments during this time. We are therefore faced with both a backlog of patient appointments, when many clinics already struggled to see all patients at the recommended time intervals, and significantly reduced capacity to keep

	people safe from infection. Any measures that might help to alleviate the pressure on eye clinics, such as longer acting drugs, are therefore even more important.
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.
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Those who already struggle to attend all their eye clinic appointments, for the reasons given above, will benefit if they have to attend less often. Many patients also suffer from other health conditions associated with advancing age, which can leave them unable to maintain their treatment regime. For some just leaving home can be extremely difficult. Only patients who are well enough, have the right transport means and the ability to make arrangements to attend can benefit. In our survey 43% of people said that they had been unable to attend appointments for health reasons and 15% cited travel reasons.

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. People with wet AMD are largely over 60 years old and most are in their 70s, 80s and 90s. As the drugs currently available are not a cure and do not work effectively in everyone, a proportion of patients will still experience significant sight loss such that they will be registered as sight impaired or severely sight impaired.
Other issues	
13. Are there any other issues that you would like the committee to consider?	The technology appraisal guidance (TAG) for the drugs currently licenced to treat wet AMD, Lucentis and Eylea, have parameters for when they can be used which include the level of vision i.e. the best-corrected visual acuity is between 6/12 and 6/96. This means that we have the phenomenon of eyes being 'too good to treat' and people having to wait for their vision to deteriorate before they can be treated with these drugs. However, the NICE Clinical Guidelines for AMD states that anti-VEGF treatment for eyes with wet AMD is clinically effective even before visual acuity drops below 6/12. We would strongly ask that the committee do not follow the TAG for Lucentis and Eylea and do not include a stipulation that vision must be lost before treatment can be administered. Brolucizumab should be available for ophthalmologists to prescribe if they consider there is a clinical need and the patient will benefit through it preserving their vision.

14. To be added by technical team at scope sign off. Note that topic-specific questions will be added only if the treatment pathway or likely use of the technology remains uncertain after scoping consultation, for example if there were differences in opinion; this is not expected to be required for every appraisal.] if there are none delete highlighted rows and renumber below	

Key messages

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

- The numbers of people with wet AMD is increasing and over burdening hospital eye clinics
- The treatment burden on patients and carers is significant and longer acting drugs can alleviate the problem.
- Any measures that reduce the need or frequency of travelling to eye clinics for an invasive, distressing and sometimes painful treatment is a step in the right direction.
- Patients should not have to wait for their vision to deteriorate before they can be treated - the ‘too good to treat’ situation.

- The COVID-19 pandemic has significantly reduced eye clinic capacity due to the infection control measures now required. Any measures that might help to alleviate the pressure on eye clinics, such as longer acting drugs, are therefore even more important.

Thank you for your time.

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

Professional organisation submission

Brolucizumab for treating wet age-related macular degeneration [ID1254]

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

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

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

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- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**Royal College of Ophthalmologists**

3. Job title or position	**Consultant Ophthalmologist,**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? **X**☐ 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).	
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 Royal College of Ophthalmologists has received £10,500 from Novartis in the last 12 months. These related to delegate fees for attendance at the RCOphth Annual Congress in May 2019 (14 delegates £7,500) and fees for consideration of CPD approval for educational meetings run by Novartis (£3,000).**

If so, please state the name of manufacturer, amount, and purpose of funding.	
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To improve visual outcomes form patients with wet Age Related Macular Degeneration predominantly by preventing progression.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by	Vision has deteriorated by less than 10 letters in the first year.

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
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Current treatment is with Lucentis, Aflibercept or Avastin intravitreal injections
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE guidance
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please	The need for long term repeated injections and/or prn treatment is well established but there are different regimes for doing this – treat and extend, fixed dosing, as required. Units tend to choose a regime based on their capacity issues rather than the regime they think gives the best results. . Criteria for stopping treatment are not generally agreed or validated and vary significantly from unit to unit.

state if your experience is from outside England.)	Patients presenting early with good vision are treated with Avastin in many units but in some they have no treatment until the vision worsens to meet NICE criteria. This is by local agreement.
• What impact would the technology have on the current pathway of care?	Very little change
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	No not yet available except in research trials. It would be used in the same way as current care.
• How does healthcare resource use differ between the technology and current care?	It is possible that patients in brolucizumab may require less frequent injections than those on Aflibercept but more research is required to answer this question definitively.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist clinics
• What investment is needed to introduce the technology? (For	Nothing over and above what should already be available.

example, for facilities, equipment, or training.)	
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	There may be some groups of patients who do better on this drug than alternatives due to the superior retinal drying as measured by OCT.
• 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?	No
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	It is better at reducing fluid in the retina than aflibercept so it may offer some benefit in patients with disease that is resistant to current treatments and particularly the subgroup of wet AMD patients who have idiopathic polypoidal choroidopathy (approx 20%). There is no data to address this question definitively at present.

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.)	No different.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Current NICE guidance for anti VEGF requires that we have to wait for vision to drop below 6/12 before starting treatment with a licensed on label drug. There are obvious advantages to starting treatment before vision is lost. It would be helpful if NICE guidance addressed this issue and allowed use of Brolucizumab before vision is lost. Current stopping criteria are not generally agreed and accepted and are open to wide interpretation.

	No additional testing.
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?	Not unless it can be used before vision drops below driving standard (6/12) see above or it turns out that less injections are needed compared to Aflibercept.
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?	There may be a small benefit over existing treatments but it is hard to be sure from the data because of the trial design.
• Is the technology a 'step-change' in the management of the condition?	No, it is possibly a small incremental change for the better.

• Does the use of the technology address any particular unmet need of the patient population?	It may benefit patients with very aggressive disease resistant to treatment as it appear to dry the retina better than existing drugs.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	No significant difference from existing products
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Not entirely. A fixed dose regime of aflibercept was used but many units now use a treat and extend regime.
• If not, how could the results be extrapolated to the UK setting?	I think more data is needed.
• What, in your view, are the most important outcomes, and were they measured in the trials?	Visual outcomes. yes Number of injections/injection interval..yes

	Number developing catastrophic visual loss (>15 letters). yes Development of dry ARMD – trial not run for enough years to reliably determine this.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	None I am aware of
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Ohji M et al. Two different treat-and-extend dosing regimens of intravitreal aflibercept in Japanese patients with wet age-related macular degeneration: 96 week results of the ALTAIR study. Presented at: Euretina; Sept. 20-23, 2018; Vienna.
20. Are you aware of any new evidence for the comparator treatment(s) since the	Ohji M et al. Two different treat-and-extend dosing regimens of intravitreal aflibercept in Japanese patients with wet age-related macular degeneration: 96 week results of the ALTAIR study. Presented at: Euretina; Sept. 20-23, 2018; Vienna. Effect of Ranibizumab and Aflibercept on Best-Corrected Visual Acuity in Treat-and-Extend for Neovascular Age-Related Macular Degeneration: A Randomized Clinical Trial.

publication of NICE technology appraisal guidance [TA294]	Gillies MC, Hunyor AP, Arnold JJ, Guymer RH, Wolf S, Ng P, Pecheur FL, McAllister IL. JAMA Ophthalmol. 2019 Apr 1;137(4):372-379. doi: 10.1001/jamaophthalmol.2018.6776. Tolerating Subretinal Fluid in Neovascular Age-Related Macular Degeneration Treated with Ranibizumab Using a Treat-and-Extend Regimen: FLUID Study 24-Month Results. Guymer RH, Markey CM, McAllister IL, Gillies MC, Hunyor AP, Arnold JJ; FLUID Investigators. Ophthalmology. 2019 May;126(5):723-734. doi: 10.1016/j.ophtha.2018.11.025. Epub 2018 Nov 29.
21. How do data on real-world experience compare with the trial data?	Not available for brolucizumab. In AMD generally quite variable. Outcomes are often measured in letters of improvement. You can only improve letters if you have lost them in the first place. The single biggest determinant of this is therefore what the vision was at presentation. Real world outcomes also depend on how well organised and efficient the service is and this varies widely.
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.	
Topic-specific questions	
23 [To be added by technical team at scope sign off. Note that topic-specific questions will be added only if the treatment pathway or likely use of the technology remains uncertain after scoping consultation, for example if there were differences in opinion; this is not expected to be required for every appraisal.]	

if there are none delete highlighted rows and renumber below	
Key messages	
24. In up to 5 bullet points, please summarise the key messages of your submission. • Brolucizumab is non inferior to existing treatments • It may require less frequent dosing than existing alternatives • It may turn out to be superior in treating IPCV and some difficult to treat cases due to its superior ability to dry the retina.. • If priced appropriately it should be made available under NICE guidance. •	

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

NHS organisation submission (CCG and NHS England)

Brolucizumab for treating wet age-related macular degeneration [ID1254]

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

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- Your response should not be longer than 10 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	NHS Bury CCG

3. Job title or position	[redacted]
4. Are you (please tick all that apply):	☒ commissioning services for a CCG or NHS England in general? ☐ commissioning services for a CCG or NHS England for the condition for which NICE is considering this technology? ☐ responsible for quality of service delivery in a CCG (for example, medical director, public health director, director of nursing)? ☐ an expert in treating the condition for which NICE is considering this technology? ☐ an expert in the clinical evidence base supporting the technology (for example, an investigator in clinical trials for the technology)? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	NHS Bury CCG is the lead commissioner for the acute trust, Pennine Acute on behalf of the North East Sector CCGs. We also commission treatment of wet AMD services from other NHS and third party providers for our population.
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
Current treatment of the condition in the NHS	
6. Are any clinical guidelines used in the treatment of the	Age-related macular degeneration. NICE guideline [NG82] Published date: January 2018

condition, and if so, which?	http://gmmmg.nhs.uk/docs/guidance/GMMMG-Macular-Drugs-Pathways-v-1-2-FINAL.pdf Local GMMMG guidance is different to NICE TAs for aflibercept and ranibizumab (somewhat extended recommendation is in the more recent NG82 but this is to treat eyes with worse vision). Following GM consultation it was agreed to treat wet AMD earlier than as restricted by NICE. Here is the rationale discussed by GMMMG in August 2017: With regards to the early treatment of eligible people with wet AMD: • NICE TAs for wet AMD restrict use of anti-VEGF to patients with visual acuity between 6/12 and 6/96, however, are based on clinical trials investigating populations solely in this visual impairment group. • There is sound evidence from published papers and local population outcomes to support early use of anti-VEGFs for wet AMD and cost effectiveness within NHS threshold. • Currently, in Greater Manchester, eyes with visual acuity better than 6/12 are not routinely treated. However, two providers, RMEH (NHS) and Optegra (private), treating predominantly Manchester, Trafford and Stockport patients are initiating the treatment early. • It is estimated that 5% of treatable wet AMD patients have vision better than 6/12. Based on rough estimates it would mean that 2 patients per 100,000 of general population would be treated early. • Wet AMD is a rapidly progressive condition. For patients diagnosed with visual acuity better than 6/12 it takes only a matter of weeks at most months to reach the 6/12 threshold. • It costs around £300 more per patient per month, when treatment is started earlier, and effectively the patient is treated for a few months longer period in total.

7. 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.)	GMMMG has a wet AMD pathway which needs to be reviewed • Current practice is variable between providers and clinicians within each service • Current situation is significant growth in spend and activity • Contractual arrangement is variable across providers (some have block contracts/year of care, others are through traditional PbR ex arrangements). o Currently GM is consulting on a GM service spec for macular services – this will help address variation across the system. • A redefined pathway which is assessed for commissioning and financial impact is what is required to manage this longer term: o The pathway will need to consider available clinical research and consider emerging new therapies and the introduction of biosimilars. o The pathway will ensure consistency/reduce unwarranted variation etc o Growth is a real concern and a new pathway will support the management of growth by ensuring we are treating appropriately and using the correct products at the correct time
8. What impact would the technology have on the current pathway of care?	• A new technology which reduces injection frequency will have a significant impact on current service delivery o i.e. the current practice across a majority of providers is to improve capacity in the service (current practice is to move to Eylea, which is marketed as requiring fewer injections). o If the evidence supports a reduction in injection frequency with no compromise on clinical outcomes then an assessment of cost of drug vs cost of activity will need to considered. o The health economics evaluation will need to be carried out to determine the cost impact on areas such as GM – this has the potential to have a significant impact (financial in particular) on GM especially if not clear about positioning of

	therapy. o The introduction of new technology options further emphasises the need for a clearly defined and GM approved clinical pathway.
The use of the technology	
9. To what extent and in which population(s) is the technology being used in your local health economy?	Patients diagnosed with Wet-AMD who meet the treatment criteria – for Lucentis and Eylea
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes
• How does healthcare resource use differ between the technology and current care?	Less frequent injections as has longer duration of action, therefore less frequent hospital visits
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care (specialist centres)

• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	None- same facilities, training and equipment as required for Lucentis and Eylea
• If there are any rules (informal or formal) for starting and stopping treatment with the technology, does this include any additional testing?	Same as for Lucentis and Eylea
11. What is the outcome of any evaluations or audits of the use of the technology?	None known
Equality	
12a. Are there any potential equality issues that should be taken into account when considering this treatment?	Not known

12b. Consider whether these issues are different from issues with current care and why.	Not known

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NICE National Institute for Health and Care Excellence

NHS organisation submission (CCG and NHS England)

Brolucizumab for treating wet age-related macular degeneration [ID1254]

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

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

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

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- Your response should not be longer than 10 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**Luton Clinical Commissioning Group**

3. Job title or position	[redacted]
4. Are you (please tick all that apply):	☐ commissioning services for a CCG or NHS England in general? ☒ commissioning services for a CCG or NHS England for the condition for which NICE is considering this technology? ☐ responsible for quality of service delivery in a CCG (for example, medical director, public health director, director of nursing)? ☐ an expert in treating the condition for which NICE is considering this technology? ☐ an expert in the clinical evidence base supporting the technology (for example, an investigator in clinical trials for the technology)? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	**Clinical Commissioning Group**
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
Current treatment of the condition in the NHS	

6. Are any clinical guidelines used in the treatment of the condition, and if so, which?	Guidance is provided by NG 82 Age related macular degeneration.
7. 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.)	NG82 provides recommendations to use anti-VEGF medications, but does not specify the regimen for use. Three evidence-based anti-VEGF medications are referred to, two of which are licensed for this indication. The third is not licensed for the treatment of wet AMD, and therefore use would be off-label, but has significant clinical evidence to support its use. All require a series of three intraocular injections as a loading dose. This may then be followed by administration *either* at regular intervals, *or* using a "treat and extend" protocol, whereby the interval to the next injection is determined by the results of monitoring immediately prior to the current injection. In effect, this tailors the delivery of the medication to the response shown by the eye. Clinicians therefore have options regarding both the anti-VEGF which they prescribe, and the regimen used. Most clinicians will have a "preferred" option, adjusting to another where clinical circumstances make this appropriate.
8. What impact would the technology have on the current pathway of care?	a) It would introduce another agent, potentially increasing the range of options available. However, the clinical data does not indicate that it is superior in effectiveness to those agents which are already available. For example, sub analyses of the primary endpoints from the two main studies, HAWK and HARRIER, looking at age and baseline BCVA clearly show that all the point estimates are close to the line of null effect and all the confidence intervals cross the line of null effect indicating there is no difference between brolucizumab and aflibercept, the comparator in the studies. Dugel PU et al. HAWK and HARRIER: Phase 3, multicenter, randomized, double-masked trials of brolucizumab for neovascular age-related macular degeneration. Ophthalmology 2019. https://www.aaojournal.org/article/S0161-6420(18)33018-5/fulltext It is difficult to easily compare the results of the HAWK/HARRIER trials with the key trials for ranibizumab (ANCHOR/MARINA) and aflibercept (VIEW) because the patients enrolled in HAWK/HARRIER had a higher baseline BCVA value (upper limit of 78 letters vs. 73 letters). The paper suggests that the higher baseline BCVA value is in line with current disease management. It is also important to note that at the time

	of writing the key clinical studies are still “in press”, although they were presented at a conference in Nov 2017. b) Brolucizumab has been investigated as an agent which could potentially offer a twelve-week dosing interval following initial loading. If this were borne out in practice, it would potentially offer an option for longer treatment intervals, which could reduce pressure for appointments. However, as detailed in q10 below, the trial data does not necessarily support this aspiration. c) No additional safety concerns were identified in the HAWK and HARRIER studies.
The use of the technology	
9. To what extent and in which population(s) is the technology being used in your local health economy?	Not yet licensed or in use
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	See above. It is unlikely that brolucizumab will be used in the “treat and extend” model. On the contrary, the treatment model used in the trials for brolucizumab involved moving to 12 weekly injections, after the initial loading doses, and “interval adjusting” to eight weeks if disease activity was present.
• How does healthcare resource use differ	On the basis of the data available it is difficult to predict resource use in terms of either finance or access. As noted in question 8, above, brolucizumab has been investigated as an agent which could potentially offer a twelve-week dosing interval following initial loading. If this were borne out in practice, it would

between the technology and current care?	potentially offer an option for longer treatment intervals, which could reduce pressure for appointments. The design and findings of the major studies mean that it is difficult to easily ascertain whether this is likely to be the case, and it is certainly possible that there will be little resource benefit (financial or access) from the use of brolucizumab. In HAWK and HARRIER, the probabilities that brolucizumab eyes would remain exclusively on the 12 week dosing interval after loading and up to week 48 were: 3mg (HAWK) 49.4% (4 assessments) 6mg (HAWK) 55.6% (4 assessments, 95% CI 50.2% - 60.8%) 6mg (HARRIER) 51.0% (6 assessments, 95% CI 45.7% - 56.1%) Potentially as many as 50% of brolucizumab 6mg treated eyes need more frequent injections than the 12 week interval under investigation in the trial. For these eyes, brolucizumab offered no advantage over aflibercept in terms of treatment interval. It should also be noted that aflibercept was being used in its eight-week treatment interval regimen, not in a treat and extend regimen. As the HAWK and HARRIER trials compared fixed treatment intervals it is difficult to interpret the actual effect in clinics where treat and extend protocols are used. In HAWK and HARRIER, aflibercept was used in a fixed dosing regimen (three loading doses, followed by injection every eight weeks). When aflibercept is used in this way, this equates to 9 injections per year. However, aflibercept is also licensed for use in a treat and extend approach. After loading, the treatment interval is extended to 2 months and may be maintained or further extended in 2-4 week increments based on visual and/or anatomic outcomes, to a maximum interval of 4 months between injections. Interestingly, the resource impact template for the 2018 NICE guidance for AMD assumes an average of 7 injections per year for both ranibizumab and aflibercept.[ii] The calculations for average number of injections is detailed in the economic analysis for the AMD guidance (appendix J, table 35[iii]). The NICE economic analysis states that the number of injections per year is not widely reported in clinical trials. The values NICE collated were directly informed by the trial evidence for that treatment (where a mean and measure of variance were provided), or was estimated based on the available evidence.

	It could be suggested that use of brolucizumab every 12 weeks after loading, with the option to reduce to dosing every 8 weeks, is an alternative to treat and extend. For those patients who stay on a 12 week dosing interval, this corresponds to 7 injections per year. However, the trial results show that at least half of patients will require more injections than this as they need more frequent dosing which makes the number of injections greater than the current NICE assumption for both ranibizumab and aflibercept. Brolucizumab has only been shown to be non-inferior to fixed dose aflibercept in the HAWK and HARRIER trials. For brolucizumab to be proven as an alternative to treat and extend regimens with aflibercept and ranibizumab, a clinical trial should be undertaken to demonstrate this. In the absence of trial data on treat and extend in brolucizumab, it is likely that the initial licence will be for fixed dosing intervals only. Against this background, it is important to remember that the patent on ranibizumab expires in 2022, and that on aflibercept in 2025. It is anticipated that there will be a robust biosimilars market, which is likely to lead to a significant reduction in price. Additionally, the patent on bevacizumab will expire in 2020 and biosimilars, which may be licensed for wet AMD, are in development. We would encourage NICE to take full account of this in health economic assessments, and to take a realistic view of the potential percentage reductions in price, comparable with other major biosimilars. It is important that the wording of technology appraisals is such that the NHS can respond to variations in pricing.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist clinics
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	n/a

• If there are any rules (informal or formal) for starting and stopping treatment with the technology, does this include any additional testing?	For the currently available agents, testing is included within the clinical protocols and is usually related to the number of intraocular injections required. Brolucizumab is not yet licensed, so it is not possible to state with certainty whether there will be agent-specific requirements.
11. What is the outcome of any evaluations or audits of the use of the technology?	n/a
Equality	
12a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
12b. Consider whether these issues are different from issues with current care and why.	N/A

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Clinical expert statement

Brolucizumab for treating wet age-related macular degeneration [ID1254]

Thank you for agreeing to give us 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.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	**Ben Burton**
2. Name of organisation	**Royal College Of Ophthalmologists**
3. Job title or position	**Consultant Ophthalmologist**

4. Are you (please tick all that apply):	an employee or representative of a healthcare professional organisation that represents clinicians? Yes - RCOPhth a specialist in the treatment of people with this condition? Yes a specialist in the clinical evidence base for this condition or technology? To some extent 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
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.)	

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to cure the condition, or prevent progression or disability.)	To improve and/or maintain vision in patients with wet AMD
8. What do you consider a clinically significant treatment response? (For example, preservation of visual function.)	A reduction in the rate of visual loss compared to natural history of untreated patients with wet AMD by at least 5 letters at 1 year
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	There is a need for longer acting cheaper treatments which are easier to deliver for a service. There are also a small percentage of patients whose disease is not well controlled on existing drugs and lose vision as a result.
What is the expected place of the technology in current practice?	
10. How is the condition currently treated in the NHS?	Long term use of Avastin, Aflbercept and Lucentis intravitreal injections on a variety of different retreatment regimes including monthly prn regimes, treat and extend regimes and fixed interval retreatments.

• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Many guidelines exist but none are universally accepted and most units in the UK do things in a slightly different way to each other.
• 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.)	No, it varies in different areas. The pressure on the service locally whether that be lack of injection room space, lack of OCT machines or lack of appropriately trained staff can be a determining factor dictating which retreatment regime is used. Monthly prn regimes result in less injections but more clinic visits and marginally worse clinical results than treat and extend regimes or fixed (usually two monthly) retreatment interval regimes. Some CCGs allow the use of switching from one drug to another and back again if felt clinically appropriate. Others allow one switch only but if this results in worsening they do not allow switching back (quite bizarre). Stopping criteria probably show the biggest variation and are hard to define in guidelines. Outside the UK I understand some countries insist on using Avastin first line for all patients and those whose disease shows inadequate response can switch to a licensed product such as Lucentis or Aflibercept. This is driven entirely by the cheaper cost of Avastin. In some areas of the UK Avastin is offered to all patients who have vision better than 6/12 as Lucentis and Aflibercept are not funded for patients with vision this good. In some parts of the country these patients are left untreated until the vision deteriorates below 6/12 and then treatment with a licensed product is started.

• What impact would the technology have on the current pathway of care?	There may be a small reduction in the number of Injections needed or it might make no real difference particularly for those units currently using Aflibercept on a treat and extend regime and extending out to 16 week intervals. There may be a small subgroup of patients who currently do not do well with available treatments and would do better with Brolucizumab because of its superior drying effect but more data is needed to confirm this particularly in subgroups such as IPCV patients.
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Many services in the UK rely on nurse and optometrist specialists running clinics with clinic booking coordinators absolutely at the limits of their capacity. The Hawk / Harrier retreatment regimes are complicated and different to current practice. Running multiple drugs on multiple different regimes adds stress to the smooth delivery of a service which in many cases will already be on the point of failure if not actually failing. In addition there have been cases of CCGs refusing to reimburse hospitals for drug use because of confusion over which retreatment regime was allowed/funded. Consequently I think that most units will want to use Brolucizumab on a treat and extend regime after three loading doses rather than introduce yet another complex pretreatment regime.
• How does healthcare resource use differ between the technology and current care?	The currently available data doesn't really tell us if there will be a saving of resource compared to treat and extend Aflibercept which is used extensively in the NHS.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist clinics/ ophthalmology AMD services.

• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Nothing above what is currently needed without this drug.
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	I would expect a few patients who are doing badly on Aflibercept may do better on Brolucizumab due to the superior drying. It is possible that fewer injections will be needed to achieve similar results
• 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?	Marginally if at all.

13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Patients with IPCV or other difficult to control wet AMD may do particularly well compared to current treatments because of the superior drying although this is not proven on the available data. Patients with vision better than 6/12 may do better with this drug as they are likely to require less injections than Avastin, or benefit from earlier treatment in those areas where Avastin is not available for this subgroup.
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	The delivery of the injection would not be any more difficult than current products. The choice of retreatment regime is important. It is not realistic to expect complex trial based retreatment regimes to be used in NHS practice and any guidance on Brolucizumab should not be too restrictive or prescriptive on retreatment regimes. Care should be taken extrapolating trial pretreatment regimes as patients had more visits between injections to monitor disease activity than one would normally do in a real world NHS pretreatment regime.

15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Same as for Lucentis and Aflibercept (which are poorly defined)
16. 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?	Keeping people able to drive with both eyes involvement is a major benefit for this patient cohort and might make the difference for some individuals of being able to continue to look after a spouse with Alzheimers or not . This has significant cost benefits but this is unlikely to come out in a QUALY measurement. Any reduction in injection or visit frequency also results in less care giver burden which may not be reflected in the QUALY calculation.

17. 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?	This may represent a small incremental change for the better although the data is difficult to reach firm conclusions from particularly as the key studies were non inferiority design.
• Is the technology a 'step-change' in the management of the condition?	No
• Does the use of the technology address any particular unmet need of the patient population?	Might help with service capacity issues and a few patients with aggressive disease which does badly with current therapy.

18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Similar to existing treatments
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	No, I think most units do not use fixed dosing Aflibercept. This might be considered the "research world" Gold Standard for the comparator arm but I think Treat and Extend is probably the real world Gold Standard comparator now.
• If not, how could the results be extrapolated to the UK setting?	I think Brolucizumab should be used on a treat and extend regime.
• What, in your view, are the most important outcomes, and were they measured in the trials?	Injection frequency, vision, complications. Yes

• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Retinal Fluid Reduction on OCT. Not a reliable predictor of long term clinical outcome. Persistent intraretinal fluid seems to be a bad prognostic indicator but persistent sub retinal fluid seems to be compatible with much better long term outcomes.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not aware of any
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No Treat and extend to a 16 week interval with Aflibercept as per ALTAIR study and other T and E real world data should be considered.

21. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA155] and [TA294]?	No
22. How do data on real-world experience compare with the trial data?	
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
23b. Consider whether these issues are different from issues with current care and why.	
Topic-specific questions	

24. Is the technology pharmacologically similar to the ranibizumab and aflibercept?	
25. Do ranibizumab and aflibercept have a significant market share for the treatment of wAMD in the NHS clinical practice?	Yes
26. How does the safety profile of brolucizumab compare to ranibizumab and aflibercept?	Similar
Key messages	

27. In up to 5 bullet points, please summarise the key messages of your statement.

- Brolucizumab may represent a small incremental improvement on existing drugs. The superior retinal drying effect is convincing and one would expect a clinical benefit from this but this is not yet proven
- Brolucizumab should be recommended as a first line option for treating wet AMD but also as an option to switch to from other drugs where adequate retinal drying has not been achieved and to switch back again if no additional benefit is observed.
- Pricing is important. The potential benefits of this drug may become more apparent over time but the available evidence would not currently support charging significantly more than current treatments. If priced too high then it should only be available as a second line therapy in patients whose disease activity is inadequately controlled by existing drugs (persistent intraretinal fluid or unrelenting growth of PED for example)
- There should be an option to use Brolucizumab with three monthly loading doses and then used on a treat and extend regime.
- Early treatment is known to be advantageous in wet AMD patients. Consideration should be given as to whether Brolucizumab can also be used in patients with vision better than 6/12 as this will likely result in better absolute long term vision, although letters of improvement in these patients will necessarily be less.

Thank you for your time.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	**Priya Boparai**
2. Name of organisation	**UK Ophthalmic Pharmacy Group**
3. Job title or position	**Co-chair UK Ophthalmic pharmacy Group. Practising ophthalmic and medicines information pharmacist at Sheffield Teaching Hospital NHS Foundation Trust**

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):
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 didn't submit one, I don't 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

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to cure the condition, or prevent progression or disability.)	To slow down the progression of AMD and central vision loss and to improve visual function.
8. What do you consider a clinically significant treatment response? (For example, preservation of visual function.)	I would consider preservation of current visual function, a reduction in progression and an initial improvement in visual acuity clinically significant responses.
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. The national wetAMD population is growing annually and this is placing increasing pressure on existing services. A treatment option that allows less frequent injections compared to currently available options would potentially allow less frequent clinic appointments per patient thereby improving clinic capacity without compromising patient care and reducing the impact of clinic appointments on the patient's life (time off work, transport costs, carer's time etc).
What is the expected place of the technology in current practice?	
10. How is the condition currently treated in the NHS?	The condition is currently treated in accordance with NICE Guideline 82 – Wet age related macular degeneration with the current treatment options being aflibercept, ranibizumab and to a lesser extent bevacizumab

• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE Clinical guideline 82 and the relevant NICE TAs – NICE TA155 and NICE TA 294.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway does differ nationally in terms of the first line treatment option of choice. NICE CG 82 specifies that there is no difference between the 3 anti VEGFs already in use (aflibercept, ranibizumab and unlicensed bevacizumab) in terms of clinical effectiveness. Therefore different centres have adopted different pathways according to the capacity of their clinic. Locally, and at numerous other centres, there is a preference for aflibercept as fewer injections are often required per annum. In terms of when to treat, nationally the pathway closely matches NICE CG 82 although some centres do also treat those with a visual acuity better than 6/12. There is also variation nationally regarding whether 1 or both eyes are injected at the same appointment if both eyes are affected. National treatment regimes include fixed interval dosing and PRN regimes as per the initial trials but many centres tend to use treat and extend regimes which allows less frequent injections without compromising care
• What impact would the technology have on the current pathway of care?	Brolucizumab would potentially allow patients to be injected less frequently thereby improving capacity. I am aware that the trials (HAWK and HARRIER) suggest that only 50% of patients were maintained on 12 weekly dosing However, even a modest reduction in injection frequency could be beneficial to services where patient numbers are increasing and there is minimal available extra capacity.
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	I would anticipate it would be initiated in the same way as current care. However some patients might require less frequent injections.

• How does healthcare resource use differ between the technology and current care?	I would anticipate that the healthcare resource per injection of both the technology and current care would be similar. However if there is a reduced injection frequency less appointments/injections would be necessary for some patients with the new technology
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care within specialist day case units where it can be administered by trained intravitreal injectors
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	A small amount of investment might be required in terms of training the injectors in the use of a different device. However, the facilities and additional equipment required will remain the same as that currently in use at centres where an alternative antiVEGF therapy is currently in use.
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	I would expect it to provide clinically meaningful benefits compared to current care due to the extended dosing interval which should hopefully help reduce the number of patients who might experience a detrimental effect due not receiving current treatment frequently enough due to the lack of capacity to do so. However it is difficult to comment with any certainty given brolucizumab was only compared to 8 weekly aflibercept rather than head to head with 12 weekly aflibercept which some patients are already treated with.
• Do you expect the technology to increase length of life more than current care?	No
• Do you expect the	Yes – due to a reduction in the number of appointments as a result of a reduction in injection frequency .

technology to increase health-related quality of life more than current care?	
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	I am not aware of any where patient groups where this would be more or less effective than the general population if it is used in the same patient subset that other anti-VEGF therapies are currently used
The use of the technology	
14. 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	I am not aware of any practical implications when compared to current care

or ease of use or additional tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	I cannot see that any additional tests will be required when compared to current treatment options
16. 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?	I am not aware of any
17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related	I do not believe it is an innovative treatment compared to currently available options

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?	No
• Does the use of the technology address any particular unmet need of the patient population?	No
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	I believe that the adverse effects reported in the trials are similar to those observed with the current treatment options. I am not aware of any new serious side effects. However, in the trials the incidence of uveitis and endophthalmitis was higher in patients treated with brolucizumab
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	The HAWK and HARRIER trials reflect UK practice in that they compared brolucizumab to aflibercept which is standard therapy in the UK. However aflibercept is also used at some centres less frequently than every 8 weeks without any adverse visual outcomes and this treatment regime was not considered in the trials .

• If not, how could the results be extrapolated to the UK setting?	n/a
• What, in your view, are the most important outcomes, and were they measured in the trials?	I believe the most important outcomes were measured in the trials
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	n/a
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
21. Are you aware of any new evidence for the comparator	I am aware that aflibercept in particular is used as a treat and extend regime where it is used effectively

treatment(s) since the publication of NICE technology appraisal guidance [TA155] and [TA294]?	
22. How do data on real-world experience compare with the trial data?	Real world experience with current treatment options suggest less frequent injections and poorer visual outcomes when compared to the relevant phase III trial data
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	I am not aware of any
23b. Consider whether these issues are different from issues with current care and why.	n/a
Topic-specific questions	
24. Is the technology	There is some thought that due to the lower molecular weight of brolucizumab It may be a more durable

pharmacologically similar to the ranibizumab and aflibercept?	drug and therefore higher doses can be achieved. It is difficult to comment on whether this provides any meaningful benefit
25. Do ranibizumab and aflibercept have a significant market share for the treatment of wAMD in the NHS clinical practice?	Yes. The majority of patients who are receiving treatment are receiving one of these agents. Some are currently receiving bevacizumab and this number is likely to increase pending the outcome of the ongoing court case and also the introduction in the future of bevacizumab biosimilars which might be licensed for intravitreal administration
26. How does the safety profile of brolucizumab compare to ranibizumab and aflibercept?	To my knowledge the safety profile is comparable. I believe that there was a greater incidence of both uveitis and endophthalmitis post injection with brolucizimab compared to aflibercept in the trials. However, these are both recognised side effects of both current treatment options.
Key messages	

27. In up to 5 bullet points, please summarise the key messages of your statement.

- The wetAMD population is increasing and services are struggling to keep up with the ever increasing numbers
- Brolucizimab potentially offers a treatment option that could allow less frequent injections in some patients thereby helping with capacity
- The lack of a head to head study (ie 12 weekly brolucizumab vs 12 weekly aflibercept/ranibizumab) does make it difficult to draw any firm conclusions
-
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NICE National Institute for Health and Care Excellence

Patient expert statement

Brolucizumab for treating wet age-related macular degeneration [ID1254]

Thank you for agreeing to give us your 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.

Information on completing this expert statement

- 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	**Bryan Naylor**
2. Are you (please tick all that apply):	☒ a patient with the condition? ☐ a carer of a patient with the condition? ☒ a patient organisation employee or volunteer?

	☐ other (please specify):
3. Name of your nominating organisation	Macular Society
4. Did your nominating organisation submit a submission?	☒ yes, they did ☐ no, they didn't ☐ I don't know
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 didn't submit one, I don't 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. How did you gather the information included in your statement? (please tick all that apply)	☒ I have personal experience of the condition ☒ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☒ I am drawing on others' experiences. Please specify how this information was gathered: I run peer support groups for those with Macular Degeneration as well as volunteering at the Macular Society (volunteer/speaker).
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	For many years I underwent regular annual aircrew medicals including sight tests. To be told that I had a fast-deteriorating visual impairment was therefore a considerable shock. Many patients report a similar reaction to the diagnosis. They, as I, hoped for a treatment which would reverse the process and had to come to terms with one which, at best slowed the rate of deterioration. Many other adaptations follow. Crossing a busy road alone becomes challenging. Inability to recognise faces of friends is often embarrassing. Reading becomes difficult and interferes with following direction signs. TV becomes less appealing when characters become indistinguishable. The need to be

	accompanied outside familiar places limits spontaneous activity. Adjusting to many such changes takes time and considerable patience and understanding from spouses, family and friends Many older patients regularly attend several clinics and often rely upon public or hospital transport do so. Anything which reduces the number or frequency such visits would be warmly welcomed. In the same vein, some patients report post injection discomfort and some report post treatment anxiety due to blurred vision. Almost all patients feel the need to be accompanied to treatment sessions. Many patients report anxiety even when they have had a number of injection treatments. Whilst most patients adapt to the treatment questions such as "how many injections will I need?" Will not have a simple answer and can cause anxiety. Educational, cultural or linguistic issues can further complicate the process. Any reduction in number of treatments or their frequency, and which does not adversely affect the efficacy of treatment is therefore to be welcomed. Carers find difficulty in appreciating the nature and extent of the condition. Some vision remains and much of daily life becomes adjusted leaving carers in uncertainty. Clinicians are aware of the mental and emotional stresses of the treatment but rarely have the time to empathise and address them.
Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	The most commonly reported reaction is that clinics are overloaded and the treatment seems procedural and patients feel processed. Some patients report considerable anxiety when told that the treatment involves injections in the eye, refusal of the treatment has been reported. Clinicians are aware of this reaction but in busy clinics have little opportunity to discuss and allay those fears.

10. Is there an unmet need for patients with this condition?	Current treatments offer little prospect of vision improvement. Patients accept that delay in the progress of the condition is thus the best outcome. Those with wet AMD are more concerned about this due to the faster progress of the deterioration. Treatments which can slow the progress, need less clinic attendances are warmly welcomed.
Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	The role of carers is important and the stresses upon them are often considerable. They face many of the challenges of the patient. Many carers are themselves older people who find the changes to their quality of life both unexpected and unwelcome. Any development in treatments which decreases this burden is therefore doubly welcome.
Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	Many patients wish to retain as much independence as possible and will submit to a clinical assessment without demur - or understanding of the technology. However, that faith in the clinicians can mask wider anxieties which affect their quality of life. Most clinicians whilst aware of these issues are not equipped to address them and are not sufficiently supported to refer patients appropriately. The patients undergoing this treatment are often not able to recognise any improvement in vision. The slowing of deterioration is not easily apparent. Frequent attendance at clinic without positive result can be demotivational for both patients and cares. A minority of patients report unhappiness with the need for frequent attendance for treatment - particularly those with multiple morbidities who also attend other clinics.

Patient population	
13. 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.	Some older AMD patients have multiple morbidities or other sensory impairments. Many have mobility issues. Hospital transport systems place a particular burden upon such people in arranging and keeping regular appointments. When treatment seems to offer little or no improvement, it is difficult for such patients to remain motivated to attend - particularly on “a bad day”. Clinicians can be understanding about DNA but the administration is often not.
Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Life with AMD is challenging for those with reasonable English. When the issue is compounded by poor language skills it can become very difficult indeed. some cultural groups also strongly discourage social interaction for older women.
Other issues	
15. Are there any other issues that you would like the committee to consider?	The incidence in both wet and dry AMD is increasing rapidly. The consequence of poor or no treatment will place a burden on both the NHS and Social Services. The development of alternative treatments, particularly ones which can be administered in the community is there for important.

Key messages
17. In up to 5 bullet points, please summarise the key messages of your statement: • Any reduction in number of treatments or their frequency, and which does not adversely affect the efficacy of treatment is therefore to be welcomed. • Develop Nurse Practitioners to administer current treatments • Develop improved community-based services • Develop integrated Social Services care Quote “I would rather lose any of my limbs than my eyesight”

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Evidence Review Group's report

Title: Brolucizumab for treating wet age-related macular degeneration

Produced by	*Warwick Evidence*
Authors	*Yen-Fu Chen, Associate Professor, Warwick Medical School, University of Warwick* *Ewen Cummins, Health Economist, MCMDC Ltd* *Osemeke Osokogu, Research Fellow, Warwick Medical School, University of Warwick* *Alexander Tsertsvadze, Independent Systematic Reviewer* *Anna Brown, Information Specialist, Warwick Medical School, University of Warwick* *Mubarak Patel, Research Associate, Warwick Medical School, University of Warwick* *Samer Elsherbiny, Consultant Ophthalmic Surgeon, Machen Eye Unit, Warwick Hospital, South Warwickshire Foundation Trust* *Aileen Clarke, Professor of Public Health, Warwick Medical School, University of Warwick* *Paul Sutcliffe, Associate Professor, Warwick Medical School, University of Warwick*
Correspondence to	*Dr Yen-Fu Chen* *Warwick Evidence* *Division of Health Sciences* *Warwick Medical School* *University of Warwick* *Coventry* *CV4 7AL*
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Declared competing interests of the authors

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Rider on responsibility for report

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

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Contributions of authors

Yen-Fu Chen (Associate Professor) coordinated the project and reviewed clinical effectiveness evidence. Ewen Cummins (Health Economist) conducted, reviewed and critiqued the cost-effectiveness evidence. Osemeke Osokogu (Research Fellow) conducted the critique of the decision problem in the company submission, quality assessed and cross-checked data from key trials. Alexander Tsertsvadze (Senior Research Fellow) reviewed and critiqued clinical effectiveness evidence. Anna Brown (Information Specialist) conducted the critique of the company's searches and conducted additional ERG searches. Mubarak Patel (Research Associate) conducted the critique of statistical analysis including the network meta-analysis of the company submission. Aileen Clarke (Professor) commented on draft versions of the report Paul Sutcliffe (Associate Professor) helped coordinate the project and provided senior advice. All authors contributed to the writing and formatting of the report.

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Glossary of terms

AMD	Age-related macular degeneration
BROL	Brolucizumab
CCG	Clinical commissioning group
cPAS	commercial patient access scheme
CRT	Central retinal thickness
CS	Company submission
CST	Central subfield thickness
DME	Diabetic macular oedema
ERG	Evidence review group
FEI	Fellow eye involvement
FFA	Fluorescein angiography
FOI	Freedom of information
FTA	Fast track appraisal
LP	Loading phase. This usually involves a monthly injection for the first three months of treatment, followed by further injections at varied (see PRN and PRNX below) or fixed (see qXw below) intervals. For example, a loading phase of three monthly injections followed by treatment at an interval of 8 weeks can be expressed as LP -> q8w
LS	Least square
NICE	National Institute for Health and Care Excellence
NARMD	Neovascular Age-Related Macular Degeneration
NMA	Network meta-analysis
OCT	Optical coherence tomography
PAS	Patient access scheme
PDR	Proliferative diabetic retinopathy

PRN	'Pro re nata' or 'treat-as-needed' dosing regimen. This usually involves regularly monitoring the patient's condition (visual acuity and/or anatomical outcomes) and treatment is given when signs of disease activity is observed.
PRNX	'Pro re nata and extend' dosing regimen. This usually involves monitoring the patient's condition and treating the patient when signs of disease activity is observed as in the PRN regimen. However the interval to next monitoring visit is extended if no disease activity is detected.
qXw q4w q8w q12w	One injection every X weeks. One injection every 4 weeks One injection every 8 weeks One injection every 12 weeks
Rani	Ranibizumab
RCT	Randomised controlled trial
RVO	Retinal vein occlusion
SAE	Serious adverse event
SD	Standard deviation
SE	Standard error
SmPC	Summary of Product Characteristics
TA	Technology appraisal
TREX	Treat-and-extend dosing regimen. In this dosing regimen a patient is initially treated and monitored within the same appointment. The interval to the next treatment/monitoring appointment can be extended if no disease activity is shown at the current appointment.
VEGF	Vascular endothelial growth factor

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

Overall, the Evidence Review Group (ERG) considered the company's case for a fast track appraisal (FTA) cost comparison to be valid, according to NICE's criteria for FTA. The main areas of uncertainty identified by the ERG include: (1) the appropriateness of excluding bevacizumab as a comparator in the cost comparison; and (2) the strength of evidence on the relative frequency of treatment injection, monitoring and rate of treatment discontinuation for the technology compared with the chosen comparators. These directly affect the estimated treatment costs and their estimation was largely based upon indirect comparisons. This is because dosing regimens adopted in clinical practice for the comparators have not been directly compared with the technology in head-to-head randomised controlled trials (RCTs). The ERG highlights uncertainty in the interpretation of the Summary of Product Characteristics (SmPC) for brolucizumab regarding to what extent regimens with dosing intervals longer than every 12 weeks are permitted, and whether such dosing regimens will be adopted in clinical practice in the future. An updated draft SmPC was provided to the ERG by the company at factual accuracy check and further clarification from the company at this stage suggested that flexible dosing regimens are allowed. The ERG has no major concerns over the claimed similarity in clinical effectiveness and adverse event profiles for the technology compared with the chosen comparators.

1.1 The technology's expected licensed indication is the same as the chosen comparators

The patient group to be covered by the expected marketing authorisation for brolucizumab, is adults with neovascular (wet) age-related macular degeneration (AMD), and is the same as the licensed indication for the two chosen comparators (aflibercept and ranibizumab). These drugs are likely to be used in the same place in the treatment pathway. The company submission covers the whole expected licensed indication and does not target any specific patient subgroups. The technology has been approved by the US Food and Drug Administration for the same indication[1] and has just received marketing authorisation from European Medicines Agency before finalisation of this report.[2]

1.2 The chosen comparators meet NICE's criteria for FTA, although bevacizumab was not included as a comparator

Both comparators chosen by the company for the cost comparison have received positive recommendation by NICE for this indication in previous technology appraisals (TA 155 for ranibizumab and TA 294 for aflibercept).[3, 4] The company did not provide data on the exact market share for the two comparators, but market research which involved interviews with 50 UK-based retinal specialists (CS Document B, Pages 108-9) which was used to determine the weighting of different dosing regimens for the cost comparison showed that the comparators are commonly used in clinical practice in the UK.

In addition to the two comparators chosen by the company, two other comparators were listed in the NICE final scope for this appraisal: bevacizumab and best supportive care. Bevacizumab does not currently have a marketing authorisation in the UK for wet AMD, but it was considered in NICE's clinical guideline NG82 for this condition.[5] The company cited a figure from market research showing that bevacizumab has a low market share of [redacted] between January 2018 and August 2019 (CS Document B, Table 1.1, Pages 9-10 and company response to ERG clarification questions, Page 18) and therefore argued that it cannot be regarded as established clinical practice in the NHS. The ERG considered whether the uptake of bevacizumab in the NHS could potentially increase in the near future (see Section 2). Acknowledging the complexity of the clinical context, the ERG concluded that the omission of bevacizumab from the list of comparators in the company submission does not directly impact upon its cost comparison case for the purpose of this FTA according to criteria set out by NICE. Nevertheless, the ERG will consider the relevance of bevacizumab and related evidence in its critique of the company submission. The ERG agreed with the company that best supportive care is not appropriate in this part of the treatment pathway.

1.3 It is plausible that the technology may incur similar or lower costs compared with the comparators but there are uncertainties in estimated treatment costs

The company's FTA cost comparison case was built upon the premises that brolucizumab has demonstrated similar clinical effectiveness (with potential superiority for anatomical outcomes) and adverse event profiles compared with the two chosen comparators. The company also indicated that treatment costs associated with brolucizumab may be lower partly because of the lower dosing (and monitoring) frequencies that may be required to maintain control of disease activity compared with the two comparators.

The ERG considered that the case is plausible, but there is some level of uncertainty based on the evidence submitted. Key considerations included:

- Non-inferiority of brolucizumab compared with aflibercept was demonstrated by evidence from two high quality randomised controlled trials (RCTs), HAWK and HARRIER.[6, 7] Brolucizumab also demonstrated superiority over aflibercept on anatomical outcomes, including central subfield retinal thickness (CST) and presence of intraretinal fluid and subretinal fluid in these two trials.

- No RCT directly compared brolucizumab with ranibizumab. The company demonstrated non-inferiority of brolucizumab compared with ranibizumab using a network meta-analysis (NMA), in which brolucizumab was indirectly compared with ranibizumab. The evidence linkage between brolucizumab and ranibizumab was established primarily through the aforementioned HAWK and HARRIER trials which compared brolucizumab with aflibercept, and two other head-to-head trials (VIEW1 and VIEW2) which compared aflibercept with ranibizumab.[8] The latter two trials were also high-quality trials that formed part of the key evidence considered in TA 155.[3] The ERG identified some methodological weaknesses in the NMA (described in detail in Section 3), in particular the exclusion of trials that could have contributed towards a broader, connected evidence network covering the technology and the two comparators. However, given the linkage of evidence through the two pairs of head-to-head trials mentioned above, the ERG considered that the weaknesses identified for

the NMA were unlikely to alter the conclusion of non-inferiority in clinical effectiveness between brolucizumab and the two comparators.

- Adverse events reported in trials of brolucizumab, aflibercept and ranibizumab appear to be similar in nature and frequency, although data for rare adverse events were sparse.

- Accepting equivalence in clinical effectiveness and safety, the focus of the case is comparison of costs between brolucizumab and each of the comparators. As these treatments need to be administered through intravitreal injections by qualified health care professionals in specialist eye services, injection frequency is directly related not only to the acquisition costs of the drug but also to costs of service provision. It is therefore one of the key drivers for treatment costs. Frequency of monitoring and rate of treatment discontinuation also directly influence treatment costs.

- In the HAWK and HARRIER trials, brolucizumab was initially given at intervals of 12 weeks following a loading phase (LP) of three monthly injections. The interval was reduced to an interval of 8 weeks when disease activity re-emerged. This regimen (displayed as LP -> q12w/q8w in some tables for brevity), which is the expected marketing authorisation for brolucizumab, was compared with aflibercept given at fixed dosing intervals of 8 weeks following a loading phase (LP -> q8w). Direct comparative evidence from the trials showed that, on average, patients treated with brolucizumab received a smaller number of injections compared with patients treated with aflibercept based on these dosing regimens. However, more flexible treat-and-extend (TREX) and treat-as-needed (PRN) dosing regimens are likely to be used for aflibercept (and ranibizumab) in clinical practice and therefore the average number of injections for aflibercept (and ranibizumab) may be lower compared with data obtained in trials. As a result, there is major uncertainty in estimated injection frequency for different treatments, and this is one of the key issues for the ERG's critique of the company submission.

- Acknowledging the use of different dosing regimen in clinical practice, the company compared the anticipated dosing regimen for brolucizumab specified

above with a weighted average of different dosing regimens for aflibercept and ranibizumab respectively, using an estimated market share of respective dosing regimens from UK market research for the weighting (CS Document B, Pages 108-9). The ERG thinks that the use of weighted average for the comparators may be reasonable to reflect UK clinical practice, but is unsure about the accuracy and representativeness of the market research data, given the limited information made available to the ERG concerning its methodology. In addition, this approach also adds complexity and uncertainty in the cost comparison models. The ERG therefore explores alternative base cases focusing on TREX and PRN regimens that are most likely used in clinical practice.

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

The population evaluated was adults with choroidal neovascularization secondary to AMD. This is in line with both the NICE final scope, and the patient populations that were included in the pivotal trials of brolucizumab: HAWK and HARRIER. Wet AMD is known to affect primarily adults aged 50 years and over.[9] For the FTA, the company used a minimum age of 50 years. The inclusion criteria for the key trials supporting the company's cost comparison generally align with the population covered by the recommendations for ranibizumab (TA155) and aflibercept (TA294) in terms of lack of permanent structural damage to the central fovea and presence of active disease, although there were some discrepancies in baseline best-corrected visual acuity (BCVA). The treatment criteria specified in NICE's previous guidance require best-corrected visual acuity (BCVA) to be between 6/12 and 6/96 on the Snellen chart, equivalent to between 70 and 25 letters based on the Early Treatment Diabetic Retinopathy Study (ETDRS) chart. The inclusion criteria for HAWK and HARRIER required baseline BCVA to be between 78 and 23 letters based on ETDRS, equivalent to slightly better than 6/9 and slightly worse than 6/96 respectively. This means the brolucizumab trials included some patients with better visual acuity than would be eligible for treatment according to previous NICE guidance. Data from subgroup analyses included in the company submission (CS Document B, Figure 3.9, Page 64) suggested that patients with better baseline BCVA generally had smaller absolute improvement in terms of changes in BCVA from baseline. The comparative effectiveness (i.e. the difference between brolucizumab and aflibercept groups) was broadly similar across subgroups defined by baseline BCVA in the HAWK and HARRIER trials.

The comparators selected by the company were aflibercept and ranibizumab. Compared to the other possible comparators provided in the final NICE scope, these are the most relevant comparators. Both have been adjudged clinical and cost-effective by NICE for treating wet AMD.[3, 4] Compared to brolucizumab and ranibizumab which inhibit only vascular endothelial growth factor-A (VEGF-A) , aflibercept inhibits VEGF-A, VEGF-B and placental growth factor. Nevertheless, these drugs are expected to be broadly comparable since VEGF-A is most commonly implicated in angiogenesis and vascular permeability, two critical issues in the pathogenesis of wet AMD.[10]

Two comparators listed in the final scope of the appraisal were not included: bevacizumab and best supportive care. While the company supplied data from market research to

demonstrate the low level of current use as mentioned earlier, the ERG deliberated on the possibility of increased uptake of the drug in the NHS given a recent court ruling [11] with interpretation of its off-label use[12] and the potential availability of biosimilar products in the future. The ERG is aware of various reasons influencing its use, and hence uncertainty in the future uptake. Factors which need to be considered include the significantly lower cost of the drug per injection and growing evidence suggesting similar clinical effectiveness when compared with other anti-VEGF drugs on the one hand;[5, 13] and issues related to the service capacity required for frequent treatment injection and patient monitoring, and uncertainty with regard to liability associated with off-label use of the drug on the other hand. The ERG has also been made aware of issues related to supply of the required preparation by its clinical advisor. On the whole the ERG considered bevacizumab to be a relevant comparator, but its omission does not directly hinder the cost comparison case as only one appropriate comparator is required according to the criteria for FTA.

The outcomes measured are in line with the final NICE scope. The primary outcome was mean change from baseline in BCVA measured according to ETDRS in both HAWK and HARRIER trials. This is different from the primary outcome assessed in the key trials included in the previous guidance for aflibercept (TA294) and ranibizumab (TA155), which was loss of fewer than 15 letters on the ETDRS scale from baseline. However, both outcomes were derived from measurements on the ETDRS scale, and a comparison between key trials (HAWK, HARRIER, VIEW 1 and VIEW2) does not suggest inconsistency in the observed response for a given outcome between the trials (see Appendix Table 33), and therefore findings between these trials are broadly exchangeable. Health-related quality of life (HRQoL) was measured in the HAWK and HARRIER trials by the tool NEI VFQ-25, which is specific for vision-related quality of life. [14] It has been used in other anti-VEGF trials. However, data for HRQoL were not required in the context of cost comparison.

A lifetime horizon of 30 years was adopted similar to the previous NICE appraisal of aflibercept.[4] All costs were considered from the NHS and Personal and Social Service points of view.

No sub-groups were considered.

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

The clinical effectiveness evidence was presented in the company submission in the form of: (1) a systematic literature review which primarily focuses on the direct comparative evidence between brolucizumab and aflibercept; (2) an NMA which was conducted to assess the comparative effectiveness of brolucizumab versus aflibercept and ranibizumab. The NMA is required as no RCT has directly compared brolucizumab against ranibizumab.

The systematic review included 38 RCTs reported in 48 publications. However, presentation of data focused on findings from three brolucizumab trials, including two pivotal trials, HAWK and HARRIER (CS Document B, Section B.3), and a phase 2 trial OSPREY (CS Appendices, Appendix H). The company used the systematic review primarily to support its NMA. Data on clinical effectiveness, safety, treatment discontinuation and injection frequency were presented for RCTs included in the base case of the NMA. Of the 38 RCTs identified, only 15 RCTs (analysed as 14 studies as data from VIEW1 and VIEW2 trials were combined and analysed as one study) were included in the NMA, for which data were presented. The ERG assessed the methodology of the systematic review and identified the following issues which may have some bearing on the interpretation of its findings.

3.1 Literature search for the systematic review

The ERG considered that an appropriate selection of databases was searched. Searches focused on RCTs using search filters but did not cover systematic reviews, meta-analyses or technology assessments, although these could have provided further trials or data to inform the systematic review and NMA. The ERG identified a few spelling errors in the drug names in the Embase and Cochrane searches and some alternative names for the drugs are omitted (including RTH258 for brolucizumab). However, trials for these drugs would likely have been identified either in the Medline search (where the spelling errors are absent), or via the drugs' other names.

The ERG updated the company's Embase, Medline and Cochrane Library searches for RCTs since they were last run in June 2019 (omitting the restrictions on conference proceedings / abstracts publication types in Embase, and amending drug name errors and omissions). An additional search was run for systematic reviews or meta-analyses on anti-VEGF treatments

in AMD published since 2015, in Medline and Embase. From other systematic reviews, the ERG found one trial of 18 months duration (Biswas et al. 2011)[15] that compared ranibizumab 0.5 mg (loading phase followed by PRN) with bevacizumab 1.25 mg (loading phase followed by PRN). The trial reported data on treatment discontinuation and injection frequency for ranibizumab (n=60 randomised / 54 analysed) that could potentially be included in the company's baseline pooling (see section 3.4 below).

The ERG also conducted a highly targeted Embase search to identify information on dosing regimens for ranibizumab and aflibercept in clinical practice in the UK. Additional information on 'real life' dosing regimens in the UK and elsewhere was identified via the search for systematic reviews and meta-analyses described above. Due to time constraints these have not been evaluated in detail (some of the reviews/studies were sponsored by manufacturers of anti-VEGFs).

3.2 Study selection for the systematic review and NMA

As mentioned above, the systematic review included in the company submission was primarily used to inform the NMA. The company adopted different inclusion criteria for the systematic review and the NMA, with the scope much broader in terms of comparators for the systematic review. It covered pegaptanib, photodynamic therapy with verteporfin, laser photocoagulation therapy and macular surgeries in addition to aflibercept and ranibizumab. Bevacizumab was not included as a comparator for the systematic review but nonetheless was included in the company's literature search. While it may be reasonable to focus on trials including aflibercept and ranibizumab used at licensed doses to construct the evidence network for the NMA (as trials connected through more distant links may introduce additional heterogeneity and evidence inconsistency without necessarily improving the precision of the estimates), the ERG identified some inconsistencies in the application of inclusion criteria for the NMA, such that several ranibizumab trials that included a trial arm using its licenced 0.5 mg dose (and which could thus have been eligible for inclusion) were excluded from the NMA. The reason cited for the exclusion was that the intervention (such as bevacizumab, against which ranibizumab was compared) was 'not a licensed treatment' (CS Appendices, Table 18, Pages 36-37). However, this criterion seems to have been applied arbitrarily as a large trial (CATT) that compared ranibizumab with bevacizumab was included in the NMA. The ERG has therefore examined the 23 of the 38 trials which were identified

by the company systematic review but were excluded from NMA for additional data that might be relevant (see section 3.4 below).

3.3 Quality assessment and data verification

The company presented quality assessment findings for the three brolucizumab trials (CS Document B, Table 3.8, Pages 44-45), which the ERG verified. The ERG noted that a positive response (indicative of lower quality) was given in the company's assessment for the two items related to imbalance in drop-outs between treatment groups and selective outcome reporting for all three trials. The ERG judged that these are likely to be errors and agreed with the overall assessment that the trials were of high quality.

The ERG has cross-checked data related to injection frequency, treatment discontinuation and serious adverse events. Some discrepancies were found the three brolucizumab trials between the figures shown in the company submission (CS Appendices, Table 22, Pages 43-45) and those presented in the clinical study reports supplied by the company for serious adverse events. However, neither set of figures showed significant differences between brolucizumab and aflibercept.

3.4 Baseline pooling

A large number of different dosing regimens for aflibercept and ranibizumab have been evaluated in RCTs identified in the company's systematic review. The company undertook an NMA for several clinical and safety outcomes where the trial evidence is well connected. Additionally, the company performed 'baseline pooling' for several outcomes including mean change in BCVA, proportion of patients gaining and losing at least 15 ETDRS letters respectively, overall discontinuation, injection frequency, and adverse events. Results for overall discontinuation and injection frequency from the baseline pooling presented in the company submission were used to inform the cost comparison and therefore the ERG's critiques in the following sections focus on these two outcomes.

For injection frequency (and other effectiveness outcomes mentioned above), the company conducted a 'regimen-based pooling', in which results from trial arms related to a specific dosing regimen were pooled. For discontinuation and adverse events, the company adopted 'molecule-based pooling', in which results from trial arms related to the same drug (used at

licensed dose) were pooled irrespective of dosing regimens (e.g., every 4 weeks, PRNX, TREX etc). The ERG has two reservations regarding the 'baseline pooling' approaches:

(1) These 'baseline pooling' analyses broke randomisation within individual trials. Although the company stated that 'Baseline pooling was conducted to estimate the absolute treatment effect for treatment regimens with more than one trial' (CS Document B, Page 74), the fact that results from these analyses were used as separate parameter inputs for individual drugs (for discontinuation) and individual dosing regimens (for injection frequency) in the cost comparison model means that these estimates of 'absolute effects' were essentially used to derive relative rates for treatment discontinuation and injection frequency through naïve indirect comparisons based on data pooled from individual trial arms.

(2) The ERG has some doubt regarding the validity of 'molecule-based pooling' (pooling results across different dosing regimens for the same drug), as it is plausible that different dosing regimens are associated with different levels of treatment discontinuation. The rationale stated by the company (CS Document B, Page 83) was that 'discontinuation was not found to be statistically significantly affected by regimen characteristics in the NMA conducted by NICE in their clinical guideline for wAMD (NG82)'.[5] The ERG believes that the lack of statistically significant difference in discontinuation rates between different dosing regimens in the previous NMA was at least in part due the relatively small volume of evidence available, rather than to active evidence of no significant differences.

These issues will be explored and explained in the sections below for each of the two outcomes used to directly inform the cost comparison.

3.4.1 Baseline (regimen-based) pooling for injection frequency

The company undertook two separate sets of baseline pooling for injection frequency, one based on data from individual trial arms between baseline and one year, and another based on data between one year and two years. The results are presented in Tables 3.17 and 3.18 of the company submission respectively (CS Document B, Pages 81-83). These estimated injection frequencies for individual dosing regimens were then used to calculated a 'weighted average regimen' for aflibercept and ranibizumab respectively in the cost comparison, as the company indicated that different dosing regimens have been used in UK clinical practice based on

market research and opinions from clinical experts (CS Document B, Page 108; also see Section 4 of this report for further details).

Based on data provided in the company submission, data for five of the dosing regimens for baseline to one year and for six of the dosing regimens for year one to year 2 were only available from a single RCT arm and therefore no pooling was required. Among the remaining dosing regimens for which pooling of data from two or more trials arms was undertaken, the ERG noted a high level of statistical heterogeneity in many of the analyses, as indicated in the small p values for Cochran Q in Tables 3.17 and 3.18 of the company submission (CS Document B, Pages 81-83). In view of this, the use of a random effects model as adopted by the company was considered appropriate.

The ERG acknowledges that obtaining injection frequency data from individual trial arms and pooling them together might be a pragmatic approach to provide some estimates for treatment regimens that are most likely to be used in clinical practice (e.g. PRN and TREX) given that the evidence network is not well connected for RCTs including these regimens. Indeed a similar approach was used in the economic model for NICE NG82.[16] However, as highlighted above, use of data pooled from individual trial arms to inform comparison is of the same nature as naïve indirect comparison, with an implicit assumption that the trials are drawn from the same population in the same countries with injection frequencies reported in different trials adjusted based on similar levels of clinical effectiveness to maintain patients on the treatment. The evidence should be interpreted with great caution as potential confounding arising from differences in patient characteristics and trial protocols between RCTs which is not adjusted for and which cannot be ruled out.

As mentioned earlier, the company excluded 23 of the 38 RCTs in their NMA and baseline pooling with some inconsistency in the inclusion/exclusion decision. Therefore, in addition to cross-checking data from the 15 RCTs included in the company baseline pooling, the ERG also examined the 23 RCTs for additional data from relevant ranibizumab and aflibercept trials arms which could have also been included in the company's baseline pooling.

An error was found in the data table for combined VIEW1 and VIEW2 trials that were included in the company's baseline pooling (CS Appendices Table 22, Page 44), with some of the injection frequencies attributed to the incorrect trial arms. However, this error did not appear to have influenced the baseline pooling of injection frequency. ERG's checking of the 23 trials excluded by the company suggests that additional data are available from a small number of these trials. Inclusion of these data may slightly lower the estimated injection

frequencies for ranibizumab and aflibercept but this is unlikely to substantially change the estimates.

3.4.2 Baseline (molecule-based) pooling for overall discontinuation

The company conducted molecule-based baseline pooling for brolucizumab (2 trials), aflibercept (5 trials) and ranibizumab (6 trials) for treatment discontinuation at 2 years (CS Document B, Table 3.19, Page 83). Both fixed effect and random effects models were used, with the results from the random effects model used in the cost comparison after being converted to an annual probability of discontinuation for each of the drugs (CS Document B, Page 110). There was no statistical heterogeneity for the six ranibizumab trials included in the pooling, but high levels of statistical heterogeneity existed among the discontinuation rates at two years for the two trials pooled for brolucizumab (11.6% in HARRIER and 18.8% in HAWK, loading phase then every 12 weeks or every 8 weeks as needed) and the five trials pooled for aflibercept (14.0% in HARRIER [loading phase then every 8 weeks], 22.2% in HAWK [loading phase then every 8 weeks], 14.3% [every 4 weeks] and 16.7% [loading phase then every 8 weeks] in the combined VIEW1 & VIEW2 trials, and 21.2% in RIVAL [TREX]).[6-8, 17, 18] The ERG notes that part of the heterogeneity came from the differences in discontinuation rates between HARRIER and HAWK trials, with the discontinuation rates significantly lower for both brolucizumab and aflibercept in the HARRIER trial than in the HAWK trial. Given that these two trials had nearly identical designs, the ERG deduces that the statistical heterogeneity observed within brolucizumab trial arms and aflibercept trial arms was likely attributed to variation in patient characteristics that may reflect the relatively unrestricted target population of patients with wet AMD and also variation in clinical practice across different geographical locations. This suggests that pooling of data using a random effects model as adopted by the company is the more appropriate approach. However this data pooling method still has major methodological drawbacks as listed above. In particular the suggestion of variation in clinical practice across different clinical locations should be a barrier to such naïve indirect comparison methods.

As mentioned above, the ERG therefore cautions that there may be uncertainty in the applicability of the estimated absolute discontinuation rates from these molecule-based baseline pooling data, given the lumping of data for different treatment regimens in addition to breaking of randomisation.

[redacted]. As for injection frequency, the ERG has also examined additional data on treatment discontinuation that might be included in the 23 trials excluded by the company. ERG's assessment suggests that inclusion of data from these trials may not substantially change the estimated discontinuation rate for aflibercept but may increase the estimated discontinuation rate for ranibizumab. ERG also recognises a general drawback of relying on trial data for estimating treatment discontinuation, as discontinuation decisions are sometimes influenced by rules stipulated in the trial protocol unrelated to lack of efficacy or adverse events.

3.5 Network meta-analysis (NMA)

As described above, NMA was undertaken for many clinical outcomes and adverse events. These demonstrated that brolucizumab has similar clinical effectiveness and adverse event profiles compared with various dosing regimens for aflibercept and ranibizumab.

To assess whether or not the transitivity assumption of the NMA was violated, the ERG made a qualitative comparison of the distributions of all reported trial-related factors (design, follow-up duration), study population inclusion/exclusion criteria, and population baseline characteristics as potential EMs across several key trials (HAWK, HARRIER, OSPREY, VIEW 1, and VIEW 2 studies).[6, 7, 19, 20] The selected trials played an important role in indirectly connecting brolucizumab 6 mg SmPC regimen with ranibizumab 0.5 mg dosing regimens (via HAWK, HARRIER, and VIEW 1&2 studies).[6, 7, 20]

The comparison is provided in Table 34 and Table 35 in the Appendix of this report. The ERG agrees with the company that the study design and population inclusion/exclusion criteria were similar across the trials compared. All five trials were randomized multi-centre double-blind active treatment–controlled phase II-III studies that enrolled adults aged 50 years or older diagnosed with wet AMD and naïve to previous anti-vascular endothelial growth factor (VEGF) therapy.

There were no marked differences in the distribution of age, sex, and race/ethnicity across the trials (see page 73, Table 35 in the Appendix of this report). The majority of study

participants in all these trials were white (at least 80%). The ERG noted some across-trial differences in the distribution of choroidal neovascularisation (CNV) lesion type and size (CS Appendices, Table 20 and Figures 6-7). Specifically, the participants in VIEW 1&2 studies were more likely to present with minimally classic CNV type compared to participants in HARRIER/HAWK studies (33.5%-35.6% vs. 9.5%, respectively). HARRIER/HAWK studies tended to have smaller baseline lesion size (2.8-4.5 mm^2 vs. 7.1 mm^2, respectively) and greater mean BCVA (60.6-61.2 letters vs. 53.6-54.8 letters) compared to those in VIEW 1&2 studies and/or OSPREY study (CS Appendices, Figure 4, Page 48). HARRIER/HAWK studies also had more patients with the mean duration of wet AMD > 30 days than OSPREY study (56.6% and 62.7% vs. 5.6%, respectively). Empirical evidence has indicated that while baseline mean BCVA, CNV lesion type, and size can modify the treatment effect of anti-VEGF in patients with wet AMD, their impact on *relative* treatment effects is less pronounced.[21] As evidence supporting similar clinical effectiveness between brolucizumab and the other anti-VEGF drugs was mainly drawn from RCTs and NMA based on RCT evidence, the differences in baseline characteristics between trials is unlikely to alter the conclusion. However, comparisons that do not preserve randomisation, such as 'baseline pooling' described above, would be more susceptible to confounding by patient characteristics.

The ERG has checked the coding for the NMA and did not identify any issues. The ERG noted that the RIVAL trial,[22] in which TREX regimens were compared between aflibercept and ranibizumab, was connected to the HARBOR trial [23] in the evidence network for treatment discontinuation from baseline to two years (CS Appendices Figure 31, Page 87) through a shared ranibizumab PRN arm which was not presented in the RIVAL trial. Removal of RIVAL trial did not have major impact on the NMA findings according to ERG's re-analysis.

3.6 Additional evidence and information not covered by the company submission

The ERG identified emerging evidence and additional information which may impact upon the estimation of comparative effectiveness, safety and costs, and/or influence clinical practice for the treatment of wet AMD in the near future. These include:

- While anti-VEGF drugs have been a major advance in treating several eye diseases including AMD, diabetic macular oedema, retinal vein occlusion, they are not a cure and have to be continued for many years. Long-term treatment over 10 years with switching between different drugs has been documented.[24] Anti-VEGF treatment has therefore created a very considerable workload for NHS ophthalmology clinics.
- Evidence from a FLUID trial of ranibizumab in wet AMD showed that a more relaxed TREX regimen tolerating some subretinal fluid was comparable in clinical effectiveness to a more intensive TREX regimen aiming for resolving all subretinal fluid and required fewer injection (15.8 vs 17) over two years.[25] This could drive the number of injections using TREX regimens further down if similar approaches are adopted in clinical practice. However, separate evidence from an international, retrospective, observational study (AURA) of ranibizumab in wet AMD suggested that the relatively high injection and monitoring frequencies in the UK compared with other countries were associated with better visual outcomes.[26]
- A Port Delivery System (PDS), which includes a refillable implant that is surgically inserted through an incision in the sclera and pars plana and which allows controlled, continuous release of ranibizumab into the vitreous humour, has been evaluated in a phase-2, LADDER trial[27] and this mode of administration is likely to be developed further.
- The European patents for ranibizumab and aflibercept will expire in 2022 and 2025 respectively.[28]

3.7 Implications of the issues identified in clinical effectiveness evidence on cost comparison

Issues related to clinical effectiveness evidence highlighted above has the following implications for cost comparison:

- Given the high-quality trial evidence supporting similarity in clinical effectiveness between brolucizumab, aflibercept, ranibizumab and bevacizumab (and no clear evidence indicating substantial difference in safety), the main considerations for selecting treatment options rests on costs, service delivery issues and patient preference. Injection frequencies stand out as the crucial issue that has implications for all these factors.
- Most patients with wet AMD require continuous treatment to maintain visual acuity and to prevent disease progression. Considering the costs of treatment and demand on specialist service provision, variable dosing regimens including treat-and-extend and treat-as-needed approaches have become standard practice in the NHS. However, there is a lack of both trial and observational evidence that directly compares the dosing regimen for brolucizumab (as specified in the SmPC) with variable dosing regimens for aflibercept and ranibizumab. Consequently, relative injection frequencies required to maintain similar clinical effectiveness between different treatment options cannot be obtained from direct comparisons and need to be estimated indirectly.
- Due to the need for a loading phase at the initiation of treatment, injection frequency in the first year do not reflect those of subsequent years, which are likely to be key drivers of costs as treatments needs to be continued long-term. However, evidence network is not well connected for RCT data beyond one year, and therefore estimation of important parameters for cost comparison including injection frequency and treatment discontinuation has been carried out using 'baseline pooling', or naïve indirect comparison of weighted average of data from individual trial arms.
- Given the limitations in both data and methods for estimating key parameters for cost comparison described above, uncertainties may not have been adequately captured in the cost comparison presented in the company submission. The ERG has attempted to highlight some of the uncertainties in its alternative cost comparison, in particular those associated with estimating injection frequencies beyond the first two year of treatment.

4 Summary of the ERG's critique of cost comparison evidence submitted

Whether it is appropriate for the assessment to proceed as a cost comparison FTA rests primarily on the clinical effectiveness. The ERG critique of the cost comparison evidence assumes that it is appropriate for the assessment to proceed as a cost comparison FTA, and seeks to answer under what circumstances brolucizumab is likely to be cost saving.

4.1 Company cost comparison

4.1.1 Direct drug cost per dose

The company submission includes the brolucizumab PAS of [redacted] which reduces the cost per injection from the list price of £816 to [redacted].

All results reported in this document do not apply the ranibizumab PAS or the aflibercept PAS. The ERG supplies a cPAS appendix which applies these.

For ease of reference, in this report the ERG also includes the cost comparison results applying a drug cost of £49 per bevacizumab injection, sourced from Appendix J (Table 40) of the NICE wet-AMD guidelines NG82.[16]

4.1.1 Administration cost per dose and monitoring cost per visit.

The company assumes 100% outpatient administration at a unit cost of £95.13. Bilateral administration is assumed to incur an additional 50% administration cost.

Monitoring is assumed to require OCT at an additional cost per visit of £114.35. There are no additional costs for bilateral monitoring.

4.1.2 Company retinal experts survey data

The company surveyed 50 UK retinal experts to estimate the proportions for the various dosing schedules.

Table 1: Ranibizumab and aflibercept dosing schedules: Company UK survey results

	Survey data		Final weight for cost comparison	
	Aflibercept	Ranibizumab	Aflibercept	Ranibizumab
Every 4 weeks (q4w)	[redacted]	[redacted]	[redacted]	[redacted]
Every 8 weeks (q8w)	[redacted]	[redacted]	[redacted]	[redacted]
Every 12 weeks (q12w)	[redacted]	[redacted]	[redacted]	[redacted]
Treat as needed (PRN)	[redacted]	[redacted]	[redacted]	[redacted]
Treat and extend (TREX)	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]

(Source: CS Document B, Table 4.4, page 109)

Responses of 'every 12 weeks' regimens for aflibercept and for ranibizumab were excluded, as were responses for 'every 8 weeks' regimen for ranibizumab. Given the questions that were posed, the reason for these exclusions is unclear. Responses of dosing schedules other than those listed above were also excluded. The remaining schedules' proportions were increased pro rata.

4.1.2.1 Company dosing and monitoring estimates

The company estimates dosing frequencies for years 1 and 2 using a random effects baseline pooling. The year 3+ dosing rates in the main company submission are simply assumed to be the same as the year 2 dosing rates. This differs somewhat from Appendix D of the company submission which, as reviewed in more detail below, is aligned with NG82 and provides somewhat lower year 3+ dosing estimates for ranibizumab and aflibercept. These are not applied in the main company submission base case or sensitivity analyses.

For fixed interval dosing regimens the company submission states that one stop administration and monitoring was assumed

For varying interval dosing regimens the number of monitoring visits was increased in line with estimates from the SALUTE trial,[29] the same source that was used during NG82.

Table 2: Aflibercept dosing and monitoring schedules

	Every 4 weeks (q4w)	Every 4 weeks then treat as needed (q4w ->PRN)*	Loading phase then every 8 weeks (LP -> q8w)	Loading phase then every 8 weeks then treat as needed (LP ->q8w -> PRN)	Loading phase then treat and extend (LP -> TREX)	Mean**
Weight	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Dosing						
Year 1	11.9	11.9	7.1	7.1	9.7	8.8
Year 2	11.9	4.8	5.5	5.0	7.3	6.8
Year 3+	11.9	4.8	5.5	5.0	7.3	6.8
Monitoring						
Year 1	11.9	11.9	7.1	7.1	9.7	8.8
Year 2	11.9	12.7	5.5	12.7	7.3	8.2
Year 3+	11.9	12.7	5.5	12.7	7.3	8.2

Source: CS Document B Table 4.4, page 109; and Table 4.14, page 121.

* Data were obtained from the economic model supplied by the company.

** Weighted average calculated using weights shown in the first row.

Table 3: Ranibizumab dosing and monitoring schedules

	Loading phase then treat as needed (LP -> PRN)	Loading phase then treat as needed and extend (LP -> PRNX)	Treat as needed (PRN)	Treat and extend (TREX)	Every 4 weeks (q4w)	Every 4 weeks then treat as needed (q4w -> PRN)	Mean*
Weight	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Dosing							
Year 1	7.1	5.5	6.9	9.5	11.8	11.8	9.2
Year 2	5.6	5.5	5.6	8.2	11.2	5.6	7.9
Year 3+	5.6	5.5	5.6	8.2	11.2	5.6	7.9
Monitoring							
Year 1	12.9	10.3	12.7	9.5	11.8	11.8	11.0
Year 2	12.7	10.1	12.7	8.2	11.2	12.7	10.1
Year 3+	12.7	10.1	12.7	8.2	11.2	12.7	10.1

Source: CS Document B Table 4.4, page 109; and Table 4.14, page 121.

* Weighted average calculated using weights shown in the first row.

Combined with the mean brolucizumab dosing from the trials and an assumption that the year 3 dosing will be the same as the year 2 average this results in the company base case values.

Table 4: Company base case dosing and monitoring schedules

	Brolucizumab	Aflibercept	Ranibizumab
Dosing			
Year 1	6.7	8.8	9.2
Year 2	4.8	6.8	7.9
Year 3+	4.8	6.8	7.9
Monitoring			
Year 1	6.7	8.8	11.0
Year 2	4.8	8.2	10.1
Year 3+	4.8	8.2	10.1

(Source: CS Document B, Table 4.7, page 111)

The company also conducts scenario analyses based upon TA294 values, and based upon expert opinion for the year 3+ values which suggests dosing across the anti-VEGFs is likely to be the same.

Table 5: Dosing and monitoring schedules: scenario analyses

	TA294 scenario			Expert opinion scenario		
	Brolucizumab	Aflibercept	Ranibizumab	Brolucizumab	Aflibercept	Ranibizumab
Dosing						
Year 1	6.7	8.0	8.0	6.7	8.8	9.2
Year 2	4.8	4.0	6.0	4.8	6.8	7.9
Year 3+	4.0	4.0	4.0	4.0	4.0	4.0
Monitoring						
Year 1	6.7	12.0	12.0	6.7	8.8	11.0
Year 2	4.8	6.0	9.0	4.8	8.2	10.1
Year 3+	6.0	6.0	6.0	4.0	4.0	4.0

The company does not report or apply the values it previously applied for ranibizumab in its submission to TA155.

4.1.2.2 Fellow eye prevalence, incidence and costs

Fellow eye administration is assumed to incur the same direct drug cost, incur an additional 50% administration cost and incur no additional monitoring cost. Given the assumed monitoring schedules the ERG thinks it is unlikely that considerations around fellow eye treatment will qualitatively affect conclusions. The company assumptions appear to be aligned with those of NG82.

4.1.2.3 Adverse events

The company base case does not cost adverse events but has the facility to include the following:

- Cataract: £913 per event,
- Endophthalmitis: £1,644 per event
- Gastrointestinal event: £441 per event
- Intraocular inflammation: £0 per event
- Retinal detachment: £1,649 per event
- Retinal pigment epithelial tear: £0 per event
- Retinal tear: £657 per event
- Stroke: £4,216 per event, with an additional small ongoing annual cost of £159

The company provides a sensitivity analysis that includes adverse events based upon the 96 week random effect model estimates. This has very little effect upon results.

4.1.2.4 Discontinuation rates

Slightly different annual discontinuation rates of 7.86%, 8.95% and 7.89% are applied to brolucizumab, aflibercept and ranibizumab drawn from the company baseline pooling. Those discontinuing are assumed to remain off treatment and not to try another treatment.

The differences between the discontinuation rates outlined above are not model drivers. Brolucizumab has the lowest discontinuation rate which increases its estimated costs compared to the other treatments.

But if the brolucizumab treatment interval cannot be lengthened beyond every 12 weeks while the variable dosing regimens for aflibercept and ranibizumab mean their real world dosing frequencies are less frequent than every 12 weeks, discontinuation rates may matter. Short term savings with brolucizumab may be outweighed by higher long term costs.

Short term discontinuation rates may also be a poor estimate of long term discontinuation rates among patients with a good response. The ERG will conduct scenario analyses that vary the year 3+ discontinuation rates.

4.1.2.5 Direct drug costs: single eye

Given drug costs per administration of [redacted] for brolucizumab, £816 for aflibercept and £551 for ranibizumab the above dosing schedules result in the following direct drug costs for aflibercept.

Table 6: Aflibercept direct drug costs

	Every 4 weeks (q4w)	Every 4 weeks then treat as needed (q4w->PRN)	Loading phase then every 8 weeks (LP->q8w)	Loading phase then every 8 weeks then treat as needed (LP ->q8w -> PRN}	Loading phase then treat and extend (LP -> TREX)	Mean
Year 1	£9,710	£9,710	£5,794	£5,794	£7,915	£7,181
Year 2	£9,710	£3,917	£4,488	£4,080	£5,957	£5,549
Year 3+	£9,710	£3,917	£4,488	£4,080	£5,957	£5,549

The company dosing schedules result in the following direct drug costs for ranibizumab.

Table 7: Ranibizumab direct drug costs

	Loading phase then treat as needed (LP -> PRN)	Loading phase then treat as needed and extend (LP -> PRNX)	Treat as needed (PRN)	Treat and extend (TREX)	Every 4 weeks (q4w)	Every 4 weeks then treat as needed (q4w -> PRN)	Mean
Year 1	£3,912	£3,031	£3,802	£5,235	£6,502	£6,502	£5,040
Year 2	£3,086	£3,031	£3,086	£4,518	£6,171	£3,086	£4,355
Year 3+	£3,086	£3,031	£3,086	£4,518	£6,171	£3,086	£4,355

The company dosing schedules result in the following direct drug costs for the company base case.

Table 8: Company base case direct drug costs

	Brolucizumab	Aflibercept	Ranibizumab
Dosing			
Year 1	[redacted]	£7,181	£5,040
Year 2	[redacted]	£5,549	£4,355
Year 3+	[redacted]	£5,549	£4,355

The company dosing schedules result in the following direct drug costs for the company scenario analyses.

Table 9: Dosing and monitoring schedules: scenario analyses

	TA294 scenario			Expert opinion scenario		
	Brolucizumab	Aflibercept	Ranibizumab	Brolucizumab	Aflibercept	Ranibizumab
Dosing						
Year 1	[redacted]	£6,528	£4,408	[redacted]	£7,181	£5,048
Year 2	[redacted]	£3,264	£3,306	[redacted]	£5,549	£4,360
Year 3+	[redacted]	£3,264	£2,204	[redacted]	£3,264	£2,204

4.1.2.6 Administration visits cost and monitoring visit cost: single eye

Two stop administration and monitoring is applied within the model. Administration is costed as 100% outpatient at £95.13. All monitoring is additional to this and is costed as OCT at £114.35.

This results in the following administration and monitoring costs for the aflibercept dosing regimens.

Table 10: Aflibercept administration and monitoring costs

	Every 4 weeks (q4w)	Every 4 weeks then treat as needed (q4w->PRN)	Loading phase then every 8 weeks (LP->q8w)	Loading phase then every 8 weeks then treat as needed (LP ->q8w -> PRN)	Loading phase then treat and extend (LP -> TREX)	Mean
Admin						
Year 1	£1,132	£1,132	£675	£675	£923	£837
Year 2	£1,132	£457	£523	£476	£694	£647
Year 3+	£1,132	£457	£523	£476	£694	£647
Monitoring						
Year 1	£1,361	£1,361	£812	£812	£1,109	£1,006
Year 2	£1,361	£1,452	£629	£1,452	£835	£938
Year 3+	£1,361	£1,452	£629	£1,452	£835	£938

This results in the following administration and monitoring costs for the ranibizumab dosing regimens.

Table 11: Ranibizumab administration and monitoring costs

	Loading phase then treat as needed (LP -> PRN)	Loading phase then treat as needed and extend (LP -> PRNX)	Treat as needed (PRN)	Treat and extend (TREX)	Every 4 weeks (q4w)	Every 4 weeks then treat as needed (q4w -> PRN)	Mean
Admin							
Year 1	£675	£523*	£656	£904	£1,123	£1,123	£875
Year 2	£533	£523	£533	£780	£1,065	£533	£752
Year 3+	£533	£523	£533	£780	£1,065	£533	£752
Monitoring							
Year 1	£1,475	£1,178	£1,452	£1,086	£1,349	£1,349	£1,258
Year 2	£1,452	£1,155	£1,452	£938	£1,281	£1,452	£1,155
Year 3+	£1,452	£1,155	£1,452	£938	£1,281	£1,452	£1,155

* Slightly less than the corresponding amount for brolucizumab.

This results in the following administration and monitoring costs for the base case.

Table 12: Company base case administration and monitoring costs

	Brolucizumab	Aflibercept	Ranibizumab
Admin			
Year 1	£637	£837	£875
Year 2	£457	£647	£752
Year 3+	£457	£647	£752
Monitoring			
Year 1	£766	£1,006	£1,258
Year 2	£549	£938	£1,155
Year 3+	£549	£938	£1,155

This results in the following administration and monitoring costs for the scenario analyses.

Table 13: Administration and monitoring schedules: scenario analyses

	TA294 scenario			Expert opinion scenario		
	Brolucizumab	Aflibercept	Ranibizumab	Brolucizumab	Aflibercept	Ranibizumab
Admin						
Year 1	£637	£761	£761	£637	£837	£875
Year 2	£457	£381	£571	£457	£647	£752
Year 3+	£381	£381	£381	£381	£381	£381
Monitoring						
Year 1	£766	£1,372	£1,372	£766	£1,006	£1,258
Year 2	£549	£686	£1,029	£549	£938	£1,155
Year 3+	£686	£686	£686	£457	£457	£457

The above illustrates that the company estimates that:

- Brolucizumab has both lower administration costs and lower monitoring costs than both aflibercept and ranibizumab for the base case.
- Brolucizumab has both lower administration costs and lower monitoring costs than both aflibercept and ranibizumab for all the individual dosing schedules of aflibercept and ranibizumab.
- Brolucizumab has both lower administration costs and lower monitoring costs than both aflibercept and ranibizumab for the scenario analyses.

4.1.2.7 Direct drug, administration and monitoring costs summary

Given the direct drug, administration and monitoring costs outlined above, brolucizumab will be estimated to be cost saving compared to aflibercept and ranibizumab regardless of which company dosing schedule is selected.

Fellow eye involvement, treatment discontinuation rates and adverse event rates would have to differ notably between treatments to change this conclusion.

The company model extrapolates to a lifetime horizon, but this does not affect these conclusions.

4.1.3 Company base case

For the company base the total and net discounted costs that result are as per Table 14 below. The ERG has appended the results for bevacizumab.

Table 14: Company base case augmented with ERG comparison with bevacizumab

	Brolucizumab	Aflibercept	Ranibizumab	Bevacizumab*
Drug	[redacted]	£53,515	£43,644	£3,881
Admin	[redacted]	£5,060	£6,089	£6,089
OCT	[redacted]	£5,383	£7,055	£7,055
FFA	[redacted]	£207	£209	£209
AE	[redacted]	£0	£0	£0
Total	[redacted]	£64,164	£45,090	£17,234
Net	[redacted]	[redacted]	[redacted]	[redacted]
* Assumes the same dosing schedule and other clinical inputs as ranibizumab.				

Given dosing schedules and drug costs brolucizumab is cost saving compared to both aflibercept and ranibizumab. But despite the dosing schedules, due to the low bevacizumab drug cost brolucizumab is cost increasing compared to bevacizumab.

4.1.4 Company sensitivity analyses

The company sensitivity analyses are as per Table 15.

Table 15: Company scenario analyses

	Aflibercept	Ranibizumab	Bevacizumab
Company base case			
SA01. Baseline age 65			
SA02. 50% female			
SA03. Discount rate 0%			
SA04. FEI developing wAMD 7.5%[1]			
SA05. Bilateral treatment multiplier			
SA06. AFLI 2mg q4w			
SA07. AFLI 3mg q4w -> PRN			
SA08. AFLI 2mg LP -> q8w			
SA09. AFLI 2mg LP -> q8w -> PRN			
SA10. AFLI 2mg LP -> TREX			
SA11. RANI 0.5mg LP -> PRN			
SA12. RANI 0.5mg LP -> PRNX			
SA13. RANI 0.5mg PRN			
SA14. RANI 0.5mg TREX			
SA15. RANI 0.5mg q4w			
SA16. RANI 0.5mg q4w -> PRN			
SA17. Discontinuation NMA fixed effects			
SA18. Discontinuation NG82 App. J			
SA19. Inject/Monitor NMA fixed effects			
SA20. Inject/Monitor Yr 3+ piecewise NMA			
SA21. Additional Year 1 BROL Injection			
SA22. Inject/Monitor NMA expert opinion			
SA23. 36.8% Day case admin (NG82)			
SA24. TA294 assumptions			
SA25. TA294 costs and assumptions			
SA26. AEs included: 96 week baseline RE			

AEs: adverse events, AFLI: aflibercept, BROL: brolucizumab, FEI: fellow eye involvement, LP: loading phase, NMA: network meta-analysis, PRN: treat as needed; PRNX: treat as needed and extend, RE: random effects, RANI: ranibizumab, TREX: treat and extend

None of the sensitivity analyses change the sign of the anticipated net costs.

The dosing regimens of SA06 to SA16 alter the net costs in the predictable way. Equalising the injection frequencies for years 3+ across treatments, SA22, has a reasonable effect upon net costs.

The other main sensitivity reported is to the TA294 costs and assumptions: injection frequencies of 8, 4 and 4 for aflibercept and 8, 6 and 4 for ranibizumab in years 1, 2 and 3+; 65% day case administration at a cost of £402; and, some other minor cost revisions.

[1] There is an inconsequential difference between the ERG calculations and those of the company for this sensitivity analysis.

4.2 ERG critique of the company submission

The cost drivers are:

1. Whether bevacizumab is a comparator.
2. The assumed dosing and monitoring schedules.
3. Longer term discontinuation rates if year 3+ dosing differs between the treatments.
4. Whether the trial proportions increasing their brolucizumab dosing frequency from every 12 weeks to every 8 weeks will apply in the longer term.
5. To what extent brolucizumab permits TREX and PRN dosing beyond every 12 weeks to every 16 weeks.
6. The comparator PASs as reviewed in the cPAS appendix.

Before considering these, the ERG briefly outlines its cross check of the company cost comparison model.

4.2.1 Model cross check

The ERG has rebuilt the cost comparison model cohort flow. It tallies with that of the company.

A possible issue is that the model assumes that only those who remain on treatment in their initial eye will have fellow eye involvement treated. This may not reflect clinical practice and the company model is not easily corrected for this. These patients might also tend to be treated with an alternative anti-VEGF in their fellow eye. The estimates of the net costs or net savings may consequently be biased. But provided that discontinuation rates are similar between the treatments it is difficult to imagine this issue causing the overall conclusions of the modelling to change; i.e. net savings are likely to remain net savings and net costs are likely to remain net costs, even if this issue is addressed.

The main discrepancy appears to be that the written company submission suggests the one stop administration and monitoring is applied, in line with NG82. But there may be a modelling error in terms of the additional costs applied for one stop administration and monitoring uplifts for fellow eye involvement compared to no uplift for purely monitoring visits. The ERG revised base case retains the company method, but a scenario analysis that explores a more literal interpretation of these uplifts is also explored.

4.2.2 Bevacizumab as a comparator

There has been a recent court ruling that permits doctors to offer patients bevacizumab for wet AMD.[11, 30] As reported in the BMJ in September 2019, this has led the MHRA to revise its guidance on bevacizumab for ophthalmic conditions to be "off-label".[12]

The company conducted a national market share survey which it summarises as suggesting that during January 2018 – August 2019 bevacizumab use for wet AMD was only [redacted] of the market.

[redacted] An alternative estimate is provided by Shalaby et al (2016) who made a freedom of information (FOI) request to all UK NHS ophthalmological units for the number of ranibizumab, aflibercept, and bevacizumab injections prescribed during January 2015.[31] They found a bevacizumab market share of 3% of all anti-VEGF injections. With regards their 3% figure it should be noted that this is the percentage of all anti-VEGF injections and is not limited to anti-VEGF for wet AMD. The 3% estimate predates the September 2018 court ruling against the company and in favour of 12 CCGs on the use of bevacizumab for wet AMD and also predates the recent change in MHRA guidance on the use of bevacizumab for wet AMD. The current market share of bevacizumab may be higher than its 2015 market share for both prevalent wet AMD patients and newly incident wet AMD patients, and perhaps more so for newly incident wet AMD patients.

The ERG thinks that the cost comparison analysis should focus primarily upon what newly incident wet AMD patients are likely to be treated with. The company cost comparison model is also based upon newly incident wet AMD patients. It is possible that the company market share data does not reflect the effects of the MHRA revised guidance, or its likely effect upon the current treatment of newly incident wet AMD patients.

ERG expert opinion expresses concerns about liability, and that clinical commissioning groups (CCGs) may need to provide indemnity if uptake of bevacizumab is to be encouraged.

4.2.3 Dosing and monitoring schedules

4.2.3.1 SmPCs

The draft SmPC for brolucizumab supplied by the company at factual accuracy check, which has the same wording as the final approved SmPC, states:

"The recommended dose is 6 mg brolucizumab (0.05 ml solution) administered by intravitreal injection every 4 weeks (monthly) for the first 3 doses. Thereafter, the physician may individualise treatment intervals based on disease activity as assessed by visual acuity and/or anatomical parameters. A disease activity assessment is suggested 16 weeks (4 months) after treatment start. 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 physician may further individualise treatment intervals based on disease activity." Company clarification at factual accuracy check suggested that it views the brolucizumab SmPC as permitting dosing intervals beyond the range of between every 12 weeks and every 8 weeks: an annual frequency of 4.35 or 6.52 based upon 100% adherence and a month being 4 weeks.

The SmPC for aflibercept states:

"The recommended dose for Eylea is 2 mg aflibercept, equivalent to 50 microlitres.

Eylea treatment is initiated with one injection per month for three consecutive doses. The treatment interval is then extended to two months.

Based on the physician's judgement of visual and/or anatomic outcomes, the treatment interval may be maintained at two months or further extended using a treat-and-extend dosing regimen, where injection intervals are increased in 2- or 4-weekly increments to maintain stable visual and/or anatomic outcomes. If visual and/or anatomic outcomes deteriorate, the treatment interval should be shortened accordingly to a minimum of two months during the first 12 months of treatment.

There is no requirement for monitoring between injections. Based on the physician's judgement the schedule of monitoring visits may be more frequent than the injection visits.

Treatment intervals greater than four months between injections have not been studied."

This suggests that dosing with aflibercept can be as infrequent as four monthly: an annual frequency of 3.26 based upon a month being 4 weeks.

The SmPC for ranibizumab states:

"The recommended dose for Lucentis in adults is 0.5 mg given as a single intravitreal injection. This corresponds to an injection volume of 0.05 ml. The interval between two doses injected into the same eye should be at least four weeks.

Treatment in adults is initiated with one injection per month until maximum visual acuity is achieved and/or there are no signs of disease activity i.e. no change in visual acuity and in other signs and symptoms of the disease under continued treatment. In patients with wet AMD, DME, PDR and RVO, initially, three or more consecutive, monthly injections may be needed.

Thereafter, monitoring and treatment intervals should be determined by the physician and should be based on disease activity, as assessed by visual acuity and/or anatomical parameters.

If patients are being treated according to a treat-and-extend regimen, once maximum visual acuity is achieved and/or there are no signs of disease activity, the treatment intervals can be extended stepwise until signs of disease activity or visual impairment recur. The treatment interval should be extended by no more than two weeks at a time for wet AMD. If disease activity recurs, the treatment interval should be shortened accordingly."

This does not appear to place any limits on extension of the dosing frequency.

As a consequence, there remains some uncertainty around to what extent brolucizumab may be extended to an interval of every 16 weeks and the extent to which aflibercept, ranibizumab and bevacizumab can and are extended to every 16 weeks.

4.2.3.2 Published resource use estimates: Company NMA articles

As mentioned in section 3.4, the company identified 38 papers for possible inclusion in its NMA, with 15 being included in the final analyses and 23 rejected. This also applies to the calculation of dosing frequencies, with only 15 being included in the final baseline pooling to arrive at the mean number of injections in year 1 and year 2 for the various dosing regimens.

The ERG has cross-checked the dosing frequencies reported by the company for the 15 papers included in the NMA. The company values agree with those of the cited papers with the exception of the values for 2 year dosing for VIEW 1&2 which appear to have been

wrongly attributed as outlined below. However after cross examination, these errors do not appear to have been carried into the company's baseline pooling.

Table 16: VIEW 1&2 pooled 2 year dosing frequencies: Company vs ERG

Regimen	Company	ERG
Aflibercept 0.5q4w -> PRN	11.2	16.2
Aflibercept 2q4w -> PRN	16.0	16.0
LP -> aflibercept 2q8w -> PRN	16.5	11.2
Ranibizumab 0.5q4w -> PRN	16.2	16.5

(Source: company data were obtained from CS Appendix D, Table 22; ERG data were obtained from published articles of VIEW 1 & 2 [8, 20])

4.2.3.3 Published resource use estimates: Review articles

The ERG has identified a number of review articles that provide resource use estimates, but due to time constraints mainly relies upon those of the relatively recent economic appendix to NG82 [16] as summarised below.

4.2.3.4 Published resource use estimates: NG82

The 2018 NG82 conducted an extensive literature review and undertook extensive economic modelling. It considered the following dosing regimens for aflibercept:

- Every 4 weeks (q4w)
- Every 8 weeks (q8w)
- Every 8 weeks then treat as needed (q8w->PRN)
- Treat and extend (TREX)

And the following for ranibizumab and bevacizumab:

- Every 4 weeks (q4w)
- Every 8 weeks (q8w)
- Loading phase then every 12 weeks (LP->q12w)
- Treat as needed (PRN)
- Loading phase then treat as needed (LP->PRN)
- Treat and extend (TREX)

PRNX is only explored as a scenario for both aflibercept and ranibizumab, because it is connected to the NMA network by a single small sample trial.

Treatment was assumed to be one-stop where monitoring and administration occur at a single outpatient visit, at a cost per visit of £89. Bilateral treatment was assumed to add 50% to the administration visit cost. Additional monitoring visits are required for PRN and PRNX. These are estimated from the SALUTE trial for years 1 and 2 and from the ARMD dataset for years 3+. The number of administration visits is netted out from the total number of visits to yield the number of monitoring visits, at an outpatient cost per visit of £116.

The year 1 and year 2 numbers of injections are estimated from pooling the relevant trial data, though some assumptions are required for some regimens: e.g. for ranibizumab 'every 8 weeks' dosing is taken to be half that of 'every 4 weeks' dosing. The year 3+ fixed interval dosing is conditioned by a 91% attendance rate derived from IVAN year 2 dosing. The year 3+ variable interval dosing is derived in a similar manner to the (unused) company estimates of its appendix D, by applying ratios to the ARMD database ranibizumab PRN dosing frequency of 3.7.

Table 17: NG82 dosing frequencies

	Aflibercept			Ranibizumab			Bevacizumab		
Year	1	2	3+	1	2	3+	1	2	3+
q4w	11.9	11.4	10.9	11.4	10.9	10.9	11.6	11.0	10.9
q8w	7.0	5.3	5.5	5.7	5.4	5.5	5.8	5.5	5.5
q8w->PRN	7.0	5.0	3.4	..	..	..	..	..	..
LP->q12w	..	..	..	5.5	3.6	3.6	5.9	3.7	3.6
PRN	..	..	..	6.9	5.7	3.7	7.5	6.6	4.1
LP->PRN	..	..	..	7.0	5.6	3.7	7.7	5.3	4.1
TREX	8.8	7.3	4.4	8.4	8.1	4.8	8.9	9.2	5.5
PRNX	6.3	5.1	3.1	6.0	5.0	3.4	6.6	5.7	3.8

Note that the Year 3+ estimates of NG82 are broadly in-line though typically slightly higher than those of the company appendix D estimates.

There is some ambiguity of presentation in the number of additional monitoring visits required for PRN and PRNX, with the SALUTE trial being cited for year 1 and 2 but the table column heading being "year 1" and this corresponding to 12 month data in the cited paper. The additional monitoring visits are calculated to be 6.1 for PRN and 4.1 for PRNX. The observational data suggests an additional 4.5 monitoring visits. In the light of this, the ERG NG82 based dosing and monitoring will apply additional monitoring visits of 6.1 for PRN and 4.1 for PRNX in year 1, and 4.5 for both PRN and PRNX thereafter.

NG82 suggests slightly higher dosing for bevacizumab than for ranibizumab.

4.2.3.5 Company expert survey of dosing regimens

The ERG asked the company to supply the questionnaire used to survey the experts and the individual responses to the questionnaire. The company response was that the questions asked were:

[redacted]Due to the survey being conducted by a third party the company states that it does not have access to the individual responses due to the need to protect respondents' anonymity and confidentiality.

As a consequence, there is no information about whether responses related to year 1, year 2 or year 3+. For aflibercept NG82 estimated a year 1 dosing frequency for both 'every 8 weeks' and 'every 8 weeks then treat as needed' of 7.0, but year 3+ dosing frequencies of 5.5 and 3.4 respectively. Given the question posed relating to dosing "after the initial loading doses," it is unclear how the survey results of [redacted] being 'every 8 weeks' should be handled: as 'every 8 weeks' or as 'every 8 weeks then treat as needed'.

There is also no information about the degree of agreement or divergence of the individual response, or the degree to which a minority of responses might have skewed results.

In the light of this, the ERG is unwilling to pool the dosing regimens as per the company base case analysis and will instead examine individual dosing regimens.

4.2.3.6 Other expert opinion about dosing regimens

The clinical expert statement by Ben Burton notes that aflibercept, ranibizumab and bevacizumab are all used. He goes on to note that in some parts of the country bevacizumab is offered to all patients whose vision is better than 6/12 because aflibercept and ranibizumab are not funded for these patients. In some parts of the country patients' vision is allowed to deteriorate below 6/12 at which point treatment with aflibercept or ranibizumab is begun. He also notes that TREX aflibercept may extend to q16w dosing, and that TREX aflibercept is

used extensively in the NHS, and this regimen "is probably the real world Gold Standard comparator now".

ERG expert opinion suggests that TREX is the usual treatment regimen with the aim of extending to every 12 weeks. The expert notes that there is currently debate about the possibility of extending to every 16 weeks. He also notes that TREX is preferred where the service can offer a one stop 'review and treat as required' service. But due to local constraints some areas cannot offer a one stop review and treat service, and in these areas it is more normal to offer a PRN service.

The ERG will compare brolucizumab with TREX as its base case, and also provide a full analysis against PRN. Comparisons with the other dosing scenarios will be presented as scenario analyses.

4.2.3.7 Brolucizumab trials dosing frequencies extrapolation

The HAWK and HARRIER trials permitted an increase in the dosing frequency among patients with an insufficient response from every 12 weeks to every 8 weeks. Patients attaining a sufficient response with every 8 weeks were not permitted to reduce their dosing frequency from every 8 weeks to every 12 weeks. The company submission presents data on the proportion increasing to 'every 8 weeks' by 44 weeks and noted that the majority of patients remained in 'every 12 weeks'. The company clarification response extends this data to 92 weeks with this suggesting that the majority of patients increased their dosing frequency to every 8 weeks by trials' end.

Table 18: Proportion of brolucizumab patients with increased 'every 8 weeks' dosing frequency

	HAWK	HARRIER	Combined
Baseline	0%	0%	0%
44 weeks	43%	49%	46%
92 weeks	59%	66%	62%

Figure redacted – academic in confidence

Figure 1: Proportion of brolucizumab patients with increased 'every 8 weeks' dosing frequency

It is difficult to speculate upon the extent to which those who required the increased 'every 8 weeks' dosing frequency during the 96 weeks would in clinical practice have it subsequently reduced to 'every 12 weeks' at some point. It is similarly difficult to speculate upon the extent that patients would increase their dosing frequency from 'every 12 weeks' to 'every 8 weeks' beyond 96 weeks.

The ERG base case will assume brolucizumab patients are dosed [redacted] every 8 weeks and [redacted] every 12 weeks for years 3+: an annual average of 5.7 doses. The ERG will provide a scenario analysis that applies the company base case estimate for year 2 to years 3+.

4.2.3.8 Brolucizumab trials' year 2 dosing adherence

For those on 'every 12 weeks' dosing the calculation of dosing adherence is simply calculated as the number of administrations divided by the number of eligible patients every 12 weeks, the averages of the values below being [redacted].

Table 19: Brolucizumab 'every 12 weeks' dosing adherence

Week	HAWK	HARRIER
56	[redacted]	[redacted]
68	[redacted]	[redacted]
80	[redacted]	[redacted]
92	[redacted]	[redacted]

For those on 'every 8 weeks' dosing the calculation is complicated due to patients being transferred to 'every 8 weeks' dosing at different times. As a consequence, those on 'every 8 weeks' dosing do not all receive administrations at the same time. There are administrations for 'every 8 weeks' dosing during every 4 week period of HAWK and HARRIER from the point at which patient transfer to 'every 8 weeks' dosing occurred.

The data available to the ERG from the company response presents the number of administrations for 'every 8 weeks' dosing on a 4 weekly basis, but the number of 'every 8 weeks' patients on a 12 weekly basis. Given the 12 weekly 'every 8 weeks' patient numbers, the ERG can sum the number of administrations for 'every 8 weeks' dosing for either:

- the corresponding 4 week data period and the preceding 4 week data period, or
- the corresponding 4 week data period and the following 4 week data period.

Table 20: Brolucizumab 'every 8 weeks' dosing adherence

	Reported 4 week period merged with			
	preceding 4 weeks		following 4 weeks	
Week	HAWK	HARRIER	HAWK	HARRIER
56	[redacted]	[redacted]	[redacted]	[redacted]
68	[redacted]	[redacted]	[redacted]	[redacted]
80	[redacted]	[redacted]	[redacted]	[redacted]
92	[redacted]	[redacted]	[redacted]	[redacted]

The accuracy of the estimates above is compromised by two elements:

- patients transferring to 'every 8 weeks' dosing during the relevant 8 week period, and
- patients dropping out of the trial during the relevant 8 week period.

Between week 56 and 92, somewhat more patients transferred to 'every 8 weeks' dosing and remained in the trial, [redacted], than dropped out, [redacted]. While those on 'every 8 weeks' dosing may have been more likely to drop out, it also seems likely that not all those dropping out were from the 'every 8 weeks' group. Assuming more transferring to 'every 8 weeks' than dropped out from 'every 8 weeks', if the dosing data from 4 weeks and the preceding 4 weeks is applied the number of patients used for the denominator might be too high and hence the adherence estimate too low. The opposite might apply. But as shown above the two sets of estimates are actually very similar.

The reason for the week 56 estimates exceeding 100% is unclear. There is no obvious drop in eligible patient numbers. The values reported for week 88 (not shown) that contribute to the week 92 estimate are also peculiar. Ignoring the week 56 and 92 values suggests an average adherence among the 'every 8 weeks' group of [redacted]%.

In the light of the above values the ERG will conduct a scenario analysis of a year 3+ brolucizumab adherence of [redacted]%.

4.2.3.9 Brolucizumab trials dosing frequencies and clinical effect

The proportion of patients in the individual trials increasing their dosing frequency from every 12 weeks to every 8 weeks is presented below.

Figure redacted – academic in confidence

Figure 2: Proportions of patients intensifying brolucizumab dosing from every 12 weeks to every 8 weeks

By week 92 the majority of patients in both HAWK and HARRIER had intensified their brolucizumab dosing to every 8 weeks.

For dosing considerations the above is complicated by the trial protocols only permitting dose intensification to every 8 weeks. Patients who had intensified to every 8 weeks were not permitted to have their dosing frequency subsequently reduced to every 12 weeks. It is therefore difficult to infer what proportion of those dosed every 8 weeks at the end of week 92 in the trials would in practice have had their treatment interval extended to every 12 weeks before week 92, and subsequent to week 92.

The company notes that these subgroups break randomisation. Among other things, the mean baseline CST (central subfield thickness) was statistically significantly different as outlined below.

Table 21: Brolucizumab patients on 'every 12 weeks (q12w)' and 'every 8 weeks (q8w)' and their mean baseline CST

	HAWK		HARRIER	
Week 48 dosing	q12w	q8w	q12w	q8w
N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Baseline CST (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Week 92 dosing[2]	q12w	q8w	q12w	q8w
N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Baseline CST (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]

Despite the mean baseline CSTs differing between the groups, the least square (LS) mean changes in CST evolve reasonably similarly between the groups and are not statistically significantly different. There is an initial swift decline, followed by a plateau as shown below.

[2] Note that there may be some discrepancies due to the company apparently reporting the split in the dosing frequencies up to week 92, but the clinical effectiveness estimates split by dosing frequencies at week 48 and at week 96.

Figure redacted – academic in confidence

Figure 3: LS mean Δ vs baseline in CST by BROL dosing subgroup at week 48

Figure redacted – academic in confidence

Figure 4: LS mean Δ vs baseline in CST by BROL dosing subgroup at week 48

But those intensifying their brolucizumab dosing to every 8 weeks do experience a somewhat smaller improvement in their BCVA compared to those remaining on ‘every 12 weeks’ dosing.

Figure redacted – academic in confidence

Figure 5: LS mean Δ vs baseline in BCVA by BROL dosing subgroup at week 48

Figure redacted – academic in confidence

Figure 6: LS mean Δ vs baseline in BCVA by BROL dosing subgroup at week 96

Table 22: LS mean change in BCVA by brolucizumab 'every 12 weeks (q12w)' and 'every 8 weeks (q8w)' dosing frequency

	HAWK		HARRIER	
Week 48 dosing	q12w	q8w	q12w	q8w
Wk 48 Δ BCVA (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Week 96 dosing	q12w	q8w	q12w	q8w
Wk 96 Δ BCVA (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]

The difference between the dosing groups is particularly marked in the HAWK trial, with those intensifying to every 8 weeks experiencing a mean gain [redacted]. The confidence intervals around the improvements in BCVA for those intensifying to every 8 weeks also do not overlap with those remaining on every 12 weeks.

Within the HARRIER trial, those intensifying to every 8 weeks, experience a mean gain of [redacted]. There is also some overlap between the confidence intervals of those intensifying to every 8 weeks and those remaining on every 12 weeks. But if the data from HAWK and HARRIER was combined it seems probable that there would be no overlap between the confidence intervals.

For the cost comparison, the main point to take from the above is that most of those intensifying brolucizumab from every 12 weeks to every 8 weeks did so before week 48. Despite this, there is no evidence of an improvement in BCVA after week 48 among those on every 8 weeks. This may suggest that in general those intensifying to 'every 8 weeks' dosing

due to lack of response to 'every 12 weeks' dosing did not experience much improvement in response from the 'every 8 weeks' dosing and so might be unlikely to return to 'every 12 weeks' dosing.

It is a moot question whether in practice patients would remain on 'every 8 weeks' dosing, and would have the treatment interval lengthened to every 12 weeks at some point, or would have brolucizumab treatment withdrawn and be trialled with another anti-VEGF. ERG expert opinion also notes that the situation compares to patients on ranibizumab and aflibercept falling back to 'every 4 weeks' dosing.

The company cost comparison does not consider the possibility of lack of response to one anti-VEGF leading to patients trying another anti-VEGF. In the light of this, the ERG will assume that those on 'every 8 weeks' brolucizumab at week 96 remain on 'every 8 weeks' brolucizumab, but that this proportion does not increase further thereafter. The ERG will conduct a scenario analysis that applies the brolucizumab year 2 average dose for year 3+ dosing, as per the company base case.

4.2.3.10 Dosing by lesion subgroup

The scope specified lesion type to define possible subgroup. The trials' mean doses for the subgroups are similar to the overall means.

Table 23: Trial dosing by subgroup: Week 44

	HAWK		HARRIER	
	Brolucizumab	Aflibercept	Brolucizumab	Aflibercept
All patients	[redacted]	[redacted]	[redacted]	[redacted]
Predominantly classic	[redacted]	[redacted]	[redacted]	[redacted]
Minimally classic	[redacted]	[redacted]	[redacted]	[redacted]
Occult	[redacted]	[redacted]	[redacted]	[redacted]

Table 24: Trial dosing by subgroup: Week 92

	HAWK		HARRIER	
	Brolucizumab	Aflibercept	Brolucizumab	Aflibercept
All patients	[redacted]	[redacted]	[redacted]	[redacted]
Predominantly classic	[redacted]	[redacted]	[redacted]	[redacted]
Minimally classic	[redacted]	[redacted]	[redacted]	[redacted]
Occult	[redacted]	[redacted]	[redacted]	[redacted]

For the cost comparison with aflibercept there seems little point further exploring lesion subgroups. The ERG has not explored this for the cost comparison with ranibizumab.

4.2.3.11 Year 3+ dosing: Company Submission and Company Appendix D

The company submission assumes that year 3+ dosing will be the same as year 2 dosing, or for the TA294 and expert opinion scenario analyses, that year 3+ dosing will be equal across treatment. The company appendix 3 outlines the NG82 approach and suggests that this is the approach adopted by the company for regimens without a fixed dosing frequency.

In short, the Neovascular Age-Related Macular Degeneration (NARMD) Database study reports ranibizumab PRN dosing of 3.7 injections in year 3.[32] The company estimates injection frequencies for other treatments and regimens by applying the relevant trial's ratio of their year 2 dosing frequency to that of ranibizumab PRN to the NARMD year 3 ranibizumab PRN 3.7 injections.

For ranibizumab TREX this has to be further transitively estimated by applying the TREX-AMD trial reported ratio between ranibizumab TREX and ranibizumab every 4 weeks of 0.68 to the CATT trial ratio between ranibizumab every 4 weeks and ranibizumab PRN of 1.78: yielding the ratio 1.78*0.68=1.21. The estimates for AFLI TREX and AFLI PRNX are similarly transitively calculated.

Table 25: Company's Year 3+ dosing estimates (data source: CS Appendix D, Table 42, Page 90)

	Trial arms		Yr2 Injections		Ratios		
Trial	Arm1	Arm2	Arm1	Arm2	Trial (Arm1/Arm 2)	Arm 1 relative to RANI RPN	Yr3+ Inj.
NARMD	RANI PRN	..	..	..	..	1 (Ref)	3.7
VIEW1&2	AFLI PRN	RANI PRN	4.9	5.6	0.88	0.88	3.2
CATT[1]	RANI q4w	RANI PRN	22.4	12.6	1.78	1.78	..
TREX-AMD	RANI TREX	RANI q4w	8.5	12.5	0.68	1.21	4.5
RIVAL	ALFI TREX	RANI TREX	7.3	8.0	0.91	1.10	4.1
SALUTE[2]	RANI PRNX	RANI PRN	5.5	6.4	0.86	0.86	3.2
VIEW1&2	AFLI PRNX	RANI PRNX	4.9	5.6	0.88	0.75	2.8

[1]Year 1 and 2 data [2]Year 1 data

Given the lack of explicit consideration of the NG82 approach in the main company submission and reasons for its rejection by the company, it is possible that the company originally adopted the NG82 approach but then revised this to the more favourable assumptions of the company base case approach once the implications of the NG82 approach became clear.

If brolucizumab was viewed as a variable dosing schedule, perhaps treat and reduce, a similar method might be employed. Transitively applying the dosing ratios of the pooled arms of HAWK and HARRIER, VIEW1&2 and the CATT trial suggests a dosing ratio of 1.09 relative to the CATT trial ranibizumab PRN arm, and consequently a brolucizumab dosing

frequency of 4.0 for years 3+. But the ERG thinks it more appropriate to treat brolucizumab as a fixed dosing schedule of either every 8 weeks or every 12 weeks for the base case.

The above company values differ a reasonable amount from those of the main company submission which simply reapplies the company year 2 estimates. They are also typically slightly less than the values applied in NG82.

Table 26: Year 3+ dosing: Company base case vs company estimates using NG82 method

	Company estimates		
	Year 2	NG82 method	NG82
RANI PRN	5.6	3.7	3.7
AFLI PRN	4.8	3.2	..
RANI TREX	8.2	4.5	4.8
ALFI TREX	5.0	4.1	4.4
RANI PRNX	5.5	3.2	3.4

Given the loading phase for ranibizumab and presumably for ranibizumab biosimilars, capacity constraints may lead to a reluctance to switch patients from brolucizumab to ranibizumab biosimilars as they become available, even if the ranibizumab biosimilars are considerably cheaper than brolucizumab. ERG expert opinion stresses the effects of capacity constraints and that these as much as the direct drug costs may determine which treatment and dosing regimen is used.

4.2.4 ERG revised base case

The alternative dosing schedule estimates for aflibercept and ranibizumab are presented below.

Table 27: Company dosing schedules: Company NG82 method for years 3+: Aflibercept

	Every 4 weeks (q4w)	Every 4 weeks then treat as needed (q4w->PRN)	Loading phase then every 8 weeks (LP->q8w)	Loading phase then every 8 weeks then treat as needed (LP ->q8w -> PRN)	Loading phase then treat and extend (LP -> TREX)
Year 1	11.9	11.9	7.1	7.1	9.7
Year 2	11.9	4.8	5.5	5.0	7.3
Year 3+	11.9	3.2	5.5	3.2	4.1

Table 28: Company dosing schedules: Company NG82 method for years 3+: Ranibizumab

	Loading phase then treat as needed (LP -> PRN)	Loading phase then treat and extend (LP -> PRNX)	Treat as needed (PRN)	Loading phase then treat and extend (LP->TREX)	Every 4 weeks (q4w)	Every 4 weeks then treat as needed (q4w -> PRN)
Year 1	7.1	5.5	6.9	9.5	11.8	11.8
Year 2	5.6	5.5	5.6	8.2	11.2	5.6
Year 3+	3.7	3.2	3.7	4.5	11.2	3.7

For its revised base case the ERG applies the company dosing schedule estimates for year 1 and year 2.

For years 3+ for ranibizumab and aflibercept it applies the company appendix D estimates, as per the tables above, which follow the method of NG82. Bevacizumab is presented as a scenario analysis, and is assumed to have the same model inputs as ranibizumab with the exception of the vial cost of £49 as taken from NG82.

For year 3+ for brolucizumab the ERG applies the 5.7 average number of injections implied by the proportions having increased their dosing frequency from every 12 weeks to every 8 weeks at the end of HAWK and HARRIER.

The ERG also applies the following revisions to its revised base case:

- Additional monitoring visits for PRN and for PRNX of 6.1 and 4.1 in year 1 respectively and 4.5 thereafter for both, drawn from NG82.

Due to varying expert opinion and a lack of clarity around the company survey of experts and the validity of the pooling of dosing regimens, the ERG presents full analyses comparing

- brolucizumab with TREX ranibizumab and TREX aflibercept, and
- brolucizumab with 'loading phase then treat as needed (LP->PRN)' ranibizumab and 'loading phase then every 8 weeks then treat as needed (LP->q8w->PRN)' aflibercept.

Table 29: ERG base case: brolucizumab vs TREX comparators

	Brolucizumab	Aflibercept	Ranibizumab	Bevacizumab
Drug	[redacted]	£39,598	£30,207	£2,686
Admin	[redacted]	£3,791	£4,266	£4,266
OCT	[redacted]	£3,565	£3,986	£3,986
FFA	[redacted]	£207	£209	£209
AE	[redacted]	£0	£0	£0
Total	[redacted]	£47,162	£38,668	£11,147
Net		[redacted]	[redacted]	[redacted]

Table 30: ERG base case: brolucizumab vs PRN comparators

	Brolucizumab	Aflibercept	Ranibizumab	Bevacizumab
Drug	[redacted]	£29,764	£23,599	£2,099
Admin	[redacted]	£2,845	£3,324	£3,324
OCT	[redacted]	£5,109	£6,364	£6,364
FFA	[redacted]	£207	£209	£209
AE	[redacted]	£0	£0	£0
Total	[redacted]	£37,923	£33,496	£11,995
Net		[redacted]	[redacted]	[redacted]

Brolucizumab results in lower costs compared to both ranibizumab and aflibercept. The cost savings are larger relative to TREX ranibizumab and TREX aflibercept than relative to PRN ranibizumab and PRN aflibercept due to the lower number of doses of ranibizumab and aflibercept required for PRN dosing for years 3+.

Brolucizumab results in higher costs compared to bevacizumab.

4.2.5 ERG scenario analyses

The ERG provides the following scenario analyses:

- SA01: Applies the other dosing regimens.
- SA02: Assumes that the year 2 brolucizumab dosing frequency applies to years 3+.
- SA03: Assumes 4.0 dosing and monitoring for year 3+ for all treatments.
- SA04: Conditions the 5.7 year 3+ dosing frequency of brolucizumab by the approximate [redacted] HAWK/HARRIER year 2 adherence rate and by the 91% adherence rate for anti-VEGFs observed during year 2 IVAN study as reported and applied in NG82,
- SA05: Varies the treatment discontinuation rates for year 3+.
- SA06: A more literal application of NG82 fellow eye administration cost and monitoring cost multipliers

Table 31: ERG scenario analyses: vs TREX dosing for comparators

	Aflibercept	Ranibizumab	Bevacizumab
ERG base case (TREX)	[redacted]	[redacted]	[redacted]
SA01a. q4w SA01a. q4w -> PRN SA01a. LP -> q8w SA01a. PRN SA01a. PRNX SA02. BROL year 2 mean dose for year 3+ SA03: Year 3+ 4.0 doses for all treatments SA04a: Year 3+ brolucizumab 96% adherence SA04b: Year 3+ brolucizumab 91% adherence SA05a: Year 3+ discontinuation rates halved SA05b: Year 3+ discontinuation rates = 0% SA06: More literal NG82 FEI multipliers SA02 + SA05a SA02 + SA05b	[redacted]	[redacted]	[redacted]

Note that the SA01 dosing scenario analyses change the dosing regimen for the comparators from TREX to that specified.

The scenario analyses change the net cost estimates much as would be expected, though the application of the ranibizumab PRNX dosing for years 3+ and result in brolucizumab no longer being cost saving relative to ranibizumab,

The sensitivity of results to discontinuation rates for years 3+ is also notable. These tend to increase net savings where savings are estimated and net costs where net costs are estimated, though the effect upon the comparison with ranibizumab is limited.

Table 32: ERG scenario analyses: vs PRN dosing for comparators

	Aflibercept	Ranibizumab	Bevacizumab
ERG base case (PRN)			
SA02. BROL year 2 mean dose for year 3+ SA03: Year 3+ 4.0 doses for all treatments SA04a: Year 3+ brolucizumab [redacted]% adherence SA04b: Year 3+ brolucizumab 91% adherence SA05a: Year 3+ discontinuation rates halved SA05b: Year 3+ discontinuation rates = 0% SA06: More literal NG82 FEI multipliers SA02 + SA05a SA02 + SA05b			

The SA01 scenario analyses would be identical to those of the previous table, so are not presented.

5 ERG commentary on the robustness of evidence submitted by the company

5.1 Strengths of clinical effectiveness evidence

- The non-inferiority of brolucizumab compared with aflibercept for clinical effectiveness was supported by evidence from two high-quality, head-to-head trials and an additional phase 2 trial. Adverse event profiles appear to be similar between the two treatments.
- Brolucizumab also demonstrated superiority in some anatomic outcomes in the two pivotal trials.
- Non-inferiority of brolucizumab compared with ranibizumab for clinical effectiveness was demonstrated in an NMA, with the main evidence linking between brolucizumab and ranibizumab through high-quality, head-to-head trials including the common comparator aflibercept.

5.2 Weakness and areas of uncertainty for clinical effectiveness evidence

- Different dosing regimens, including various PRN and TREX regimens are adopted in clinical practice for treatment with comparators and these have not been directly compared with brolucizumab in RCTs. Estimation of potential drivers for treatment costs, including injection frequency, monitoring appointment and treatment discontinuation therefore relies upon evidence collected and pooled from different trials using arm-based data that do not preserve randomisation of the original trials.
- Some potentially relevant RCTs that could have contributed data towards NMA and 'baseline pooling' analyses adopted by the company to estimate injection frequency and treatment discontinuation were excluded. The ERG's assessment suggests that inclusion of additional data from these RCTs may slightly lower the estimated injection frequencies for ranibizumab and aflibercept; and may increase the estimated discontinuation rate for ranibizumab while not significantly affecting the estimated discontinuation rate for aflibercept. However detailed appraisal of individual trials will be required for assessing the appropriateness of incorporating these data.

- There are uncertainties in several parameter inputs for the cost comparison model due to lack of data, including the balance between different dosing regimens for ranibizumab and aflibercept in different years after initiation of the treatment, the monitoring schedule associated with each dosing regimen, rate of switching from every 12 weeks to every 8 weeks for brolucizumab, and validity of extrapolating a discontinuation rate from year 2 to subsequent years for all treatments.

5.3 Company cost comparison summary

Whether it is appropriate for the assessment to proceed as a cost comparison FTA rests primarily on the clinical effectiveness. The ERG critique of the cost effectiveness evidence assumes that it is appropriate for the assessment to proceed as a cost comparison FTA, and seeks to answer under what circumstances brolucizumab is likely to be cost saving, and to highlight the uncertainties around this.

The company cost comparison includes the brolucizumab PAS [redacted]

[redacted]The effect of the ranibizumab PAS and the aflibercept PAS is presented in the separate cPAS appendix.

The company presents a lifetime cost comparison model with an annual cycle. Patients are newly incident and start on a given treatment. Those who discontinue do not trial a second treatment. The perspective and discounting is as per the NICE methods guide.

Dosing frequencies for years 1 and 2 for the various possible dosing regimens are estimated by pooling single arm data from the trials of the NMA that were used for the clinical effectiveness estimates. The company base case assumes that the year 2 dosing frequencies will continue to apply for year 3+.

The intention was to assume one stop administration and monitoring. As a consequence, only the variable PRN and PRNX treatment regiments should include dedicated monitoring visits in addition to administration visits. The assumptions and costs around these are largely aligned with those of NG82.

Annual discontinuation rates are estimated from the literature and are similar across treatments. These are applied over the patient lifetime. It seems possible that short term discontinuation rates may not apply in the longer term among those who have responded to and are stabilised on their treatment.

Fellow eye involvement is also modelled, with a [redacted] annual incidence. The assumptions around this are also largely aligned with those of NG82. A possible exception is that the fellow eye is only treated if the other eye remains on treatment. This may bias any estimated net savings (costs), possibly tending to reduce them. But it seems unlikely to cause the sign of the net savings (costs) to be reversed so should not affect conclusions.

Adverse events are only included as a scenario analysis. Their inclusion has little effect upon results.

The company estimates that brolucizumab results in quite large direct drug cost savings relative to both aflibercept and ranibizumab. This is mainly due to the weighted average dosing frequencies that are applied for ranibizumab and aflibercept, and the assumption that year 2 dosing frequencies apply indefinitely thereafter. The quite high annual discontinuation rates also cause the analysis to focus on the short term and as a consequence the initial 'every 12 weeks' dosing for brolucizumab.

5.4 Company cost comparison: strengths

Much of the structure and assumptions of the company analysis mirror that of NG82.

The electronic model is simple and transparently presented.

The model cohort flows cross check with the ERG rebuild.

The dosing data extracted from the literature largely cross checks with that of the ERG and any discrepancies appear minor.

The company submission is straightforward in its presentation, with the exception of the year 3+ dosing estimates.

5.5 Company cost comparison: weaknesses

Bevacizumab is not considered as a comparator despite being specified in the scope. The company presents survey data which suggests it had a market share of little more than [redacted] in the year to August 2019. But the company cost comparison is based upon newly incident patients. As a consequence, the company survey data may be a poor guide to current and future use of bevacizumab in the modelled population, given the recent MHRA reclassification of bevacizumab ophthalmic use as "off-label".

There is little information about the company commissioned survey of 50 retinal experts.

There is no obvious reason for the company to have excluded 'every 8 weeks' and 'every 12 weeks' dosing responses for ranibizumab and 'every 12 weeks' dosing responses for

aflibercept. It seems possible that these responses could relate to TREX regimens, and relate to patients stabilised on either every 8 weeks or every 12 weeks. Other unspecified responses have also been excluded by the company. It seems questionable to pool the remaining responses to arrive at an "average" dosing regimen. The ERG prefers separate presentations of TREX and PRN dosing, which appear to be the most commonly used, with scenario analyses for the other possible dosing regimens.

The company submission states that one stop administration and monitoring is modelled, but it appears that the uplifts for fellow eye involvement may not be entirely aligned with those of NG82. This has only a limited effect upon results and does not alter conclusions.

The main company submission assumes that the mean year 2 dosing frequencies will apply for year 3+. This is at odds with the company appendix which applies the method of NG82 to estimate the year 3+ dosing frequencies for aflibercept and ranibizumab. The ERG prefers the company estimates that apply the NG82 method.

The company submission states that during the first year the majority of brolucizumab patients remained on 'every 12 weeks' dosing. This is correct but misleading. By week 92 the majority of brolucizumab patients, [redacted], had transferred to 'every 8 weeks' dosing due to a lack of response. Those transferring to every 8 weeks tended to have thicker retinas at baseline. It may be questionable whether the pooled HAWK and HARRIER 'every 8 weeks' patient population had a clinically significant response, and there is no evidence of an improved response after transferring to increasing doses i.e. every 8 weeks. As a consequence, these patients may tend to remain on every 8 weeks and not have their treatment interval subsequently extended back to every 12 weeks. If so the ERG thinks that the best estimate for the year 3+ brolucizumab dosing is the mean dosing frequency at the end of the year 2, rather than the mean dosing frequency during year 2. This has a reasonable effect upon model results. It can be argued that this should be further conditioned by adherence rates, the 91% for year 2 anti-VEGFs in IVAN as reported and applied in NG82 being an obvious possible source. The ERG calculates an approximate year 2 dosing adherence in HAWK and HARRIER of [redacted] for brolucizumab, which when applied has limited effect upon results.

The brolucizumab SmPC may be ambiguous to a degree. It can be read as limiting brolucizumab dosing to between every 8 weeks and every 12 weeks, although the company interpretation of an updated draft SmPC at factual accuracy check suggested flexibility in extensions to the dosing intervals. The aflibercept and ranibizumab SmPCs are more explicit and liberal in terms of extensions to their dosing intervals. Extensions to every 16 weeks are

being explored. If brolucizumab cannot be extended to every 16 weeks, it may result in higher costs in the medium term.

5.6 ERG analyses

The ERG revised base case(s) apply the dosing frequencies that the company estimated for year 1 and year 2. They also apply the dosing frequencies that the company estimated using the NG82 method for year 3+ for ranibizumab and aflibercept. But they apply the dosing frequency implied by the end of year 2 balance between 'every 8 weeks' dosing and 'every 12 weeks' dosing for brolucizumab for year 3+, rather than the company preferred year 2 average dosing frequency.

- The ERG also assumes an additional monitoring visits for PRN and for PRNX of 6.1 and 4.1 in year 1 respectively and 4.5 thereafter for both, drawn from NG82.

Due to expert opinion and a lack of clarity around the company survey of experts and the validity of the company pooling of the dosing regimens, the ERG presents base case analyses comparing:

- brolucizumab with TREX ranibizumab and TREX aflibercept, and
- brolucizumab with LP->PRN ranibizumab and LP->q8w->PRN aflibercept.

Brolucizumab results in lower costs than both ranibizumab and aflibercept. But note that these results do not include either the ranibizumab or the aflibercept PAS.

Brolucizumab results in higher costs compared to bevacizumab.

The ERG conducted a range of scenario analyses the more important of which are:

- Brolucizumab is cost saving with the exception of the comparison with ranibizumab PRNX.
- Any cost increases (savings) increase if year 3+ discontinuation rates are lower than year 1 and 2 discontinuation rates.
- All the ERG analyses estimate that brolucizumab results in significantly higher costs than bevacizumab, including the ERG application of the company base case assumptions and scenario analyses within this comparison.

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7 Appendix Comparison of key trials included in the NMA

Table 33: Comparability of clinical outcomes between key trials with direct comparison between brolucizumab, aflibercept and/or ranibizumab

Outcome	Trial	Brolucizumab 6 mg	Aflibercept 2 mg		Ranibizumab 0.5 mg
		Loading phase then every 12 weeks or every 8 weeks as needed (LP -> q12w/q8w)	Loading phase then every 8 weeks (LP -> q8w)	Every 4 weeks (q4w)	Every 4 weeks (q4w)
Mean change from baseline in BCVA: 1 year	OSPREY	6 (NR)*	7.2 (13.2)	-	-
	HARRIER	6.9 (11.7)	7.5 (11.7)	-	-
	HAWK	6.6 (13.5)	6.8 (13.5)	-	-
	VIEW1	-	7.9 (15)	10.9 (13.8)	8.1 (15.3)
	VIEW2	-	8.9 (14.4)	7.6 (12.6)	9.4 (13.5)
Mean change from baseline in BCVA: 2 year	HARRIER	6.1 (NR)	6.6 (NR)	-	-
	HAWK	5.9 (14.8)	5.3 (14.8)	-	-
Gained ≥ 15 letters on the ETDRS scale: 1 year	HARRIER	29.3%	29.9%	-	-
	HAWK	33.6%	25.5%	-	-
	VIEW1	-	30.6%	37.5%	30.9%
	VIEW2	-	31.4%	29.4%	34.0%
Gained ≥ 15 letters on the ETDRS scale: 2 year	HARRIER	29.1%	31.5%	-	-
	HAWK	34.2%	27.1%	-	-
Lost ≥ 15 letters on the ETDRS scale: 1 year	HARRIER	3.8%	4.8%	-	-
	HAWK	6.4%	5.6%	-	-

	VIEW1	-	5.6%	4.9%	6.2%
	VIEW2	-	4.6%	5.5%	5.2%
Lost ≥ 15 letters on the ETDRS scale: 2 year	HARRIER	7.1%	7.5%	-	-
	HAWK	8.1%	7.5%	-	-
Change in CRT: 1 year	HARRIER	-193.8 (131.6)	-143.9 (131.4)	-	-
	HAWK	-172.6 (127.1)	-143.5 (127.1)	-	-
	VIEW1	-	-128.5 (108.5)	-116.5 (98.4)	-116.8 (109)
	VIEW2	-	-149.2 (119.7)	-156.8 (122.8)	-138.5 (122.2)
Change in CRT: 2 year	HARRIER	-197.7 (134.1)	-155.1 (134.1)	-	-
	HAWK	-174.8 (137.9)	-148.7 (137.9)	-	-

Based on data reported in CS Appendices, Table 21, Pages 40-41.
*Loading phase then every 8 weeks then every 12 weeks (LP -> q8w -> q12w)

Table 34: Study characteristics and eligibility criteria for study participants (for assessing transitivity assumption)

Characteristic	HAWK[33]	HARRIER[33]	OSPREY[34]	VIEW 1 & 2 (Pooled)[8, 20]
Design	3-arm phase III 2-year double-blind multicentre RCT	2-arm phase III 2-year double-blind multicentre RCT	2-arm phase II 1-year double-blind, multicentre RCT	4-arm phase III 2-year double-blind multicentre RCTs (n=2)
Target Population	Adults over the age of 50 years with wAMD		Adults over the age of 50 years with wAMD	Adults over the age of 50 years with wAMD
Intervention(s)	Brolucizumab 6 mg LP -> q12w/q8w Brolucizumab 3mg LP -> q12w/q8w	Brolucizumab 6 mg LP -> q12w/q8w	Brolucizumab 6 mg LP-> q8w -> q12w	Aflibercept 0.5 mg q4w -> PRN Aflibercept 2 mg q4w -> PRN Aflibercept LP -> q8w -> PRN
Comparator(s)	Aflibercept LP -> q8w		Aflibercept LP -> q8w	Ranibizumab 0.5 mg q4w -> PRN
Eligibility criteria				
Inclusion criteria	• Patients ≥ 50 years at screening • Active CNV lesions secondary to AMD that affected the central subfield in the study eye at time of screening • Total area of CNV (including both classic and occult components) must have comprised >50% of the total lesion area in the study eye at time of screening and confirmed by the CRC • IRF/SRF affecting the central subfield of the study eye at time of screening • BCVA between 78 and 23 letters, in the study eye using ETDRS testing		• Patients ≥ 50 years at screening • Untreated active CNV lesion due to AMD in the study eye • Leakage on FA and subretinal, intraretinal, or subretinal pigment epithelium fluid as assessed by SD-OCT in the study eye • Total area of CNV (including both classic and occult components) must have comprised >50% of the total lesion area in the study eye • Subretinal blood, if present, must have spared the fovea and must have been ≤ 50% of the lesion in the study eye	• Patients ≥ 50 years at screening • Active subfoveal CNV lesions (any subtype) secondary to AMD; juxtafoveal lesions with leakage affecting the fovea also were allowed • CNV comprising at least 50% of total lesion size • BCVA between 73 and 25 letters

		• BCVA between 73 and 23 letters, inclusive in the study eye • Patient's fellow eye must have had a BCVA of 20 letters	
Exclusion criteria	• Any active intraocular or periocular infection or active intraocular inflammation in either eye at baseline • Central subfield of the study eye affected by fibrosis or geographic atrophy or total area of fibrosis ≥ 50% of the total lesion in the study eye at time of screening • Subretinal blood affecting the foveal centre point and/or ≥ 50% of the lesion of the study eye at time of screening • Any approved or investigational treatment for wAMD in the study eye at any time • Retinal pigment epithelial rip/tear in the study eye at baseline, vitreous haemorrhage within 4 weeks prior to baseline	• Any active intraocular or periocular infection or active intraocular inflammation in either eye at baseline • Any approved or investigational treatment for exudative AMD in the study eye • Any current or history of macular or retinal disease other than exudative AMD in the study eye • Any serous pigment epithelial detachment under the foveal centre or RPE tear/rip in the study eye • Current vitreous haemorrhage or a history of rhegmatogenous retinal detachment	• Patients with prior treatment for AMD (including an investigational agent or anti-VEGF therapy) in the study eye
Follow-up assessment of primary outcome	48 wks	12 wks, 16 wks	52 wks
LP=loading phase; ETDRS=early treatment diabetic retinopathy study; qXw=one injection every X weeks; Afli=aflibercept; Bro=brolucizumab; FA=fluorescein angiography; BCVA=best-corrected visual acuity; CNV= choroidal neovascularization; wAMD=wet age-related macular degeneration; SD-OCT=spectral-domain optical coherence tomography; wk(s)=week(s); PRN=pro re nata (as needed) dosing regimen; VEGF=vascular endothelial growth factor			

Table 35: Baseline characteristics of study participants across trials (for assessing transitivity assumption)

Characteristic	HAWK[33]			HARRIER[33]		OSPREY[34]		VIEW 1 & 2 (Pooled)[8, 20]			
	LP-Bro 3q12/q8w **n=358**	LP-Bro 6q12/q8w **n=360**	LP-Afli 2q8w **n=360**	LP-Bro 6q12/q8w **n=370**	LP-Afli 2q8 **n=369**	LP-Bro 6q8w-q12w **n=44**	LP-Afli 2q8w **n=45**	Afli 0.5q4w **pooled n=597**	Afli 2q4w **pooled n=613**	LP-Afli 2q8w **pooled n=607**	Rani 0.5q4w **pooled n=595**
Age mean (SD)	76.5 (8.7)			75.1 (8.2)		78.0 (9.4)		78.4 (8.1)	77.7 (7.9)	77.9 (8.4)	78.2 (7.6)
Sex n (%) Males	469 (43.5)			317 (42.9)		36 (40.4)		134 (44.5)	110 (36.2)	123 (40.9)	132 (43.4)
Race/ethnicity n (%)											
White	874 (81.1)			681 (92.2)		86 (96.6)		510 (85.4)	521 (85.0)	504 (83.0)	509 (85.5)
Asian	158 (14.7)			45 (6.1)		2 (2.2)		66 (11.1)	70 (11.4)	73 (12.0)	60 (10.1)
Black/African American	3 (0.3)			1 (0.1)		1 (1.1)		1 (0.2)	1 (0.2)	3 (0.5)	2 (0.3)
Hispanic	NR			NR		1 (1.1)		NR	NR	NR	NR
Other	35 (3.2)			9 (1.2)		NR		20 (3.3)	21 (3.4)	27 (4.5)	24 (4.0)
# of days since diagnosis of wAMD n (%)											
≤ 30 days	468 (43.4)			275 (37.3)		84 (94.4)		NR	NR	NR	NR
> 30 days	610 (56.6)			463 (62.7)		5 (5.6)		NR	NR	NR	NR
BCVA letters read Mean (SD)	60.6 (13.7)			61.2 (12.8)		54.8 (13.0)		53.6 (13.8)	54.0 (13.6)	53.6 (13.5)	53.9 (13.4)
BCVA letters read n (%)											
≤ 55	326 (30.2)			209 (28.3)		31 (34.8)		NR	NR	NR	NR
> 55	752 (69.8)			530 (71.7)		58 (65.2)		NR	NR	NR	NR
CST total (μm) Mean (SD)	462.5 (160.3)			469.5 (161.6)		492.9 (146.1)		NR	NR	NR	NR

CST total (μm) – n (%)							
<400	460 (42.7)	278 (37.6)	26 (29.2)	NR	NR	NR	NR
≥ 400	618 (57.3)	461 (62.4)	63 (70.8)	NR	NR	NR	NR
CRT (μm) Mean (SD)	NR	NR	NR	296 (132)	299 (126)	306 (134)	296 (123)
CFT (μm) Mean (SD)	NR	NR	NR	NR	NR	NR	NR
Type of CNV – n (%)							
Predominantly classic	351 (32.6)	298 (40.5)	44 (49.4)	161 (27.0)	159 (25.9)	159 (26.2)	152 (25.5)
Minimally classic	105 (9.7)	67 (9.1)	20 (22.5)	200 (33.5)	217 (35.4)	216 (35.6)	205 (34.5)
Occult	621 (57.7)	370 (50.3)	25 (28.1)	234 (39.2)	233 (38.0)	228 (37.6)	231 (38.8)
CNV lesion size (mm^2) Mean (SD)	4.5 (4.2)	2.8 (3.4)	NR	7.1 (4.9)	7.4 (5.5)	7.2 (5.4)	7.1 (5.3)
Presence of fluid – n (%)							
SRF	739 (68.6)	519 (70.2)	80 (89.9)	NR	NR	NR	NR
IRF	584 (54.2)	288 (39.0)	76 (85.4)	NR	NR	NR	NR
SRF and/or IRF	NR	NR	NR	NR	NR	NR	NR
Sub-RPE	473 (43.9)	252 (34.1)	NR	NR	NR	NR	NR

BCVA=best-corrected visual acuity; CST= central subfield (retinal) thickness; SRF=subretinal fluid; IRF=intraretinal fluid; CNV= choroidal neovascularization; CRT= central retinal thickness; CFT= central foveal thickness; wAMD=wet age-related macular degeneration; RPE=retinal pigment epithelium

8 Addendum

This addendum describes further revisions made to the main ERG report (presented earlier in Chapter 1 to 7) since its initial completion in January 2020. The revision focuses on modelling and the results are referred to as 'addendum base case' and 'addendum scenario analyses' to allow easy distinction between the updated findings and the results presented in the main ERG report. Results presented in this addendum reflect the updated position of the ERG following the receipt of further information from the company after the factual accuracy check and discussions between ERG and NICE technical team on technical issues.

8.1 Summary of the ERG's dosing and monitoring assumptions in the main report

This section summarises ERG's further explanation (dated 30 January 2020) of key modelling assumptions *before* the ERG received the company's response to factual accuracy check and provision of further information in March 2020.

The ERG base case differs from the company base case in terms of dosing and monitoring in four main ways.

1. The ERG concentrates upon TREX and PRN dosing for aflibercept and ranibizumab, while the company pools estimates across a range of regimens based upon the company survey of 50 retinal experts.
2. For brolucizumab the ERG applies the HAWK/HARRIER week 92 proportions on q12w dosing and q8w dosing to estimate the average dose for years 3+, while the company applies the HAWK/HARRIER year 2 average dose for years 3+ despite the proportions on q8w increasing throughout year 2.
3. The ERG applies the company's year 3+ dosing estimates that use the NG82 method for the aflibercept and ranibizumab variable TREX and PRN dosing regimens, as presented in the company appendix, while the company assumes year 2 dosing will continue for years 3+ for the aflibercept and ranibizumab variable TREX and PRN dosing regimens.
4. The ERG derives different numbers of dedicated monitoring visits for PRN dosing regimens from NG82 compared to those of the company, despite both referencing the SALUTE trial.

The reasons for the ERG approach are summarised below.

8.1.1 TREX and PRN dosing instead of company pooling

Submissions by NHS and professional organisations as well as ERG expert opinion suggest that most patients are treated using TREX, though some centres may treat using PRN if clinic arrangements are ill suited to one stop monitoring and treatment. ERG expert opinion suggests that the current goal of TREX is typically to achieve q12w, though not all patients do so.

The company was unable to provide any additional data about its survey of 50 retinal experts. There is no information about the degree of agreement or divergence of the individual responses, the number of patients per respondent, or the degree to which a minority of respondents may have skewed results. There is no information on the "other" dosing regimens which the company rejects: perhaps some were already trialling aflibercept q16w. The company survey may not have permitted q16w responses, but this not clear.

There is no information available about the company survey other than the questions that were asked and the final results.

The company survey asked about the experts' [redacted]. Given the difference in observed dosing frequencies between years 1 and 2 for the variable frequency treatment regimens the lack of clarity in the question about duration of prior treatment is a weakness. TREX and PRN do not preclude patients being treated q4w, q8w or q12w for a period, or indeed for the duration of their future treatment.

The company rejects responses of q8w and q12w dosing for ranibizumab, and q12w dosing for aflibercept. This skews the company estimated dosing frequencies. There is no explanation of or exploration of why non-trivial proportions were reported for q8w and q12w. Perhaps these patients were being treated with q8w or q12w dosing under TREX or PRN and were reported as q8w or q12w rather than as TREX or PRN.

It is possible that some reported as q4w were in a unit where TREX is practised but were not suitable for extension, or were on q4w and if remained stable would have their treatment interval extended under TREX. The latter should not have their dosing extrapolated over their lifetime as q4w. The TREX and PRN trials presumably may have included some patients

who did not extend, with these patients also contributing to the annual average dosing frequencies in these trials.

An additional though perhaps less immediately relevant concern is that if TREX and PRN are now being pushed to q16w some patients with lengthy dosing frequencies could fall out of the "[redacted]" window of the survey. It is an oddly precise phrase to use. To the ERG "remaining on anti-VEGF treatment" is more general and reasonable.

Given the above the ERG was unwilling to pool the dosing regimens and instead examined individual dosing regimens, focussing upon TREX and PRN but with the other regimens presented as scenario analyses.

8.1.2 Brolucizumab proportions on q8w and q12w: End of Trial and year 3+

At the end of the trials and year 2 the average proportion of patients on q8w brolucizumab rather than q12w brolucizumab was [redacted]%. This suggests an average annual dosing frequency of 5.7 doses.

It can also be noted that in response to the ERG clarification question C1 the company responded: "The recommended dose is 6 mg (0.05 mL) administered every four weeks (monthly) for the first three doses (loading dose phase). 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, a q12w dosing regimen should be considered. In patients with disease activity, a q8w dosing regimen should be considered. Physicians may further individualise treatment intervals based on disease activity.[35]

[redacted] [*ERG emphasis*]" though in free text slightly qualified this by adding "In summary, routine brolucizumab dosing **is not expected** [*ERG emphasis*] to fall outside the q12w to q8w range". To the ERG this suggests that the company views the draft SmPC as specifying that brolucizumab should be given either as q8w or q12w, and that it is not possible to lengthen the treatment interval beyond q12w.

As a consequence, though the majority of brolucizumab patients transferring from q12w to q8w by week 92 which is in a sense variable dosing, the ERG thinks it is more appropriate to treat brolucizumab as a fixed dosing regimen than as a variable dosing regimen akin to TREX or PRN.

The ERG base case can be criticised for not applying a dosing adherence estimate to the brolucizumab dosing regimen for years 3+. NG82 estimated a 91% dosing adherence for the fixed interval dosing regimens. The data available to the ERG suggests a year 2 dosing adherence during HAWK and HARRIER of around [redacted]. The ERG applies this estimate in a scenario analysis with limited effect. Due to the proportion transferring to q8w and the data available to the ERG, there remains some uncertainty about the year 2 treatment adherence rate for brolucizumab.

Among those who were on q8w dosing at week 48 and among those who were on q8w dosing at week 96 the benefits of treatment in terms of CSFT and BCVA occurred relatively early in the trials, before they were switched to q8w dosing. In the opinion of the ERG this suggests that if these patients remain on brolucizumab they are likely to remain on q8w dosing rather than subsequently have their administration lengthened back to q12w dosing.

There is an argument that those transferring to brolucizumab q8w dosing during the trials would in practice, given the changes in mean BCVA during HAWK and HARRIER among this subgroup, have their brolucizumab withdrawn and be trialled on another anti-VEGF. This may come to be the case, but the company cost comparison model does not consider treatment switching among non-responders. There is also the caveat of the baseline differences between those switching to brolucizumab q8w and those remaining on q12w dosing; e.g. those switching to q8w had notably thicker baseline CSFT. These patients may be harder to treat and might tend to have higher dosing than the average patient if switched to ranibizumab or aflibercept TREX or PRN. These considerations and a lack of evidence complicate formal consideration of treatment switching, both from brolucizumab to other anti-VEGFs and from other anti-VEGFs to brolucizumab, within a cost comparison model.

8.1.3 TREX and PRN year 3+ estimates instead of reapplying year 2

The company base case simply reapplies the year 2 dosing frequency to years 3+.

For fixed dosing regimens, due to loading doses, the number of injections differs between year 1 and year 2. But the year 2 value for fixed dosing regimens does apply to years 3+.

This is not the case for the variable dosing regimens: TREX and PRN. NG82 used dosing data from the ARMD database to estimate a year 3 mean number of injections of 3.7 for ranibizumab PRN. Year 3 data was not available for the other variable dosing regimens. NG82 assumed that their year 3 dosing would be the same proportion of the 3.7 ranibizumab

PRN year 3 dosing as the proportion that their year 2 dosing relative to the ranibizumab year 2 dosing. The company calculations that apply the NG82 method are presented in table 25 of the ERG main report.

The ERG prefers the NG82 method for the variable dosing regimens mainly due to the amount of work, consideration and consultation that went into NG82. It is also appealing in itself given that the goal of the variable dosing regimens is to extend the treatment interval and that the NG82 year 3 dosing data for ranibizumab PRN suggests that this occurs. It is possible that this will still overestimate the dosing required for aflibercept and ranibizumab TREX and PRN if these are now being pushed to q16w. It is also possible that this was the initial approach of the company until its implications became clear. The ERG would not be comfortable rejecting the NG82 approach, particularly if this would imply that NG82 got it all wrong.

All dosing estimates for aflibercept and ranibizumab in the ERG base case(s) are company estimates. The year 1 and year 2 dosing estimates for brolucizumab in the ERG base case(s) are company estimates. The only dosing estimate derived by the ERG is the year 3+ dosing estimate for brolucizumab of 5.7, based upon the end of trial proportions on q8w and q12w as outlined in section 8.1.2 above.

The dosing estimates applied in the ERG base case(s) are presented below.

Table 36 ERG base case(s) dosing frequencies

		TREX		PRN	
	Brolucizumab	Aflibercept	Ranibizumab	Aflibercept	Ranibizumab
Year 1	6.7	9.7	9.5	7.1	7.1
Year 2	4.8	7.3	8.2	5.0	5.6
Year 3+	5.7	4.1	4.5	3.2	3.7

8.1.4 Dedicated monitoring visits for PRN

As summarised in greater detail in section 4.2.3.4 of the main ERG report, for PRN dosing the ERG relies on the estimates of NG82 for the estimates of the dedicated monitoring visits that are required in addition to administration visits: 6.1 in year 1 and 4.5 in years 2+. NG82 suggests that its estimates were based upon the SALUTE trial, though as outlined in section 4.2.3.4 of the main ERG report there is some ambiguity in its presentation.

This differs from the company despite the company also relying upon the SALUTE trial. The company estimates additional dedicated monitoring visits for:

- aflibercept LP->q8w->PRN of 0.0 for year 1 and 7.7 for year 2+; and,
- ranibizumab LP->PRN of 5.8 for year 1 and 7.1 for year 2+.

The reasons for the discrepancies between the ERG and the company are unclear.

8.2 ERG comments on company's response (received 3 March 2020) to ERG dosing and monitoring assumptions

This section presents ERG's further comments after receiving the company's response to factual accuracy check in February 2020 and supply of additional information in March 2020.

8.2.1 Anticipated brolucizumab dosing

The ERG accepts that the revised draft brolucizumab SmPC permits variable dosing with brolucizumab. But the only brolucizumab dosing information available is from the HAWK and HARRIER trials.

HAWK and HARRIER after the loading phase placed all patients on q12w (every 12 weeks), but required those with insufficient response to have the dosing frequency increased to q8w (every 8 weeks). Ranibizumab and aflibercept PRN and TREX dosing regimens start with a loading phase and then permit the dosing interval to be extended.

The ERG still thinks that the dosing in the HAWK and HARRIER trials should not be viewed as a variable dosing regimen in the same sense as ranibizumab and aflibercept PRN and TREX dosing regimens. As a consequence, the ERG also rejects the company application of the NG82 method for estimating the year 3+ dosing for variable dosing regimens to the HAWK/HARRIER data.

The ERG accepts during HAWK and HARRIER the patients with insufficient response who had their dosing frequency increased to q8w were not permitted to be rechallenged with q12w dosing. ERG expert opinion is that in practice some q8w patients would be rechallenged with

q12w dosing. But there is no information about what proportion would be rechallenged with q12w dosing, and among those who are rechallenged with q12w dosing what proportion would have to return to q8w dosing.

This means that the ERG extrapolation of the end of HAWK/HARRIER year 2 dosing is likely to overestimate brolucizumab use in practice, and so is biased against brolucizumab. There is no information about the extent of this bias.

The company suggests that some experts think that year 3+ dosing for brolucizumab may be lower than the year 2 average. It is unclear what information the company provided these experts with. The original company submission and the published paper are keen to stress that the majority of patients in HAWK/HARRIER remained on q12w dosing at week 48. They do not mention that the majority of patients in HAWK/HARRIER were on q8w dosing at week 96.

The ERG main report provided a scenario analysis that applied the company preferred HAWK/HARRIER year 2 average to years 3+ (SA02), and a scenario analysis that applied 4.0 doses to years 3+ for all treatments (SA03).

8.2.2 Application of the NG82 method to estimate year 3+ dosing for variable interval regimens

The company repeatedly states that the ERG applies the method of NG82 to derive dosing estimates for the variable dosing TREX and PRN regimens for years 3+. This is incorrect. Table 42 of the company submission appendices supplies the company estimates for the variable dosing TREX and PRN regimens for years 3+ which the company derived by applying the method of NG82. The ERG only ever applies the company dosing estimates for these regimens.

The 3.7 mean number of ranibizumab injections for year 3 PRN ranibizumab is taken from Tufail et al (2014).[3] This was based upon an analysis the electronic medical records of 14

[3] Tufail A, et al. The Neovascular Age-Related Macular Degeneration Database: Multicenter Study of 92 976 Ranibizumab Injections. Report 1: Visual Acuity. Ophthalmology 2014;121:1092-1101

NHS centres in England and Northern Ireland treating patients with loading doses of ranibizumab, followed by ranibizumab PRN. Virtually all patients were being treated with ranibizumab, very few having been switched to bevacizumab, <1% in 1 of the 14 centres.

The company suggests that the 3.7 year 3+ dosing estimate that it applies in its Appendices Table 42 (also shown in ERG main report Table 25) may be too low due to patients discontinuing ranibizumab treatment. Within the Tufail et al supplementary data the number of ranibizumab injections in year 3 among the eyes followed up for at least three years includes around 8.5% of eyes with 0 injections in year 3: 78 eyes out of 917 (values taken from graph). These patients may have either not needed treatment in year 3 or have discontinued treatment.

The 8.5% can be read alongside the 7.9% annual discontinuation rate for ranibizumab within the company cost comparison model.

The ERG values taken from the graph suggest mean year 3 injections of 3.9 when those with 0 injections in year 3 are included and of 4.3 when those with 0 injections in year 3 are excluded. The 3.9 is not exactly aligned with the 3.7 reported in Tufail et al, but suggests a multiplier of 4.3 / 3.9 = 1.09. This suggests possibilities of additional scenario analyses that could be explored by applying the ERG multiplier to the company estimates as below.

Table 37: Revised Table 25 of the ERG main report - Company's Year 3+ dosing estimates (data source: CS Appendix D, Table 42, Page 90), showing revised Year 3+ dosing estimates with ERG multiplier applied

	Trial arms		Yr2 Injections		Ratios			
Trial	Arm1	Arm2	Arm1	Arm2	Trial (Arm1/Arm 2)	Arm 1 relative to RANI RPN	Yr3+ Inj.	Revised (with multiplier 1.09)
NARMD	RANI PRN	..	..	..	..	1 (Ref)	3.7	4.0
VIEW1&2	AFLI PRN	RANI PRN	4.9	5.6	0.88	0.88	3.2	3.5
CATT[1]	RANI q4w	RANI PRN	22.4	12.6	1.78	1.78	..	..
TREX-AMD	RANI TREX	RANI q4w	8.5	12.5	0.68	1.21	4.5	4.9
RIVAL	ALFI TREX	RANI TREX	7.3	8.0	0.91	1.10	4.1	4.4
SALUTE[2]	RANI PRNX	RANI PRN	5.5	6.4	0.86	0.86	3.2	3.5
VIEW1&2	AFLI PRNX	RANI PRNX	4.9	5.6	0.88	0.75	2.8	3.0

[1]Year 1 and 2 data [2]Year 1 data

Note that Tufail et al infer mean numbers of visits of 8.2 in year 3 for ranibizumab PRN, suggesting monitoring visits additional to treatment visits of 4.5 in year 3. This is aligned with the ERG values taken from NG82.

8.2.3 Company second expert survey (supplied in company submission dated 3 March 2020)

The ERG thinks that the questions posed in the second company expert survey are not neutrally phrased but are highly leading. Some elements are impossible to disagree with: e.g. We believe that in clinical practice that patients will be able to re-extend from q8wk to q12wk **if clinically appropriate** [ERG emphasis]. The responses the company wants from the respondents are more than obvious.

The company incorrectly suggests that the ERG has not considered fixed dosing regimens in section 8.1 of the company response (3 March 2020).

The company experts in section 8.1 of company response (3 March 2020) suggest that when fixed dosing is used it is mainly limited to the first year of treatment. This is not easily reconciled with the responses to section 8.2 of the response. The ERG thinks that section 8.2 of the response also suggests that the experts think variable dosing regimens may be underestimated for ranibizumab, though the responses taken as a whole are not unambiguous.

The previous ERG comments on dosing and the q4w responses of the original company survey can be read alongside section 8.1 of the company response (3 March 2020). It should also be borne in mind that for q4w dosing the company cost comparison model assumes q4w dosing for all years that the patient remains on treatment, and does not limit this to the early years or year 1.

The ERG doubts that the company has communicated sufficient information for the respondents to judge whether 4.76 or 5.7 is a more reasonable value to extrapolate.

There does appear to be reasonable consensus that capacity constraints may have limited the number of ranibizumab PRN doses to 3.7 in year 3 of the study used by the company and NG82, and that visual outcomes would have been affected. But note that Tufail et al, the source for the 3.7 year 3 estimate, report a mean loss of only 2 letters in year 3.

The ERG has further examined Tufail et al. While not an argument made by the company, the ERG notes that Tufail et al report mean doses for years 1, 2 and 3 of 5.7, 3.7 and 3.7 respectively. The values for year 1 and year 2 are somewhat below those of both NG82 and the company NMA estimates. It can also be noted that there was no decline in the average number of doses between year 2 and year 3. In the light of this, the ERG agrees that dosing in the Tufail et al study is below that which more usually applies, and that this may have been due to capacity constraints.

8.3 Revised ERG dosing and monitoring assumptions and ERG addendum base case and scenario analyses

8.3.1 Introduction to ERG addendum base case and scenario analyses

The above, coupled with the comments in the main ERG report, makes it difficult to use the company dosing estimates for years 3+ which apply the NG82 method for variable dosing regimens for ranibizumab and aflibercept. Given the nature of the HAWK/HARRIER trials the ERG also rejects applying the NG82 method to the HAWK/HARRIER trial data to estimate dosing for years 3+. In short, there appears to be no readily comparable dosing data for years 3+.

Given the clinical effectiveness conclusions and the possibility of re-challenging brolucizumab q8w patients with q12w dosing, the most straightforward approach for the ERG revised base case presented in this addendum is to assume the same 4.0 doses for years 3+ for all comparators. The other possible dosing regimens can then be explored as sensitivity analyses.

The ERG made one further change in PRN monitoring assumption during the preparation of this addendum. The NICE technical team outlined that in the PRN set of analyses for the previous ERG base case, or starting analysis, the common annual dosing of 4.0 injections implied 4.0 injection visits, but that none of the treatments had the additional 4.5 year 3+ PRN monitoring visits added to them.

The ERG was relatively unconcerned by this because the similarity of treatments' discontinuation rates meant that adding common additional monitoring costs to all treatments would largely net out. But there is an inconsistency in that brolucizumab was in effect assumed to transition from fixed dosing in years 1 and 2 to PRN dosing in year 3 without incurring the additional 1st year PRN monitoring visit costs. On reflection this seems unreasonable, so for the ERG revised PRN base case, the ERG assumes an additional 6.1 monitoring visits in year 3: the first year of brolucizumab PRN dosing.

There is uncertainty as to the additional dosing that would be required for aflibercept LP→q8w→PRN as the move from loading phase to dose extension to PRN is more gradual

than for the other treatments. This is reflected in the company dosing and monitoring assumptions for aflibercept, which the ERG applies. The company suggests that an additional 1.6 monitoring visits should be added to aflibercept PRN to equalise its monitoring visits with those of brolucizumab. This would add £183 to the aflibercept costs.

Note that the above considerations only apply when brolucizumab is assumed to be being dosed as PRN on the same basis as aflibercept and ranibizumab, with a common 4.0 injections annually from year 3. For the scenarios where brolucizumab in years 3+ is being dosed at the HAWK/HARRIER end of year 2 or year 2 average this is viewed as still being a fixed brolucizumab dosing regimen compared to the PRN dosing regimens for ranibizumab and aflibercept. Consequently, the PRN additional monitoring visits are not added to the brolucizumab arm.

8.3.2 Read across between the main ERG report and ERG addendum

The dosing assumptions between the main report and ERG addendum analyses presented below are broadly the same with only ordering of the scenario analyses changing.

Table 38: Read across between dosing analyses in the ERG main report and addendum

Analysis	Main report	ERG addendum
All treatments year 3+ 4.0 injections	SA03	Addendum base case*
BROL 5.7 year 3+, other Tx company NG82 dosing estimates	Base case	Addendum SA02
BROL 5.7 year 3+, other regimens company estimates	SA01	Addendum SA01
BROL 4.8 year 3+, other Tx company NG82 dosing estimates	SA02	Addendum SA03
BROL dosing conditioned by adherence rates	SA04	n.a.
Varying discontinuation rates for year 3+	SA05	Addendum SA04
More literal application of NG82 FEI costs	SA06	n.a.
*The read across is imperfect for ERG PRN addendum base case due to the considerations outlined in section 8.3.1 above.		

8.3.3 Dosing and monitoring assumptions of ERG addendum (16 June 2020)

The dosing assumptions for the ERG addendum base case, addendum SA02 and addendum SA03 are presented below. Addendum SA01 applies the dosing estimates of the company submission for the comparator treatment regimens. Addendum SA04 applies the dosing assumptions of the ERG addendum base case.

Table 39: ERG addendum Base Case: TREX

	BROL	AFLI	RANI
Administration frequencies			
Year 1	6.7	9.7	9.5
Year 2	4.8	7.3	8.2
Year 3+	4.0	4.0	4.0
Monitoring frequencies (total visits)			
Year 1	6.7	9.7	9.5
Year 2	4.8	7.3	8.2
Year 3+	4.0	4.0	4.0

Table 40: ERG addendum SA02: TREX

	BROL	AFLI	RANI
Administration frequencies			
Year 1	6.7	9.7	9.5
Year 2	4.8	7.3	8.2
Year 3+	5.7	4.1	4.5
Monitoring frequencies (total visits)			
Year 1	6.7	9.7	9.5
Year 2	4.8	7.3	8.2
Year 3+	5.7	4.1	4.5

Table 41: ERG addendum SA03: TREX

	BROL	AFLI	RANI
Administration frequencies			
Year 1	6.7	9.7	9.5
Year 2	4.8	7.3	8.2
Year 3+	4.8	4.1	4.5
Monitoring frequencies (total visits)			
Year 1	6.7	9.7	9.5
Year 2	4.8	7.3	8.2
Year 3+	4.8	4.1	4.5

Table 42: ERG addendum Base Case: PRN

	BROL	AFLI	RANI
Administration frequencies			
Year 1	6.7	7.1	7.1
Year 2	4.8	5.0	5.6
Year 3+	4.0	4.0	4.0
Monitoring frequencies (total visits)			
Year 1	6.7	7.1	13.2
Year 2	4.8	9.5	10.1
Year 3	10.1	8.5	8.5
Year 4+	8.5	8.5	8.5

Table 43: ERG addendum SA02: PRN

	BROL	AFLI	RANI
Administration frequencies			
Year 1	6.7	7.1	7.1
Year 2	4.8	5.0	5.6
Year 3+	5.7	3.2	3.7
Monitoring frequencies (total visits)			
Year 1	6.7	7.1	13.2
Year 2	4.8	9.5	10.1
Year 3+	5.7	7.7	8.2

Table 44: ERG addendum SA03: PRN

	BROL	AFLI	RANI
Administration frequencies			
Year 1	6.7	7.1	7.1
Year 2	4.8	5.0	5.6
Year 3+	4.8	3.2	3.7
Monitoring frequencies (total visits)			
Year 1	6.7	7.1	13.2
Year 2	4.8	9.5	10.1
Year 3+	4.8	7.7	8.2

8.3.4 ERG addendum base case (16 June 2020)

The ERG model amendments for the addendum are limited to:

- Assuming the same 4.0 year 3+ dosing for all comparators for the variable dosing regimens.
- Assuming additional monitoring visits for PRN and for PRNX of 6.1 and 4.1 respectively in year 1, and 4.5 thereafter for both, drawn from NG82.

Note that for the comparison with PRN comparators, for the common dosing assumption of 4.0 for year 3+ it is similarly assumed that brolucizumab patients have moved to PRN dosing in year 3. In effect year 3 is year 1 of brolucizumab PRN and as a consequence as additional 6.1 monitoring visits are incurred in year 3, but only 4.5 thereafter.

Table 45: ERG addendum base case: brolucizumab vs TREX comparators

	Brolucizumab	Aflibercept	Ranibizumab	Bevacizumab
Drug	[redacted]	£39,043	£28,177	£2,506
Admin	[redacted]	£3,740	£3,989	£3,989
OCT	[redacted]	£3,520	£3,743	£3,743
FFA	[redacted]	£207	£209	£209
AE	[redacted]	£0	£0	£0
Total	[redacted]	£46,510	£36,118	£10,447
Net		[redacted]	[redacted]	[redacted]

Note that for PRN aflibercept the dosing is based upon the company estimated for LP->q8w->PRN and for PRN ranibizumab the dosing is based upon the company estimates for LP->PRN.

Table 46: ERG addendum base case: brolucizumab vs PRN comparators

	Brolucizumab	Aflibercept	Ranibizumab	Bevacizumab
Drug	[redacted]	£34,205	£24,818	£2,207
Admin	[redacted]	£3,253	£3,490	£3,490
OCT	[redacted]	£5,469	£6,510	£6,510
FFA	[redacted]	£207	£209	£209
AE	[redacted]	£0	£0	£0
Total	[redacted]	£43,134	£35,026	£12,415
Net		[redacted]	[redacted]	[redacted]

8.3.5 ERG addendum scenario analyses (16 June 2020)

The ERG addendum scenario analyses are as follows.

- Addendum SA01: Applies the company estimates of dosing and monitoring frequencies for the other dosing regimens for the comparators, while applying the end of year 2 mean 5.7 dosing for brolucizumab. For this scenario brolucizumab is viewed as a fixed dosing regime, and so does not incur any of the additional PRN monitoring visits.
- Addendum SA02: Applies the estimates of the company that used the NG82 method for the comparator dosing in years 3+, while applying the end of year 2 mean 5.7 dosing for brolucizumab. For this scenario brolucizumab is viewed as a fixed dosing regime, and so does not incur any of the additional PRN monitoring visits.
- Addendum SA03: Applies the estimates of the company that used the NG82 method for the comparator dosing in years 3+, while applying the year 2 HAWK/HARRIER brolucizumab dosing frequency for years 3+. For this scenario brolucizumab is viewed as a fixed dosing regime, and so does not incur any of the additional PRN monitoring visits.
- Addendum SA04: Varies the treatment discontinuation rates for year 3+.

In light of the ERG 11 March 2020 response to the additional company submission the ERG provides the following additional scenario analyses.

- Addendum SA05: Applying the company weighted averaging to the different aflibercept and ranibizumab dosing regimens. Note that this excluded the company survey responses of q8w and q12w for ranibizumab and q12w for aflibercept. This is a weighted mean of the net costs/savings of the TREX and PRN base cases, alongside SA01a and SA01c. Note that SA01a and SA01c retain the original ERG dosing assumptions, as it seems unreasonable to unilaterally apply a year 3+ dosing assumption of 4.0 for brolucizumab in these analyses. This addendum scenario differs from the company approach, which weights the dosing to arrive at mean doses and reports the implied costs/savings of these mean doses.

Table 47: ERG addendum scenario analyses: vs TREX dosing for comparators

	Aflibercept	Ranibizumab	Bevacizumab
ERG addendum base case (TREX)	[redacted]	[redacted]	[redacted]
Addendum SA01a. q4w	[redacted]	[redacted]	[redacted]
Addendum SA01b. q4w -> PRN	[redacted]	[redacted]	[redacted]
Addendum SA01c. LP -> q8w	[redacted]	[redacted]	[redacted]
Addendum SA01d. PRN	[redacted]	[redacted]	[redacted]
Addendum SA01e. PRNX	[redacted]	[redacted]	[redacted]
Addendum SA02. Yr 3+ Co. NG82 dosing + 5.7 BROL	[redacted]	[redacted]	[redacted]
Addendum SA03: Yr 3+ Co. NG82 dosing + BROL yr 2 mean	[redacted]	[redacted]	[redacted]
Addendum SA04a: Yr 3+ discontinuation rates halved	[redacted]	[redacted]	[redacted]
Addendum SA04b: Yr 3+ discontinuation rates = 0%	[redacted]	[redacted]	[redacted]
Addendum SA05: Company weighted average	[redacted]	[redacted]	[redacted]

Table 48: ERG addendum scenario analyses: vs PRN dosing for comparators

	Aflibercept	Ranibizumab	Bevacizumab
ERG addendum base case (LP->PRN)	[redacted]	[redacted]	[redacted]
Addendum SA02. Yr 3+ Co. NG82 dosing + 5.7 BROL	[redacted]	[redacted]	[redacted]
Addendum SA03: Yr 3+ Co. NG82 dosing + BROL yr 2 mean	[redacted]	[redacted]	[redacted]
Addendum SA04a: Yr 3+ discontinuation rates halved	[redacted]	[redacted]	[redacted]
Addendum SA04b: Yr 3+ discontinuation rates = 0%	[redacted]	[redacted]	[redacted]

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

ERG responses to company's ERG report factual accuracy check

Brolucizumab for treating wet age-related macular degeneration [ID1254]

Issue 1 Interpretation of brolucizumab SmPC posology wording

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Throughout the report, the ERG highlights the uncertainty in the SmPC wording for brolucizumab and speculates on Novartis' possible interpretation of the wording and the limitations for brolucizumab dosing regimens. **Page 8:** The report highlights the "uncertainty in the interpretation of the Summary of Product Characteristics (SmPC) for brolucizumab with regard to whether regimens with dosing intervals longer than every 12 weeks are	Proposed amendments: **Page 8:** "[redacted]." **Page 36 (#5):** ~~*"Whether the brolucizumab SmPC permits TREX and PRN to extend brolucizumab dosing beyond every 12 weeks to every 16 weeks."*~~ **Page 37:** [redacted]	[redacted], in line with the ERG interpretation of the dosing regimens for ranibizumab and aflibercept. As previously noted in the clarification response, the referenced SmPC was a draft SmPC and was therefore subject to change based on ongoing consultation with the EMA. An updated draft SmPC is available to support our interpretation of the posology. A copy of the latest SmPC	No factual error, since the ERG report was written before the updated draft SmPC was made available. The revised ERG report (Page 8, Page 36, Page 38 and Page 60-61) takes note of the text in the updated draft SmPC. During the preparation of this response, the ERG became aware that brolucizumab was approved by the European Medicines Agency on 18 February 2020, and [redacted]. The

permitted, and whether such dosing regimens will be adopted in clinical practice in the future” **Page 36:** The ERG considers one of the cost drivers of the cost-comparison analysis to be: “Whether the brolucizumab SmPC permits TREX and PRN to extend brolucizumab dosing beyond every 12 weeks to every 16 weeks.” **Page 37:** When quoting the SmPC posology wording verbatim, the ERG report states: “The recommended dose is 6 mg (0.05 ml) administered by intravitreal injection every 4 weeks (monthly) for the first three doses. Thereafter, Beovu is administered every 12 weeks (3 months). The physician may individualise treatment intervals based on disease activity as assessed by visual acuity and/or anatomical parameters. The treatment interval could be as frequent as every 8 weeks (2 months).”	**Page 38***:* “[redacted] ***Page 59****: ~~“The brolucizumab SmPC may be ambiguous to a degree. It can be read as limiting brolucizumab dosing to between every 8 weeks and every 12 weeks. This appears to be the company interpretation of the draft SmPC. If so this could limit extensions to the dosing frequency.~~* [redacted] **Page 59–60:** *~~“If brolucizumab cannot be extended to every 16 weeks, it may result in higher costs in the medium term”~~*	for brolucizumab has been included alongside this response form.	ERG has kept the mark-up of the text from the updated draft SmPC as CIC, [redacted]. Formally the updated draft SmPC constitutes new data. The ERG supplies a short addendum at the end of this document (see ERG addendum 1) to highlight the differences in posology wording between different versions of the SmPC made available to the ERG.

Page 38: "Company clarification appears to suggest, though it is not entirely unambiguous, that it views the brolucizumab SmPC as only permitting dosing between every 12 weeks and every 8 weeks: an annual frequency of 4.35 or 6.52 based upon a month being 4 weeks." **Page 59:** "The brolucizumab SmPC may be ambiguous to a degree. It can be read as limiting brolucizumab dosing to between every 8 weeks and every 12 weeks. This appears to be the company interpretation of the draft SmPC. If so this could limit extensions to the dosing frequency. **Page 59–60:** The report speculates on the consequences of a statement that is incorrect: "If brolucizumab cannot be extended to every 16 weeks, it may result in higher costs in the medium term"			

Issue 2 Reporting of aflibercept posology wording

Description of problem	Description of proposed amendment	Justification for amendment	
Page 38: The ERG describes potential annual injection frequencies for brolucizumab (proposed amendment above, for page 38) and aflibercept: "This suggests that dosing with aflibercept can be as infrequent as four monthly: an annual frequency of 3.26 based upon a month being 4 weeks" These statements are misleading and could lead to misinterpretation as they do not state that they are associated with the assumption that 100% of patients would receive a given regimen. A similar amendment for brolucizumab would also be appropriate. (Suggested above, in Issue 1).	Proposed amendments: **Page 38:** *"This suggests that dosing with aflibercept can be as infrequent as four monthly**: if 100% of patients were to receive four monthly dosing, this would equate to an annual frequency of 3.26 based upon a month being 4 weeks**"*	Accurate reporting of injection frequency calculations to avoid incorrect interpretation.	No factual error. No revision required. If the ERG text is to be criticised it is that dosing might be even less frequent for those on this regimen due to less than 100% adherence to treatment.

Issue 3 List of key uncertainties

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 8: The ERG highlights their #1 area of uncertainty as the "appropriateness of excluding bevacizumab as a comparator in the cost comparison". Later the ERG state that: "Acknowledging the complexity of the clinical context, the ERG concluded that the omission of bevacizumab from the list of comparators in the company submission does not directly impact upon its cost comparison case"	**Page 8**: ~~*"appropriateness of excluding bevacizumab as a comparator in the cost comparison".*~~ *(*Propose removal from the list of key uncertainties). **Page 8*, (after list of key uncertainties): An additional factor to consider is the appropriateness of excluding bevacizumab as a comparator in the cost-comparison.***	Ensuring consistency across ERG report.	No factual error, no change required

Issue 4 Reporting of supportive clinical evidence

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 23: The ERG highlight evidence from the FLUID trial of ranibizumab in wet AMD, which showed that "a more relaxed TREX regimen tolerating some subretinal fluid was comparable in clinical effectiveness to a more	Proposed amendment **Page 23:** *"In the FLUID trial, a more relaxed TREX regimen tolerating some subretinal fluid was comparable in clinical effectiveness to a more intensive TREX regimen aiming for resolving all subretinal fluid and required fewer*	Ensuring the interpretation is not reliant on one study, and that a range of published evidence is included.	The point made by the company is reasonable, but there is no factual error. The statement about the FLUID trial is correct. In an ideal world, the ERG would carry out a systematic review of all

intensive TREX regimen aiming for resolving all subretinal fluid and required fewer injection (15.8 vs 17) over two years.[1] This could drive the number of injections using TREX regimens further down if similar approaches are adopted in clinical practice" It is important to highlight a wider portfolio of relevant evidence in order to avoid misinterpretation of the data presented.	*injection**s** (15.8 vs 17) over two years.[1] This could drive the number of injections using TREX regimens further down if similar approaches are adopted in clinical practice.* ***However, the AURA study found that increased injection and monitoring frequencies, and increased rates of re-treatment in the UK compared with other countries, resulted in improved visual outcomes compared to reduced frequencies.[2]"***		comparator dosing studies but that is not possibly in the STA/FTA system. We have added a comment on the AURA study to the ERG report (Page 23) as follows: "*However, separate evidence from an international, retrospective, observational study (AURA) of ranibizumab in wet AMD suggested that the relatively high injection and monitoring frequencies in the UK compared with other countries were associated with better visual outcomes."*

Issue 5 Description of modelling approach

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 51: The ERG comments on the potential modelling approach for brolucizumab, classifying it as a fixed dosing regimen: "If brolucizumab was viewed as a variable dosing schedule, perhaps treat and reduce, a similar method might be employed" "But the ERG thinks it more appropriate to treat brolucizumab as a fixed dosing schedule of	Proposed amendments: **Page 51: *"~~If brolucizumab was viewed~~*** [redacted] " *~~"But the ERG thinks it more appropriate to treat brolucizumab as a fixed dosing schedule of either every 8 weeks or every 12 weeks for the base case"~~*	Accurate interpretation of brolucizumab posology. In line with the updated posology, it is factually inaccurate to speculate whether brolucizumab can be considered a fixed or variable dosing regimen.	No factual error, no revision required. Given the available evidence and that the majority of brolucizumab patients had had their dosing frequency increased to every 8 weeks by week 96, the ERG still thinks that its approach is the most appropriate for the cost comparison.

either every 8 weeks or every 12 weeks for the base case"			

Issue 6 Reference to unlicensed bevacizumab

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG report does not clearly clarify in many instances that bevacizumab is an unlicensed treatment option. **Page 23**: The report additionally highlights factors influencing treatment decisions between anti-VEGF therapies in wet AMD: "Given the high-quality trial evidence supporting similarity in clinical effectiveness between brolucizumab, aflibercept, ranibizumab and bevacizumab (and no clear evidence indicating substantial difference in safety), the main considerations for selecting treatment options rests on costs, service delivery issues and patient preference."	Proposed amendments: Novartis believes that it would be more appropriate to denote bevacizumab as "***unlicensed*** *bevacizumab*" throughout the report order in order to prevent misinterpretation. **Page 23:** *"Given the high-quality trial evidence supporting similarity in clinical effectiveness between brolucizumab, aflibercept, ranibizumab ~~and bevacizumab~~ (and no clear evidence indicating substantial difference in safety), the main considerations for selecting treatment options rests on costs, service delivery issues and patient preference.*	It is important that the ERG is clear that bevacizumab is an unlicensed treatment option throughout their report. Bevacizumab is neither standard of care nor has a marketing authorisation in the UK for wAMD. Whilst aflibercept and ranibizumab are licensed treatments for wAMD and have also been assessed to be clinically and cost-effective by NICE, bevacizumab is not licensed for wAMD as it has not undergone the rigorous regulatory scrutiny and related risk/benefit analysis for use in such indication.	It is correct that bevacizumab is not licensed for eye use, but that is only because the manufacturer has never asked for it to be licensed. There is a substantial body of evidence on the effectiveness and safety of bevacizumab, notably from the independent government funded trials, CATT and IVAN. Bevacizumab was also thoroughly appraised in the NICE AMD clinical guidelines. No factual error. There is no need to use the word "unlicensed" more than once. Note that the use is "off-label" not "unlicensed" since bevacizumab is licensed for other purposes.

Issue 7 Reporting of bevacizumab market share data

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 9: The report discusses the market share data presented by the company: "bevacizumab has a low market share of [redacted]". The company submission provides more recent data, up to August 2019. This is noted on page 37 and page 58 of the ERG report.	Proposed amendment: **Page 9**: *Bevacizumab has a low market share of* [redacted].	Accurate reporting of the most recent data available in the company submission. The data also show that the market share of bevacizumab continues to remain at [redacted]	No factual error. The table 1.1 reference in the CS states the date range that the ERG reports on page 9 for (CS Document B, Table 1.1, Pages 9-10). The company clarification response to B1 extended this data to August 2019. As a consequence, the ERG thinks it is appropriate to revise the ERG report page 9 to "bevacizumab had a low market share of [redacted]". Given the confidential nature of the market share data reported by the company, we have updated the ERG report to highlight alternative market share data that are available in the literature in Section 4.2.2. The ERG further notes emerging evidence indicating that use of bevacizumab varies widely in Europe with it being the dominant drug in some countries, with the highest proportion of use being 97% of anti-VEGF use. (Bro et al. Off-label Use of Bevacizumab for Wet Age-Related Macular Degeneration in Europe .Graefes Arch Clin Exp Ophthalmol 2019 Dec 30 [Online ahead of print]

Issue 8 Reporting of the impact of the MHRA decision on bevacizumab

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 37: The ERG report speculates on the possible effects of the MHRA revised guidance regarding the use of bevacizumab: "It is possible that the company market share data does not reflect the effects of the MHRA revised guidance, or its likely effect upon the current treatment of newly incident wet AMD patients"	Proposed amendment: **Page 37: "***It is possible that the company market share data does not reflect the effects of the MHRA revised guidance**.~~, or its likely effect upon the current treatment of newly incident wet AMD patients"~~*	There is no evidence presented to suggest the likely effect that the MHRA revised guidance will have in the uptake of bevacizumab. Novartis would also like to emphasise that future uptake is not relevant to the NICE decision problem; comparators are based on current standard practice in the NHS.	No factual error. No revision required. The text is explicitly "its likely effect upon the **current treatment of newly incident** wet AMD patients"; i.e. now.

Issue 9 Reporting of NG82 stance on bevacizumab

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 9: The report notes that bevacizumab "was considered in NICE's clinical guideline NG82 for this condition." The report omits key limitations stated in NG82 about the comparison with unlicensed bevacizumab.	***Page 9:*** *But it [bevacizumab] was considered in NICE's clinical guideline NG82 for this condition.* ***NG82 highlights that bevacizumab is unlicensed for this indication, and any use of bevacizumab outside the UK marketing authorisation is taken at the prescriber's discretion and they would take full responsibility for this decision.***	Accurate reporting of information relating to the use of unlicensed bevacizumab from NG82.	No factual error. No revision required. Also note that in the opinion of the ERG, the main consideration around the use of bevacizumab is the recent change in guidance from the MHRA.

	Informed consent from the patient is also required."		

Issue 10 Reporting of bevacizumab evidence

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 14: The report highlights that "there is growing evidence suggesting similar clinical effectiveness" between bevacizumab and licensed VEGF inhibitors.	**Page 14:** that *"there is* ***~~growing~~*** *evidence suggesting similar clinical effectiveness"*	This statement relating to "growing evidence" is misleading; the references also highlight the lack of long-term research on bevacizumab efficacy, and there are limited recent data.	The ERG disagrees that the evidence base on bevacizumab is not growing. Please see ERG's Addendum 2 ERG appended at the end (Page 24) of this document for a list of examples of bevacizumab studies from the last three years. These include a mixture of primary research studies and systematic reviews.

Issue 11 Reporting of the company base case

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 34: With regards to the cost-comparison results presented in Table 14, the title refers to the "Company base case" only.	**Page 34:** *"Company base case* ***and ERG comparison with unlicensed bevacizumab****"*	The table titled company base case also includes results for a comparison versus unlicensed bevacizumab. The company base case did not include this comparison for the reasons stated in the submission. The title of Table 14 should reflect that the company	There is no need to use the term "unlicensed" (or more precisely, "off-label" as we indicated above) more than once. The ERG accepts that the title should be revised to: "Company base case augmented with ERG

		does not present a comparison with unlicensed bevacizumab.	comparison with bevacizumab" and have implemented this change (Page 34).

Issue 12 Description of market survey data

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 41: The report discusses concerns with the lack of information included from the company market research survey: "The ERG does not understand how supplying anonymised disaggregate response data would compromise respondents' anonymity and confidentiality, or indeed why respondents' anonymity and confidentiality need to be protected." This statement is potentially misleading and could imply that Novartis is deliberately withholding individual participant data. However, data protection regulations legally prohibit these data being made available.	**Page 41:** ~~*"The ERG does not understand how supplying anonymised disaggregate response data would compromise respondents' anonymity and confidentiality, or indeed why respondents' anonymity and confidentiality need to be protected."*~~	Novartis acknowledges the limitations identified with the market research survey by the ERG. As aforementioned, Novartis will be able to provide additional aggregated information as part of the technical engagement response that will address many of the ERG's concerns. However, Novartis will not be able to provide disaggregated data. The survey was conducted according to EU data protection regulation and applicable market research Codes of Conduct and/or Guidelines, which meant that participants were assured that their identity would be kept strictly confidential. Participants were further assured that their feedback would be anonymously aggregated, and hence the independent company conducting this survey are bound by this and are unable to share disaggregated results with Novartis.	The ERG acknowledges the need for the market research company to comply with relevant EU data protection regulations and agrees to remove this text (removed from Page 42).

Issue 13 Description of modelling approach

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 36: The ERG highlight that the submission "suggests the one stop administration and monitoring" approach, in line with NG82. However, a possible "modelling error" is highlighted". The potential error is unclear.		Novartis would be happy to provide an additional comment here if further clarification could be provided.	The ERG has provided NICE with a separate response on this point.

Issue 14 Description of modelling approach

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 51: The report speculates on the development of the modelling approach "It appears that the company originally adopted the NG82 approach, revised this to the more favourable company base case assumption of the Company Submission but forgot to revise Appendix D to reflect this".	Proposed amendment: **Page 51** ~~*"It appears that the company originally adopted the NG82 approach, revised this to the more favourable company base case assumption of the Company Submission but forgot to revise Appendix D to reflect this".*~~	This is a factually inaccurate representation of the approach taken in the company submission and this statement could be misleading to the reader. This sentence should be removed as it is speculative from the ERG. The NG82 approaches were incorporated as scenario analyses; these are clearly detailed within the company submission (Section B4.4.2).	The ERG has revised the text (Page 52) to read: "Given the lack of explicit consideration of the NG82 approach in the main company submission and reasons for its rejection by the company, it is possible that the company originally adopted the NG82 approach but then revised this to the more favourable assumptions of the company base case approach

			once the implications of the NG82 approach became clear.

Issue 15 Description of modelling approach

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 54: In the ERG base case table vs PRN comparators, the cost associated with OCT is listed as £5,109 for the aflibercept arm, £37,923 for the total arm and -£6,454 for the net cost. However, these values are factually inaccurate based on the described amendments to the model.	**Page 54** [redacted]	Accurate reporting for data from the amended model.	The ERG revised model results in the values of the ERG report. As the company has not had sight of the ERG revised model it is unclear whether this is an ERG error, a company error or a simple misunderstanding. NICE will not share the ERG revised model with the company. As a consequence, the ERG cannot respond on this point without an electronic copy of the revised company model together with an account of the changes made that result in the estimated £5,767 OCT cost for aflibercept. The ERG would be grateful if the company could submit this, and also clarify whether it finds any discrepancies within the ERG aflibercept scenario analyses.

	Brolucizumab	Aflibercept	Ranibizumab	Bevacizumab
Drug	[redacted]	£29,764	£23,599	£2,099
Admin	[redacted]	£2,845	£3,324	£3,324
OCT	[redacted]	~~£5,109~~**£5,767**	£6,364	£6,364
FFA	[redacted]	£207	£209	£209
AE	[redacted]	£0	£0	£0
Total	[redacted]	**£38,581**~~£37,923~~	£33,496	£11,995
Net		[redacted]	[redacted]	[redacted]

Issue 16 Reporting of NMA methodology

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 16: The ERG identified some inconsistencies in the application of inclusion criteria for the NMA, such that several ranibizumab trials that included a trial arm using its licenced 0.5 mg dose (and which could thus have been eligible for inclusion) were excluded from the NMA. The reason cited for the exclusion was that the intervention (such as bevacizumab, against which ranibizumab was compared) was 'not a licensed treatment'. However, this criterion seems to have been applied arbitrarily as a large trial (CATT) that compared ranibizumab with bevacizumab was included in the NMA.	Proposed amendment **Page 16:** ~~The ERG identified some inconsistencies in the application of inclusion criteria for the NMA, such that several ranibizumab trials that included a trial arm using its licenced 0.5 mg dose (and which could thus have been eligible for inclusion) were excluded from the NMA. The reason cited for the exclusion was that the intervention (such as bevacizumab, against which ranibizumab was compared) was 'not a licensed treatment'. However, this criterion seems to have been applied arbitrarily as a large trial (CATT) that compared ranibizumab with bevacizumab was included in the NMA~~	This statement is a factually inaccurate description of the NMA methodology. Trials were included if they presented multiple licensed treatment arms. The CATT trial was included as it included multiple treatment arms using licensed treatments (two ranibizumab arms). The unlicensed bevacizumab arms were excluded from the analysis, as detailed in Table 23, Table 42 and Table 52 of the Appendix D (only data from ranibizumab arms were considered).	No factual error. No change required. The ERG welcomes the clarification that "Trials were included if they presented multiple licensed treatment arms". This would be a reasonable inclusion criterion for the NMA. However, the criterion was not clearly stated in the submission documents and was not given as the reason for excluding trials. More importantly, the rationale for applying this criterion would be to ensure that any included trials can provide data for at least one randomised comparison that contributes to the evidence network within an NMA. However, as we highlighted in the ERG report, the key analyses that contributed to parameters for cost comparison were what the company described as 'baseline pooling', which only took data from individual trial arms. This criterion, while being suitable for the NMA, does not serve the purpose of selecting trials for baseline pooling well.

Issue 17 Typographical error

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 16: With reference to the study by (Biswas et al. 2011)[3]: "The trial reported data on treatment discontinuation and injection frequency for ranibizumab (n=60) that could potentially be included in the company's baseline pooling" The number of patients within the ranibizumab arm of this trial was n=54 not n=60.	Proposed amendment: **Page 16:** *"The trial reported data on treatment discontinuation and injection frequency for ranibizumab **(n=54)** that could potentially be included in the company's baseline pooling"*	Accurate reporting of data.	No factual error. The trial randomised 60 patients to the ranibizumab arm, which would be the number to be used in an intention-to-treat analysis for treatment discontinuation. The ERG acknowledges that the cited paper only reported outcomes for 54 patient in the ranibizumab, and has revised the text (Page 16) to read "(n=60 randomised / 54 analysed)"

Issue 18 Typographical error

Description of problem	Description of proposed amendment	Justification for amendment	ERG responses
Page 29: The ERG reported that the cost of gastrointestinal events were "£3,441 per event"	Proposed amendment: **Page 29:** *"Gastrointestinal event: **£441** per event"*	The cost included for a gastrointestinal event was £441.43.	Proposed amendment accepted (Page 29).

Issue 19 Typographical error

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
In relation to the VIEW 1&2 pooled 2 year dosing frequencies in Table 16, on **Page 39:** Regimen Aflibercept 0.5q4w -> PRN Aflibercept 2q4w -> PRN LP -> aflibercept 2q8w -> PRN Ranibizumab 0.5q4w -> PRN The regimens examined in the VIEW1&2 trials did not include a PRN aspect, therefore "PRN" should be removed from the regimen notations within Table 16.	Proposed amendment: **Page 39:** Regimen Aflibercept 0.5q4w ~~-> PRN~~ Aflibercept 2q4w ~~-> PRN~~ LP -> aflibercept 2q8w ~~-> PRN~~ Ranibizumab 0.5q4w ~~-> PRN~~	Accurate reporting of data. The regimens examined in the VIEW1&2 trials did not include a PRN aspect, therefore "PRN" should be removed from the regimen notations within Table 16.	The ERG disagrees, and wishes to highlight that this (not highlighting the PRN phase of these trials) was an important, and potentially misleading factual error in various parts of company submission documents where year 2 data from these trials were presented. It is the ERG's understanding that the PRN regimens were built-in by design for year 2 of VIEW 1&2 trials. For example, below are verbatim extracts from Schmidt-Erfurth U, et al. Intravitreal Aflibercept Injection for Neovascular Age-related Macular Degeneration: Ninety-Six Week Results of the VIEW Studies. Ophthalmology 2014;121(1):193-20. "During weeks 52 through 96, patients received their original dosing assignment using an as-needed regimen with defined retreatment criteria and mandatory dosing at least every 12 weeks." "Patients received on average 16.5, 16.0, 16.2, and 11.2 injections over 96 weeks". The injection frequencies mentioned in the above passage are exactly what the ERG reported in Table 16.

Issue 20 Typographical error

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>ERG response</th></tr>
<tr>
<td>The ERG Table 25 summarise Table 42 in the company submission appendices, however there is a value missing in the RANI PRN column.

Page 51: Table 1: Company Appendix D: Year 3+ dosing estimates
<table>
<tr><td></td><td colspan="2">Ratios</td></tr>
<tr><td>Trial</td><td>Trial</td><td>RANI RPN</td></tr>
<tr><td>NARMD</td><td>..</td><td></td></tr>
<tr><td>VIEW1&2</td><td>0.88</td><td>0.88</td></tr>
<tr><td>CATT[1]</td><td>1.78</td><td></td></tr>
<tr><td>TREX-AMD</td><td>0.68</td><td>1.21</td></tr>
<tr><td>RIVAL</td><td>0.91</td><td>1.10</td></tr>
<tr><td>SALUTE[2]</td><td>0.86</td><td>0.86</td></tr>
<tr><td>VIEW1&2</td><td>0.88</td><td>0.75</td></tr>
</table>
[1]Year 1 and 2 data [2]Year 1 data</td>
<td>Proposed amendment:

Page 51: Table 2: Company Appendix D: Year 3+ dosing estimates
<table>
<tr><td></td><td colspan="2"><s>Ratios</s>
Relative frequencies</td></tr>
<tr><td>Trial</td><td>Trial</td><td>Rani PRN</td></tr>
<tr><td><s>NARMD</s>
CATT
VIEW 1&2</td><td colspan="2">Reference from ARMD database</td></tr>
<tr><td>VIEW1&2</td><td>0.88</td><td>0.88</td></tr>
<tr><td>CATT[1]</td><td>1.78</td><td>1.78</td></tr>
<tr><td>TREX-AMD</td><td>0.68</td><td>1.21</td></tr>
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<tr><td>VIEW1&2</td><td>0.88</td><td>0.75</td></tr>
</table>
[1]Year 1 and 2 data [2]Year 1 data</td>
<td>Accurate reporting of company submission.</td>
<td>Table 25 in the ERG report is based on data reported in Table 42 of the company submission appendices, but ERG has modified the structure of the table and changed some headings in the table to facilitate data presentation. In response to the company's comment, we have revised the title of Table 25 in the ERG report (Page 51) to read: "Table 25; Company's Year 3+ dosing estimates (data source: CS Appendix D, Table 42, Page 90)", and modified some of the column headings.

The discrepancies in some of the column and row headings that the company highlighted here are ERG's intentional modifications to facilitate interpretation and are not errors. For example, the year 3 injection frequency of 3.7 comes from NARMD, not the CATT and VIEW 1&2 trials, and so the ERG cannot see why the row heading should read "CATT VIEW 1&2". Please provide further information if the company still thinks this is an error.</td>
</tr>
</table>

Issue 21 Confidentiality highlighting

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 47: The ERG reports AIC data which are not highlighted accordingly.	**Page 47:** Among other things, the [redacted] as outlined below.	These data are AIC and should be denoted accordingly.	The numeric values are not given. The ERG asks NICE to decide whether the text falls into AiC classification.

Issue 22 Confidentiality highlighting

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 49: The ERG reports AIC data which are not highlighted accordingly.	**Page 49:** [redacted]	These data are AIC and should be denoted accordingly.	The numeric values are not given. The ERG asks NICE to decide whether the text falls into AiC classification.

Issue 23 Confidentiality highlighting

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 37: The Draft SmPC wording for brolucizumab is not highlighted as CIC	The SmPC for brolucizumab states: [redacted]	This information is CIC and should be denoted accordingly. The final SmPC wording will be available in the public domain on receipt of full marketing authorisation.	The ERG accepts the proposed CIC mark-up for the draft versions of SmPC provided by the company. However we become aware that brolucizumab has received its marketing authorisation from the European Medicines Agency while preparing for this response document, [redacted] updated draft SmPC provided by the company during the factual accuracy check (and which is used in the revised ERG report, Page 38).

References

1. Guymer RH, Markey CM, McAllister IL, et al. Tolerating Subretinal Fluid in Neovascular Age-Related Macular Degeneration Treated with Ranibizumab Using a Treat-and-Extend Regimen: FLUID Study 24-Month Results. Ophthalmology 2019;126:723-734.
2. Hykin P, Chakravarthy U, Lotery A, et al. A retrospective study of the real-life utilization and effectiveness of ranibizumab therapy for neovascular age-related macular degeneration in the UK. Clinical ophthalmology (Auckland, N.Z.) 2016;10:87-96.
3. Biswas P, Sengupta S, Choudhary R, et al. Comparative role of intravitreal ranibizumab versus bevacizumab in choroidal neovascular membrane in age-related macular degeneration. Indian journal of ophthalmology 2011;59:191-196.

ERG Factual Accuracy Check Addendum 1: differences in posology wording between different versions of the draft SmPC

The company has provided a revised draft SmPC at factual accuracy check. The relevant paragraph that has changed in the posology section is provided below. The ERG has further divided this paragraph into sections to permit an easier comparison.

At submission	At factual accuracy check*
[redacted]	[redacted]

The key changes between the two draft SmPCs are;

- The draft SmPC supplied at factual accuracy check specifies "[redacted]".
- The change from "[redacted]" to "[redacted]" coupled with "[redacted]".

Both SmPCs specify that the physician may "[redacted]". The company asserts that the revised wording means that the company clarification response, and the ambiguity of its clarification response, should be disregarded and that the draft SmPC provided at factual accuracy check means that "[redacted]The

new SmPC implies more flexible dosing and that intervals longer than 12 weeks are permissible, presumably including cessation of brolucizumab until recurrence of exudate AMD. It can also be noted, as per the ERG report section 4.2.3.1, that both the aflibercept SmPC and the ranibizumab SmPC are explicit about extending the treatment interval relative to the dosing frequencies mentioned in the SmPCs.

ERG Factual Accuracy Check Addendum 2: Recent evidence on bevacizumab efficacy, including long-term observational studies (in relation to: Factual Accuracy Check Issue 10)

Trials and observational studies

van der Reis, M. I., et al. (2020). "A systematic approach to evaluate practice-based process- and outcome data applied to the treatment of neovascular age-related macular degeneration." BMC ophthalmology **20**(1): 21.

BACKGROUND: Following the principles of value-based health care, outcomes and processes of daily-practice eye care need to be systematically evaluated. We illustrate an approach that can be used to support data-driven quality improvements. We used patient data regarding the treatment of neovascular age-related macular degeneration (nAMD). METHOD(S): In a cohort study, we reviewed medical records of patients with nAMD confirmed on fluorescein angiography (FA). Patients were treated with intravitreal injections with bevacizumab; ranibizumab; or photodynamic therapy (PDT). Visual acuity (VA), ophthalmic exam results and treatments were recorded. VA was compared between treatments by linear mixed model. Diagnosis was re-evaluated on the original FAs. Outcome analysis was performed by 1) selecting VA as the relevant outcome parameter; 2) Preventing selection by comparing treatments with historical untreated cohort and cohorts from the literature, 3) correcting for confounding due to lesion type, and 4) identifying relevant process variables that affect the outcome. These were severity of disease at presentation, and doctor- and patient dependent process variables. RESULT(S): In total, 473 eyes were included. At 12months, change in VA was 0.54, 0.48, 0.09, and 0.07 LogMAR in the no-treatment, photodynamic therapy (PDT), bevacizumab, and ranibizumab groups, respectively. Lesion type on FA differed between groups. Diagnosis of nAMD could not be confirmed in 104 patients. Patient delay, inaccurate diagnosis and treatment intervals may have impacted outcomes. CONCLUSION(S): The effect of PDT was small to absent. Anti-VEGFs were effective and appeared as effective as in RCTs. Correct selection of a comparator cohort and addressing confounding, including confounding by indication and effect modification, are needed to achieve valid results and interpretation. Patient delay, diagnosis accuracy, indication for and application of treatment can potentially be improved to improve treatment outcomes. In a value-based care perspective, systematic evaluation of diagnostic accuracy, treatment indication, protocols, and outcomes of new interventions is needed at an early stage to improve outcomes.

Amarakoon, S., et al. (2019). "Bevacizumab in age-related macular degeneration: a randomized controlled trial on the effect of on-demand therapy every 4 or 8 weeks." Acta Ophthalmologica **97**(1): 107-112.

Purpose: Intravitreal anti-vascular endothelial growth factor (VEGF) injections are an effective treatment for neovascular age-related macular degeneration (nARMD). Bevacizumab appears to be a cost-effective off-label anti-VEGF alternative to ranibizumab, but an optimal injection schedule has not yet been determined. In this study, we investigate whether on-demand bevacizumab treatment every 8 weeks is non-inferior to on-demand bevacizumab every 4 weeks in treating nARMD. Method(s): A total of 120 nARMD patients were randomly assigned to an on-demand regimen of intravitreal bevacizumab (IVB) every 4 (n = 60) or 8 weeks (n = 60). The primary outcome was visual acuity (VA) change after 1 year of treatment. Result(s): Visual acuity (VA) improved between baseline and 1 year in both treatment groups. The mean change in the VA score at 1 year was not significantly different between bevacizumab administration on-demand every 4 weeks [5.6 +/- 10.2 Early Treatment Diabetic Retinopathy Study (ETDRS) letter] or 8 weeks (4.6 +/- 12.0 ETDRS letters). A reduction in the central retinal thickness was observed in both groups. At 1 year, the mean decrease in central foveal thickness ranged from 61 +/- 90 mum in the 4-week group to 91 +/- 83 mum in the 8-week group (p = 0.07). The mean number of IVB treatments during

the study period was 8.7 +/- 2.3 in the 4-week group and 5.9 +/- 1.0 in the 8-week group. Conclusion(s): At 1 year, bevacizumab administration on-demand every 8 weeks was non-inferior to administration every 4 weeks. The results strongly suggest that bevacizumab acts longer than 4 weeks in ARMD, reducing the burden of injections for patients. Copyright © 2018 Acta Ophthalmologica Scandinavica Foundation. Published by John Wiley & Sons Ltd

Bro, T. and S. Hagg (2019). "Worth changing? Clinical effects of switching treatment in neovascular age-related macular degeneration from intravitreal ranibizumab and aflibercept to bevacizumab in a region in southern Sweden." European Journal of Ophthalmology.

Purpose: To examine the clinical effects of switching intravitreal drug treatment from the approved vascular endothelial growth factor inhibitors, ranibizumab and aflibercept, to off label use of bevacizumab in patients with wet age-related macular degeneration. Method(s): This retrospective study scrutinized medical records of patients with wet age-related macular degeneration who switched therapy to bevacizumab due to a policy decision. Best corrected visual acuity, central retinal thickness, and number of injections before and 1 year after the switch was compared. The non-inferiority margin of best corrected visual acuity was five Early Treatment Diabetic Retinopathy Study letters. Result(s): A switch from ranibizumab was evaluable in 93 eyes and from aflibercept in 19 eyes. Neither of the groups had a significant non-inferior visual acuity 16 month after the switch. Mean best corrected visual acuity in Early Treatment Diabetic Retinopathy Study letters was 63.8 (95% confidence interval: 61.3-66.4) before and 62.2 (95% confidence interval: 59.3-65.1) after in the ranibizumab group and 68.2 (95% confidence interval: 63.3-73.1) before and 67.7 (95% confidence interval: 62.8-72.6) after in the aflibercept group. Mean central retinal thickness in micrometers decreased from 254 (95% confidence interval: 247-261) to 250 (95% confidence interval: 225-275) in the ranibizumab group and from 265 (95% confidence interval: 255-276) to 262 (95% confidence interval: 251-273) in the aflibercept group. The treatment was changed again after the switch in 18% of the patients in the ranibizumab group and 19% in the aflibercept group and these subjects were excluded from the analyses. Conclusion(s): In patients with neovascular age-related macular degeneration, a switch from ranibizumab or aflibercept to bevacizumab seems possible without a significant decrease in visual acuity in most patients. Copyright © The Author(s) 2019.

Ponsioen, T. L., et al. (2019). "Benchmarking anti-VEGF treatment of wet age-related macular degeneration." Acta Ophthalmologica **97 (Supplement 262)**: 38. [conference abstract]

Purpose: To demonstrate the power of benchmarking using an (inter-) national quality registration for the treatment of wet Age-related Macular Degeneration (wAMD), Save Sight Registry (SSR, formerly Fight Retinal Blindness!, FRB!). Method(s): SSR is in use by several clinics in the Netherlands since 2016 to register data, according to ICHOM specifications, of the treatment of patients with wAMD with intraocular anti-VEGF injections. The web-based system allows for benchmarking between an individual clinic and other clinics in the Netherlands, as well between Dutch clinics and clinics outside the Netherlands ("the rest of the world") using the same registration. An example of both levels of benchmarking is presented. Result(s): At 12 months, the clinic compared to the rest of the Netherlands: Change in VA 7.2 letters vs 5.1, median number of visits 11 vs 13, median number of injections 11 vs 9. At 12 months, the Dutch clinics compared to the rest of the world: Change in VA 5.7 letters vs 4.8, median number of visits 13 vs 9, median number of injections 10 vs 8. Conclusion(s): The SSR allows for benchmarking either between an individual clinic and the rest of the country, or between the clinics within one country compared to "the rest of the world". The shown examples demonstrate that with slightly more visits/injections, the visual results seem to be slightly better, even when bevacizumab is the drug used as the drug of first choice to start anti-VEGF therapy as is mandatory in the Netherlands.

Schroeder, M., et al. (2019). "Twelve per cent of 6142 eyes treated for neovascular age-related macular degeneration (nAMD) presented with low visual outcome within 2 years.

Analysis from the Swedish Macula Registry (SMR)." Acta Ophthalmologica.

Purpose: To analyse characteristics from the SMR to explore the risk factors for visual acuity (VA) below <= 35 letters of the Early Treatment Diabetic Retinopathy Study (ETDRS) due to nAMD during a two-year follow-up. Method(s): This study evaluates 6142 treatment-naive eyes, with focus on a subgroup of 780 eyes with final VA outcome of <= 35 letters, regarding differences of baseline characteristics, change of VA, number of injections and choice of drug to predict visual outcome. Result(s): Patients with final VA <= 35 letters were older; p < 0.0001, and received fewer injections, 6.2 +/- 3.8 vs. 8.7 +/- 5.4; p < 0.00001. Only 4% of all patients with >= 70 letters baseline VA decreased to a final VA of <= 35 letters. The two groups with a final VA of <= 35 letters and VA > 35 letters presented the following baseline lesion locations; p = 0.001; 61% vs. 57% subfoveal, 18% vs. 21% juxtafoveal and 4% vs. 6% extrafoveal. Lesion size, in the group with final VA <= 35 letters, was 2805 +/- 2093 mum vs. 2440 +/- 1637 mum in the group with a VA of > 35 letters; p = 0.005. A logistic regression analysis including baseline VA, best- or worse-seeing eye, age, membrane size, membrane location, symptom duration showed VA; p = < 0.0001, best- or worse-seeing eye; p = 0.026, age; p = < 0.0001, and membrane size; p = 0.002 to predict a decline of VA within 2 years. Conclusion(s): In eyes treated for wet AMD and studied for 2 years, 12.7% of eyes declined to a final VA of <= 35 letters. Visual acuity, worse-seeing eye treated, age and membrane size turned out as the baseline characteristics that had significantly influenced visual decline to <= 35 letters during the two-year follow-up. Copyright © 2019 The Authors. Acta Ophthalmologica published by John Wiley & Sons Ltd on behalf of Acta Ophthalmologica Scandinavica Foundation.

Extract from page 4:

> "We could not identify any association between the choice of drug and visual outcome above or ≤ 35 letters. However, we discovered that eyes were preferably treated with bevacizumab and ranibizumab monotherapy in the group with final VA ≤ 35 letters."

Stanca, H. T., et al. (2019). "Bevacizumab in Wet AMD treatment: A tribute to the thirteen years of experience from the beginning of the anti VEGF era in Romania." Experimental and Therapeutic Medicine **18**(6): 4993-5000.

This study aimed to identify and describe anatomical and functional changes on short (1-3 months) and medium (6-12 months) term after intravitreal injections of bevacizuma(Avastin, Genentech) in patients with choroidal neovascularization (CNV) in the context of exudative form of age-related macular degeneration (AMD). We performed a retrospective, analytical, interventional study, based on a series of cases with exudative form of AMD, which also comprised a prospective component related to the inclusion and treatment of the patients with a very new interventional method for that time (2006) an-the follow-up of the effects of intravitreal injection of beva cizumab (1.25 mg) therapy in three monthly doses for short (1-3 months) and medium (6-18 months) periods of time. The follow-up of these patients was made by determining visual acuity (VA) as best corrected visual acuity (BCVA) at baseline and at every visit, slit lamp examination with contact or noncontact lenses each time, and optical coherence tomography and/or angiofiuorography, applied only for certain patients, at various times of the study. In total, 376 intravitreal injections were administered to 117 eyes of 96 patients. The VA improve-in the assessment of 3 months in 77 eyes (66%), either subjec tive (by the patient) or objectively quantified (by the physician). In 40 eyes (34%), there was no change in VA. In patients for whom optical coherence tomography could be performed, a significant reduction of the macula's thickness was found. The use of bevacizumab in subretinal neovascular membrane treatment is effective and safe on short and medium term, with the improvement of BCVA and reduction of macular edema in a signifcant number of cases.

Burton, B. J. L. and T. Parveen (2018). "Outcome of avastin treatment for wet agerelated

macular degeneration in patients with visual acuity score 85 or better at first presentation." Investigative Ophthalmology and Visual Science. Conference **59**(9). [conference abstract]

Purpose: In the UK treatment for Wet Age related macular degeneration is not funded by the NHS until vision has fallen to 85 letters or below as dictated by NICE guidance. If the affected eye is the worse seeing eye then this means the patient will lose their driving license before they are elligible for treatment. With increasing numbers of patients now being diagnosed before they have developed signifiacant visual loss this leaves NHS clinicians seeing more patients that they cannot treat. We have treated this group of patients with Avastin in the hope that they will maintain good vision, benefitting the patient, and not lose vision below 85 letters so that they do not go on to use much more expensive treatments such as Lucentis and Afliibercept, benefitting the NHS and the tax payer. We report the the results of this patient group with 4 years of follow up. Method(s): A retrospective chart review was conducted at James Paget University Hospital of patients presenting with wet AMD and vision better than 85 letters in the affected eye. The long term visual acuity change and number of injections with Avastin was recored as well as the number of clinic appointments. Patients were treated on a monthly prn regime after an initial period of monthly injections times three. Result(s): 50 patients were reported on with at least one years follow up. 6 patients develope dloss of vision blow 85 letters with the result that two were switched to Lucenti san d4 were switched to Afliibercept. Visual acuity declined from a mean of 93.2 lettersat baseline by -2.5 letters at 12 months, -3.9 letters at year 2, 4.4 letters at year 3 and 7.3 letters at year 4 with a mean letter score of 85.9. Average number of injections were 6.16 in year 1, 4.52 in year 2, 4.14 in year 3 and 1.80 in year 4. Conclusion(shamd): The vast majority of patients with wet AMD treated early, before vision drops below 85 letters, maintain good vision using Avastin. This is likely to represent a significant financial saving for the UK health service by avoiding the need for these patients to switch to a more expensive anti VEGF such as Lucentis or Afliibercept. There is increasing evidence that early treatment in wet AMD offers the best long term visual outcomes and delaying treatment until the vision drop sbelow 85 letters is unlikely to ever be in the patients best interests.

Maberley, D. A. L., et al. (2018). "One-year effectiveness study of intravitreous bevacizumab in neovascular age-related macular degeneration: a population-based retrospective cohort study." Canadian Journal of Ophthalmology **53**(6): 627-631.

Objective: To assess effectiveness of intravitreous bevacizumab in a cohort of patients with neovascular age-related macular degeneration (nAMD) in British Columbia, Canada. Design(s): Retrospective cohort study. Participant(s): Patients with new-onset AMD who completed 1 year of bevacizumab treatment. Method(s): A cohort of 4507 patients with nAMD (5174 eyes) aged 50 years and older treated on an as-needed basis with bevacizumab was followed from June 1, 2010, to May 31, 2014, and then evaluated after completing a follow-up treatment at 1 year. Descriptive statistics were used to characterize eyes treated with bevacizumab. Multivariable regression models were used to quantify visual acuity (VA) changes over time, adjusting for baseline prognostic variables. Result(s): On average, patients received 8.6 injections (SD 2.4) per eye during the year of treatment. There was an average gain of 5.2 letters over the 1-year study period. Among eyes treated with bevacizumab, improvement in VA was greater for eyes with poorer baseline VA and for eyes receiving more injections. The odds ratio for VA at 1 year was 9.35 (95% CI 6.00-14.6) for eyes with VA 20/50-20/80 versus 20/20-20/40 and increased to 74.5 (95% CI 47.7-116.4) for eyes 20/400 or worse versus 20/20-20/40. Conclusion(s): Intravitreous bevacizumab is effective in treating nAMD, especially for eyes with poor baseline VA. Gains in VA were greatest by month 3 and were generally maintained thereafter. Copyright © 2018 Canadian Ophthalmological Society

Rao, P., et al. (2018). "Real-World Vision in Age-Related Macular Degeneration Patients Treated with Single Anti-VEGF Drug Type for 1 Year in the IRIS Registry." Ophthalmology **125**(4): 522-528.

Purpose: The purpose of this study is to compare real-world visual acuity (VA) in

patients with neovascular age-related macular degeneration (nAMD) treated with a single anti-vascular endothelial growth factor (VEGF) drug monotherapy for 1 year from the American Academy of Ophthalmology (AAO) Intelligent Research in Sight (IRIS) Registry. Design(s): Retrospective, nonrandomized, comparative study. Participant(s): IRIS Registry patients with nAMD who received bevacizumab, ranibizumab, or aflibercept only for 1 year between 2013-2016. Method(s): Participants were divided into 3 groups based on monotherapy type. Multivariate analysis of covariance models (ANCOVA) was constructed in a stepwise fashion. Main Outcome Measure(s): The logarithm of the minimum angle of resolution (logMAR) VA at 1 year and mean change in logMAR VA between baseline and 1 year were compared between drug types. Result(s): Of 13 859 patients, 6723 received bevacizumab, 2749 received ranibizumab, and 4387 received aflibercept only for 1 year. A total of 84 828 injections were performed. The mean number of injections (standard deviation) at 1 year was higher in the ranibizumab (6.4 [+/-2.4]) and aflibercept groups (6.2 [+/-2.4]) compared to bevacizumab group (5.9 [+/-2.4]; P < 0.0001). In the age-adjusted model, both ranibizumab and aflibercept achieved better logMAR VA at 1 year compared with bevacizumab (0.50 [+/-0.49], 0.49 [+/-0.44], 0.55 [+/-0.57]; P < 0.0001). However, this difference was not significant after multivariate adjustment (age, baseline VA, diabetes, posterior vitreous detachment, number of injections, race, insurance). There was no statistical difference in the age-adjusted or multivariate-adjusted mean logMAR VA change (standard deviation) at 1 year among treatment groups (-0.048 [0.44] bevacizumab, -0.053 [0.46] ranibizumab, -0.040 [0.39] aflibercept; P = 0.46). A higher percentage of patients achieved a >=3-line VA improvement at 1 year in the bevacizumab group (22.7%) compared with ranibizumab (20.1%; P = 0.0093) and aflibercept (17.8%; P < 0.0001). However, after multivariate adjustment, aflibercept exhibited a greater log odds of a >=3-line VA loss compared with bevacizumab only (1.25 log odds ratio; P < 0.0016). Conclusion(s): This study suggests that all 3 drugs improve VA similarly over 1 year of monotherapy. Copyright © 2017 American Academy of Ophthalmology

Au, A., et al. (2017). "Comparison of anti-VEGF therapies on fibrovascular pigment epithelial detachments in age-related macular degeneration." British Journal of Ophthalmology **101**(7): 970-975.

Background: The aim is to compare the therapeutic effects of three antivascular endothelial growth factor (VEGF) drugs (bevacizumab, aflibercept and ranibizumab) on fibrovascular pigment epithelial detachments (fvPEDs) in age-related macular degeneration (AMD). Method(s): This was a retrospective, comparative, consecutive case series of 88 unique eyes with fvPEDs in neovascular AMD treated with anti-VEGF monotherapy for a minimum of 6 months. All eyes were treatment naive. Diagnosis was confirmed retrospectively by fluorescein angiography and spectral-domain optical coherence tomography. Exclusion criteria included serous/drusenoid PEDs or patients who switched anti-VEGF. Mean follow-up across all therapies was 313.9+/-85.3 days. Result(s): Average age of all patients was 80.6 years. Baseline maximum subfoveal PED height was 326.8+/-185.1 mum, 394.5+/-238.6 mum and 258.0+/-145.3 mum for bevacizumab, aflibercept and ranibizumab, respectively (p=0.05). All patients had subretinal fluid, intraretinal fluid or a combination of the two at an initial presentation. Central retinal thickness decreased at all time points compared with baseline across all three anti-VEGF therapies. Subfoveal PED height decreased in patients treated with aflibercept at all time points and decreased in patients treated with bevacizumab at 1-month, 3-month and 6-month time points. Aflibercept reduced PED height more than bevacizumab at 1-month and 12-month follow-ups (p=0.02 and p=0.03, respectively) and ranibizumab at 1-month and 6-month follow-ups (p=0.03 and p=0.02, respectively). No differences in best-corrected visual acuity were appreciated at any time point between drugs. Conclusions There was a significant reduction in subfoveal PED height for aflibercept and bevacizumab compared with baseline. A direct comparison of drugs demonstrated a beneficial reduction of PED height, albeit inconsistently, favouring aflibercept. There were no differences in visual acuity across the groups at any time point. Copyright © Published by the BMJ Publishing Group Limited.

Berg, K., et al. (2017). "An 8-year follow-up of anti-vascular endothelial growth factor treatment with a treat-and-extend modality for neovascular age-related macular degeneration." Acta Ophthalmologica **95**(8): 796-802.

Purpose: To investigate long-term visual results of treatment with anti-vascular endothelial growth factor (VEGF) agents for neovascular age-related macular degeneration (nAMD) following a treat-and-extend regimen. Method(s): Retrospective review of 155 patients who initiated treatment with bevacizumab for nAMD in one eye. At the final 8-year visit, 40 patients (26%) remained for follow-up. Mean change in best-corrected visual acuity (BCVA) was calculated compared to baseline values. Result(s): Mean BCVA improved significantly from baseline during the first year of treatment, with -0.11 logMAR units equivalent to 6.1 approximate Early Treatment Diabetic Retinopathy Study (approxETDRS) letters (p = <0.001). Mean BCVA was still significantly improved after 4 years of treatment for the entire group of patients and after 6 years of treatment for the subgroup of 40 patients who remained at the final 8-year visit. Thereafter, BCVA gradually declined and at 8 years, there was a mean change of 0.05 logMAR units equivalent to 2.1 approxETDRS letters below baseline (p = 0.530). Mean number of injections during the first year was 6.1 +/- 2.8 and during year 8 was 5.4 +/- 3.5. At 5 years, fundus autofluorescence showed some degree of macular atrophy in all eyes. At the final 8-year visit, 87.5% of the eyes had stable neovascular lesions with no fluid on optical coherence tomography (OCT). Conclusion(s): In an everyday clinical setting, treatment of nAMD patients with a treat-and-extend modality provided improvement and stability of vision for several years. After 8 years of follow-up, there was a decline in visual acuity (VA) that could be explained by macular atrophic development.

Park, D. H., et al. (2017). "A comparison of responses to intravitreal bevacizumab, ranibizumab, or aflibercept injections for neovascular age-related macular degeneration." International Ophthalmology **37**(5): 1205-1214.

Purpose: To compare the responses of intravitreal injections of bevacizumab, ranibizumab, or aflibercept for the treatment of neovascular age-related macular degeneration (nAMD). Method(s): This retrospective study examined 232 eyes of 232 patients who received intravitreal anti-vascular endothelial growth factor (VEGF) injections due to treatment-naive nAMD. All patients, who were followed-up for at least 1 year, were treated with intravitreal injections monthly until 3 months, and then as needed. We evaluated the effects of intravitreal injections for treatment of nAMD using the central macular thickness (CMT), subretinal fluid (SRF), pigment epithelial detachment (PED) size, and best-corrected visual acuity (BCVA). Result(s): CMT, SRF, PED size, and BCVA (LogMAR) were significantly decreased after treatment with all three anti-VEGF agents. Overall, the bevacizumab, ranibizumab, and aflibercept treatments showed no significant differences in their responses. However, the aflibercept injections decreased PED size more quickly than bevacizumab injections (P = 0.034). Conclusion(s): Bevacizumab, ranibizumab, and aflibercept injections are effective treatments for nAMD and have similar responses, although the number of injections of aflibercept was fewer than other anti-VEGF agents. In addition, aflibercept injections may be a better choice than other anti-VEGF agents for cases of severe increases in PED height.

AAO report:

Bakri, S. J., et al. (2019). "Safety and Efficacy of Anti-Vascular Endothelial Growth Factor Therapies for Neovascular Age-Related Macular Degeneration: A Report by the American Academy of Ophthalmology." Ophthalmology **126**(1): 55-63.

Purpose: To review the evidence on the safety and efficacy of anti-vascular endothelial growth factor (VEGF) therapies for the treatment of neovascular age-related

macular degeneration (AMD). Method(s): A literature search of the PubMed and Cochrane Library databases was last conducted in February 2017; there were no date restrictions, and the search was limited to studies published in English. The combined searches yielded 191 citations, 28 of which were selected because they were clinical trials and were deemed clinically relevant for the Ophthalmic Technology Assessment Committee Retina/Vitreous Panel to review in full. The panel methodologist then assigned a level of evidence rating to each study. Result(s): Sixteen of the 28 citations provided level I evidence supporting the use of anti-VEGF agents for neovascular AMD, including intravitreal ranibizumab, aflibercept, and bevacizumab. Eight studies reviewed provided level II evidence, and 4 studies provided level III evidence, but only the level I studies are included in this assessment. There are long-term follow-up data on the efficacy of ranibizumab and bevacizumab (>=5 years), but these data are subject to the bias of incomplete follow-up. Conclusion(s): Review of the literature indicates that intravitreal injection of anti-VEGF therapy is safe and effective for neovascular AMD over 2 years, the period for which data are available. Further research is needed to evaluate the long-term safety and comparative efficacy of these agents. Copyright © 2018 American Academy of Ophthalmology
see pg 60 'Bevacizumab'

Systematic reviews / meta-analyses:

Low, A., et al. (2019). "Comparative effectiveness and harms of intravitreal antivascular endothelial growth factor agents for three retinal conditions: A systematic review and meta-analysis." British Journal of Ophthalmology **103**(4): 442-451.

Intravitreal antivascular endothelial growth factor (VEGF) agents are widely used to treat ocular conditions but the benefits and harms of these treatments are uncertain. We conducted a systematic review to compare the effects of aflibercept, bevacizumab and ranibizumab on best-corrected visual acuity (BCVA) changes, quality of life and ocular or systemic adverse events in patients with neovascular age-related macular degeneration (NVAMD), diabetic macular oedema (DME) and central or branch retinal vein occlusion (RVO). We searched published and unpublished literature sources to February 2017 for randomised controlled trials and cohort or modelling studies reporting comparative costs in the USA. Two reviewers extracted data and graded the strength of the evidence using established methods. Of 17 included trials, none reported a clinically important difference (>= 5 letters) in visual acuity gains between agents. Nine trials provide high-strength evidence of no difference between bevacizumab and ranibizumab for NVAMD. Three trials provide moderate-strength evidence of no difference between bevacizumab and ranibizumab for DME. There was low-strength evidence of similar effects between aflibercept and ranibizumab for NVAMD, aflibercept and bevacizumab for RVO and all three agents for DME. There was insufficient evidence to compare bevacizumab and ranibizumab for RVO. Rates of ocular adverse events were low, and systemic harms were generally similar between groups, although 1 DME trial reported more arterial thrombotic events with ranibizumab versus aflibercept. Overall, no agent had a clear advantage over another for effectiveness or safety. Aflibercept and ranibizumab were significantly less cost-effective than repackaged bevacizumab in two trials. Systematic review registration number: CRD42016034076.

Solomon, S. D., et al. (2019). "Anti-vascular endothelial growth factor for neovascular age-related macular degeneration." Cochrane Database of Systematic Reviews: CD005139. Background: Age-related macular degeneration (AMD) is the most common cause of uncorrectable severe vision loss in people aged 55 years and older in the developed world. Choroidal neovascularization (CNV) secondary to AMD accounts for most cases of AMD-related severe vision loss. Intravitreous injection of anti-vascular endothelial growth factor (anti-VEGF) agents aims to block the growth of abnormal blood vessels in the eye to prevent

vision loss and, in some instances, to improve vision.
Objectives:
• To investigate ocular and systemic effects of, and quality of life associated with, intravitreous injection of three anti-VEGF agents (pegaptanib, ranibizumab, and bevacizumab) versus no anti-VEGF treatment for patients with neovascular AMD
• To compare the relative effects of one of these anti-VEGF agents versus another when administered in comparable dosages and regimens
Search methods: To identify eligible studies for this review, we searched the Cochrane Central Register of Controlled Trials (CENTRAL), which contains the Cochrane Eyes and Vision Trials Register (searched January 31, 2018); MEDLINE Ovid (1946 to January 31, 2018); Embase Ovid (1947 to January 31, 2018); the Latin American and Caribbean Health Sciences Literature Database (LILACS) (1982 to January 31, 2018); the International Standard Randomized Controlled Trials Number (ISRCTN) Registry (www.isrctn.com/editAdvancedSearch - searched January 31, 2018); ClinicalTrials.gov (www.clinicaltrials.gov - searched November 28, 2018); and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en - searched January 31, 2018). We did not impose any date or language restrictions in electronic searches for trials.
Selection criteria: We included randomized controlled trials (RCTs) that evaluated pegaptanib, ranibizumab, or bevacizumab versus each other or versus a control treatment (e.g. sham treatment, photodynamic therapy), in which participants were followed for at least one year.
Data collection and analysis: Two review authors independently screened records, extracted data, and assessed risks of bias. We contacted trial authors for additional data. We compared outcomes using risk ratios (RRs) or mean differences (MDs). We used the standard methodological procedures expected by Cochrane.
Main results: We included 16 RCTs that had enrolled a total of 6347 participants with neovascular AMD (the number of participants per trial ranged from 23 to 1208) and identified one potentially relevant ongoing trial. Six trials compared anti-VEGF treatment (pegaptanib, ranibizumab, or bevacizumab) versus control, and 10 trials compared bevacizumab versus ranibizumab. Pharmaceutical companies conducted or sponsored four trials but funded none of the studies that evaluated bevacizumab. Researchers conducted these trials at various centers across five continents (North and South America, Europe, Asia, and Australia). The overall certainty of the evidence was moderate to high, and most trials had an overall low risk of bias. All but one trial had been registered prospectively.
When compared with those who received control treatment, more participants who received intravitreous injection of any of the three anti-VEGF agents had gained 15 letters or more of visual acuity (risk ratio [RR] 4.19, 95% confidence interval [CI] 2.32 to 7.55; moderate-certainty evidence), had lost fewer than 15 letters of visual acuity (RR 1.40, 95% CI 1.27 to 1.55; high-certainty evidence), and showed mean improvement in visual acuity (mean difference 6.7 letters, 95% CI 4.4 to 9.0 in one pegaptanib trial; mean difference 17.8 letters, 95% CI 16.0 to 19.7 in three ranibizumab trials; moderate-certainty evidence) after one year of follow-up. Participants treated with anti-VEGF agents showed improvement in morphologic outcomes (e.g. size of CNV, central retinal thickness) compared with participants not treated with anti-VEGF agents (moderate-certainty evidence). No trial directly compared pegaptanib versus another anti-VEGF agent and followed participants for one year; however, when compared with control treatments, ranibizumab and bevacizumab each yielded larger improvements in visual acuity outcomes than pegaptanib.
Visual acuity outcomes after bevacizumab and ranibizumab were similar when the same RCTs compared the same regimens with respect to gain of 15 or more letters of visual acuity (RR 0.95, 95% CI 0.81 to 1.12; high-certainty evidence) and loss of fewer than 15 letters of visual acuity (RR 1.00, 95% CI 0.98 to 1.02; high-certainty evidence); results showed similar mean improvement in visual acuity (mean difference [MD] -0.5 letters, 95% CI -1.5 to 0.5; high-certainty evidence) after one year of follow-up, despite the substantially lower cost of

bevacizumab compared with ranibizumab. Reduction in central retinal thickness was less among bevacizumab-treated participants than among ranibizumab-treated participants after one year (MD -11.6 μm, 95% CI -21.6 to -1.7; high-certainty evidence); however, this difference is within the range of measurement error, and we did not interpret it to be clinically meaningful.
Ocular inflammation and increased intraocular pressure (IOP) after intravitreal injection were the most frequently reported serious ocular adverse events. Researchers reported endophthalmitis in less than 1% of anti-VEGF-treated participants and in no cases among control groups. The occurrence of serious systemic adverse events was comparable across anti-VEGF-treated groups and control groups; however, the numbers of events and trial participants may have been insufficient to show a meaningful difference between groups (evidence of low- to moderate-certainty). Investigators rarely measured and reported data on visual function, quality of life, or economic outcomes.
Authors' conclusions: Results of this review show the effectiveness of anti-VEGF agents (pegaptanib, ranibizumab, and bevacizumab) in terms of maintaining visual acuity; studies show that ranibizumab and bevacizumab improved visual acuity in some eyes that received these agents and were equally effective. Available information on the adverse effects of each medication does not suggest a higher incidence of potentially vision-threatening complications with intravitreous injection of anti-VEGF agents compared with control interventions; however, clinical trial sample sizes were not sufficient to estimate differences in rare safety outcomes. Future Cochrane Reviews should incorporate research evaluating variable dosing regimens of anti-VEGF agents, effects of long-term use, use of combination therapies (e.g. anti-VEGF treatment plus photodynamic therapy), and other methods of delivering these agents.

Pham, B., et al. (2019). "Anti-vascular endothelial growth factor treatment for retinal conditions: A systematic review and meta-analysis." BMJ Open **9 (5) (no pagination)**(e022031).

Objectives: To evaluate the comparative effectiveness and safety of intravitreal bevacizumab, ranibizumab and aflibercept for patients with choroidal neovascular age-related macular degeneration (cn-AMD), diabetic macular oedema (DMO), macular oedema due to retinal vein occlusion (RVO-MO) and myopic choroidal neovascularisation (m-CNV). Design(s): Systematic review and random-effects meta-analysis. Method(s): Multiple databases were searched from inception to 17 August 2017. Eligible head-to-head randomised controlled trials (RCTs) comparing the (anti-VEGF) drugs in adult patients aged >=18 years with the retinal conditions of interest. Two reviewers independently screened studies, extracted data and assessed risk of bias. Result(s): 19 RCTs involving 7459 patients with cn-AMD (n=12), DMO (n=3), RVO-MO (n=2) and m-CNV (n=2) were included. Vision gain was not significantly different in patients with cn-AMD, DMO, RVO-MO and m-CNV treated with bevacizumab versus ranibizumab. Similarly, vision gain was not significantly different between cn-AMD patients treated with aflibercept versus ranibizumab. Patients with DMO treated with aflibercept experienced significantly higher vision gain at 12 months than patients receiving ranibizumab or bevacizumab; however, this difference was not significant at 24 months. Rates of systemic serious harms were similar across anti-VEGF agents. Posthoc analyses revealed that an as-needed treatment regimen (6-9 injections per year) was associated with a mortality increase of 1.8% (risk ratio: 2.0 [1.2 to 3.5], 2 RCTs, 1795 patients) compared with monthly treatment in cn-AMD patients. Conclusion(s): Intravitreal bevacizumab was a reasonable alternative to ranibizumab and aflibercept in patients with cn-AMD, DMO, RVO-MO and m-CNV. The only exception was for patients with DME and low visual acuity (<69 early treatment diabetic retinopathy study [ETDRS] letters), where treatment with aflibercept was associated with significantly higher vision gain (>=15 ETDRS letters) than bevacizumab or ranibizumab at 12 months; but the significant effects were not maintained at 24 months. The choice of anti-VEGF drugs may depend on the specific retinal

condition, baseline visual acuity and treatment regimen. Copyright © Author(s) (or their employer(s)) 2019.

Wang, X., et al. (2018). "Comparing bevacizumab and ranibizumab for treatment of neovascular age-related macular degeneration: A meta-analysis of noninferiority randomized controlled trials." International Journal of Clinical and Experimental Medicine **11**(11): 11663-11672.

Neovascular age-related macular degeneration (nAMD) is the main cause of blindness in populations aged over 50 years old. The objective of this meta-analysis was to compare the efficacy and safety of off-label use of bevacizumab with licensed ranibizumab for the treatment of nAMD. Five noninferiority randomized controlled trials (RCTs) comparing bevacizumab with ranibizumab for treatment of nAMD were included. Three reviewers independently extracted data. Data on efficacy and safety outcomes were collected. Pooled risk ratios, weighted mean difference (WMD), and associated 95% confidence interval (CI) were calculated. There were 1,346 patients in the bevacizumab group and 1,392 patients in the ranibizumab group. There were no significant differences between the two drugs in the change of BCVA (WMD=-0.63; 95% CI,-1.72 to 0.46, P=0.26). The mean difference was-0.63 letters with a lower limit in the 95% CI of-1.72 letters. This lower bound was above all the noninferiority margins chosen in the RCTs (-3.5 to-5). Bevacizumab was more effective in reducing central retinal thickness than ranibizumab (WMD=11.14; 95% CI, 2.12 to 20.15, P=0.02). The pooled risk ratios comparing the incidences of death, arteriothrombotic events, venous thrombotic events, >= 1 serious systemic events, and ocular adverse events were not statistically different. The pooled evidence confirmed that bevacizumab is non-inferior to ranibizumab for treatment of nAMD. However, bevacizumab tended to have better anatomical outcome. There was no difference in adverse events between the two drugs. Further trials are still needed to strengthen results because of the limited number of studies.

Other information:

Fell, G. and A. Foss (2019). "Avastin for wet AMD: what will break the gridlock?" BMJ Opinion. Retrieved 19 February 2020, from https://blogs.bmj.com/bmj/2019/03/26/avastin-for-wet-amd-what-will-break-the-gridlock/ .

Davio, K. (2018). "UK Health System Wins the Right to Treat AMD With Bevacizumab." Retrieved 19 February 2020, from https://www.centerforbiosimilars.com/news/uk-health-system-wins-the-right-to-treat-amd-with-bevacizumab .

Royal College of Ophthalmologists (2018). "New NICE Age Related Macular Degeneration guidance supports potential cost savings for the NHS." 23 January 2018. Retrieved 19 February 2020, from https://www.rcophth.ac.uk/2018/01/new-nice-age-related-macular-degeneration-guidance-supports-potential-cost-savings-for-the-nhs/ .

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

ERG response to company factual accuracy check of ERG report 26/06/2020 (addendum)

Brolucizumab for treating wet age-related macular degeneration [ID1254]

Issue 1 Inconsistent application of additional PRN monitoring visits for brolucizumab versus aflibercept

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 85: "But there is an inconsistency in that brolucizumab was in effect assumed to transition from fixed dosing in years 1 and 2 to PRN dosing in year 3 without incurring the additional 1st year PRN monitoring visit costs. On reflection, this seems unreasonable, so for the ERG revised PRN base case, the ERG assumes an additional 6.1 monitoring visits in the first year of brolucizumab PRN dosing" **Page 58:** [The ERG PRN base case compares brolucizumab with] "loading phase then every 8 weeks then treat as need (LP→q8w→PRN) aflibercept" The ERG applies 6.1 additional monitoring visits for the first year that brolucizumab is used as a PRN regimen. However, for the first year that aflibercept is used as a PRN regimen (Year 2), only 4.5 additional monitoring visits are applied. Consequently, the number of monitoring visits for aflibercept PRN	When considering aflibercept LP→q8w→PRN, 6.1 additional monitoring visits should be applied in Year 2 (the first year of PRN use), rather than the 4.5 monitoring visits currently applied. For the ERG PRN base case, aflibercept should incur 11.1 monitoring visits in Year 2, compared to the 9.5 used currently (Table 42). The additional monitoring visits in Year 2 for aflibercept should be applied in the following analyses: • ERG PRN base case • Addendum SA01b • Addendum SA02 (versus PRN dosing for comparators) • Addendum SA03 (versus PRN dosing for comparators) The results of Addendum SA05 should be updated to reflect the	The addendum to the ERG report has introduced a new assumption, whereby in the first year that a treatment is used as a PRN dosing regimen, an additional 6.1 monitoring visits are incurred. However, while this new assumption has been applied for brolucizumab, it has not been applied for aflibercept. By only including additional monitoring visits for brolucizumab, these analyses are implicitly weighted towards aflibercept, and should be updated consistently.	No factual error. No revision required. But the ERG accepts that more information is reasonable. There is uncertainty as to the additional dosing that would be required for aflibercept LP→q8w→PRN as the move from loading phase to dose extension to PRN is more gradual than for the other treatments. This is reflected in the company dosing and monitoring assumptions for aflibercept, which the ERG applies. The ERG remains of the opinion that for the brolucizumab arm stepping directly from fixed dosing in year 2 to PRN dosing in year 3 the most reasonable assumption is to apply the year 1 PRN additional monitoring visits. The ERG accepts that there is a lack of evidence on this. The report has been amended to state: But there is an inconsistency in that brolucizumab was in effect assumed

is underestimated in the ERG PRN base case and a number of the scenario analyses.	updated incremental costs of the ERG PRN base case.		to transition from fixed dosing in years 1 and 2 to PRN dosing in year 3 without incurring the additional 1st year PRN monitoring visit costs. On reflection, this seems unreasonable, so for the ERG revised PRN base case, the ERG assumes an additional 6.1 monitoring visits in year 3: the first year of brolucizumab PRN dosing. There is uncertainty as to the additional dosing that would be required for aflibercept LP→q8w→PRN as the move from loading phase to dose extension to PRN is more gradual than for the other treatments. This is reflected in the company dosing and monitoring assumptions for aflibercept, which the ERG applies. The company suggests that an additional 1.6 monitoring visits should be added to aflibercept PRN to equalise its monitoring visits with those of brolucizumab. This would add £183 to the aflibercept costs.

Issue 2 Description of the comparator prices used in the ERG scenario analyses

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 90: "Updating the ERG addendum scenario analyses for the comparator price reductions results in the following"	~~"Updating the ERG addendum scenario analyses for the comparator price reductions results in the following"~~	We believe this sentence is included in error.	Proposed revision accepted.

This is factually inaccurate. The scenario analyses presented below consider the list prices for each comparator.			

Issue 3 Presentation of a dual base case

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 76: "ERG expert opinion suggest that most patients are treated using TREX, though some centres may treat using PRN if clinic arrangements are ill suited to one stop monitoring and treatment" **Page 77:** "The ERG examined individual dosing regimens, focussing upon TREX and PRN, but with the other regimens presented as scenario analyses" Inclusion of a dual-base case strongly implies to the reader that TREX and PRN regimens are of equal importance, and see equivalent usage, in clinical practice. However, this is inconsistent with the ERG expert opinion above, which states that most patients are treated with TREX.	Novartis suggest that the ERG base case should solely focus on the comparison versus comparator TREX dosing regimens. Novartis suggest that the comparison versus comparator PRN dosing regimens would be better suited to a scenario analysis.	We thank the ERG for considering our comments and updating their base case assumptions. We also acknowledge that the ERG sees value in presenting an alternative to the approach in the Novartis submission, which presents a weighted base case combining fixed and flexible regimens for both comparators, to reflect the variability in clinical practice. However, including a PRN-only comparison in the ERG base case is not appropriate because it is no longer widely used in clinical practice. The use of a dual base case is misleading to the reader, implying that TREX and PRN dosing regimens see equal usage, and are of equal importance, in clinical practice. This implication is factually	No factual error. No revision required.

Additionally, feedback from UK clinical experts submitted by Novartis also indicated that TREX is the most commonly adopted dosing regimen. With regards to the use of PRN regimens, UK clinical expert feedback submitted previously highlighted that the use of PRN regimens is both limited and declining; real-world effectiveness of PRN regimens has been observed to be inferior to TREX regimens, and monitoring visits without treatment are an inefficient use of clinical resources. We therefore believe that a comparison assuming that all patients on aflibercept and ranibizumab receive PRN dosing is entirely inappropriate.		inaccurate, and inconsistent with other sections of the ERG report and feedback from UK clinical experts, including the ERG adviser.	

Issue 4 Insufficient description of Addendum Scenario SA05

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 90: "Applying the company weighted averaging to the different aflibercept and ranibizumab dosing regimens" "This is a weighted mean of the SA01 scenarios' net costs/savings	**Page 90: "**~~This is a weighted mean of the SA01 scenarios' net cost/savings using the treatment specific company weights~~" **Page 90:** " **This is a weighted mean of the net costs/savings of the**	In replicating the results of this scenario it appears that the ERG take the average from the TREX base-case, the PRN base-case, SA01a and SA01c, however the scenarios make different	No factual error. No revision required. But the ERG accepts that more information is reasonable. The report has been amended to state:

using the treatment specific company weights" The description of this scenario is limited and does not provide the reader sufficient information in order to fully understand the approach taken.	**TREX and PRN base cases, alongside SA01a and SA01c. However, it is important to note that SA01a and SA01c have not been updated to include the ERG's updated assumption for brolucizumab injection frequency in Year 3+ (4.0), and instead use the previous assumption (5.7).**	assumptions about year 3+ dosing than the base-case; 5.7 injections for brolucizumab where the base-case analysis assumes 4. We suggest that a more detailed description of this scenario would be beneficial, allowing the reader to more easily understand the exact methodology that has been used. Given that this analysis is presented as a new scenario within the ERG's addendum, it is implied that this scenario would include the ERG's updated assumptions for brolucizumab (i.e. 4.0 injections in Year 3+). Since this may not be the case, it is important to clearly highlight this to the reader to avoid any misunderstanding.	This is a weighted mean of the net costs/savings of the TREX and PRN base cases, alongside SA01a and SA01c. Note that SA01a and SA01c retain the original ERG dosing assumptions, as it seems unreasonable to unilaterally apply a year 3+ dosing assumption of 4.0 for brolucizumab in these analyses.

Issue 5 Addendum structure

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 75–84: The ERG begins the addendum to this report by reiterating their preferred assumptions from the original ERG report in extensive detail. The ERG then provides a critique of the responses that were provided by Novartis. The addendum outlines the ERG's original assumptions and concerns in	Section 8.1 could be shortened, instead cross-referencing previous sections in the ERG report and Novartis 'additional information request' response document, thereby retaining focus on the new section 8.2 and section 8.3 for this addendum. Alternatively, the ERG could	The current structure of this addendum does not provide a balanced summary of the viewpoints of both Novartis and the ERG.	No factual error. No revision required.

considerable detail. However, very minimal summary is provided of Novartis' response to the ERG report, except in the context of the ERG's critique. It is our understanding that this addendum is intended to be a consolidation of several documents into one for ease of reference. Therefore, the response previously provided by Novartis should also be included in more detail. Alternatively, section 8.1 could be shortened, instead cross-referencing previous sections in the ERG report as well as the Novartis 'additional information request' response document.	introduce a new Section, Section 8.2, that summarises the company responses to the original ERG report. The current Section 8.2 would then become Section 8.3, detailing the ERG's critique of these responses.		

Issue 6 Speculative conclusion

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 84: "The ERG doubts that the company has communicated sufficient information for the respondents to judge whether 4.76 or 5.7 is a more reasonable value to extrapolate" Novartis suggest that it is unreasonable to assume that these physicians would be insufficiently aware of brolucizumab, the associated trial data and potential	"**The wording of the company survey contained limited** information for the respondents to judge whether 4.76 or 5.7 is a more reasonable value to extrapolate. **The ERG, however, accepts that it is plausible to assume that the respondents would have had a reasonable amount of background knowledge of brolucizumab, the associated trial data, and its**	All experts are independent retinal specialists practicing within the NHS, with vast experience in delivering retinal services in the UK, with awareness of the brolucizumab trial data. Their responses would be based on the totality of their understanding of brolucizumab data and how they expect to use it in clinical practice, as well their knowledge of anti-VEGF therapies,	No factual error. No revision required. The proportion of brolucizumab patients on q8w dosing at the end of year 2 was not presented within the original company submission. It also does not appear within the main trial reference.

use in clinical practice, outside of the information provided in the company survey. However, this is what is implied by the wording of the addendum.	**potential use in clinical practice."**	experience with comparator regimens and the service set up in the UK. Novartis suggest it would be more reasonable to present both possibilities, allowing the reader to then draw their own conclusions.	

Company response to ID1254 Brolucizumab: Additional information request post scrutiny decision

Dear Louise,

Novartis would like to thank NICE for the opportunity to respond to the Evidence Review Group (ERG)'s summary of dosing and monitoring assumptions for ID1254: brolucizumab for treating wet age-related macular degeneration (wAMD).

This document comprises 4 key parts and an appendix of supplementary information, detailing Novartis' response on the ERG's assumptions and preferred approach. It should be noted that as part of this response, Novartis has sought additional clinical expert feedback from 8 clinical experts in the UK, which is referenced throughout the document and detailed in full in Appendix B and the reference pack accompanying this response.

The contents of this response are as follows:

We hope that these responses address the uncertainties identified by NICE and the ERG with regards to the appraisal of brolucizumab for treating wAMD.

Kind regards,

Raisa Sidhu
HE&OR Manager, Novartis Pharmaceuticals UK Ltd

1. Anticipated real-world dosing of brolucizumab

The ERG considered brolucizumab as a fixed dosing regimen, administered either q12w (every 12 weeks) or q8w (every 8 weeks), based on interpretation of the draft brolucizumab summary of product characteristics (SmPC) posology wording and the results of the HAWK and HARRIER trials.

Novartis believe that there are important limitations with this approach, and propose it would be more reflective of anticipated real-world usage to consider brolucizumab as a variable dosing regimen in line with aflibercept and ranibizumab, for the following reasons:

- The European Medicines Agency (EMA) approved brolucizumab SmPC posology wording provides flexibility for brolucizumab to be administered according to a variable dosing regimen (Section 1.1).[1]
- Extrapolation of HAWK and HARRIER q12w/q8w dosing proportions at Week 92 is not appropriate. The trials did not allow for the subsequent re-extension to q12w for patients with a q8w need, while clinical experts have unanimously highlighted that re-extending patients without disease activity would be reflective of future clinical practice for brolucizumab (Section 1.2). Furthermore, post-hoc analysis from HAWK and HARRIER support re-extension, with patients receiving brolucizumab able to get dry faster and remain dry for longer compared with aflibercept (Section 1.2).

1.1 The SmPC posology wording provides the flexibility for brolucizumab to be administered as a variable dosing regimen

Novartis can confirm that the brolucizumab SmPC posology wording permits the use of variable dosing regimens, which can include dosing intervals longer than every 12 weeks. [1]

As previously noted, the referenced SmPC within the company submission and response to the ERG clarification questions was a draft SmPC and was therefore subject to change based on ongoing consultation with the EMA. The finalised SmPC is now available to support Novartis' interpretation of the posology:[1] *The recommended dose is 6 mg brolucizumab (0.05 ml solution) administered by intravitreal injection every 4 weeks (monthly) for the first 3 doses. Thereafter, the physician may individualise treatment intervals based on disease activity as assessed by visual acuity and/or anatomical parameters. A disease activity assessment is suggested 16 weeks (4 months) after treatment start. 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 physician may further individualise treatment intervals based on disease activity. If visual and anatomical outcomes indicate that the patient is not benefiting from continued treatment, Beovu should be discontinued.*

Consequently, it is reasonable to suggest that brolucizumab should be viewed as a variable dosing regimen, in line with aflibercept and ranibizumab, and that treatment would be extended as part of TREX and PRN regimen dosing where appropriate in UK clinical practice.

Additionally, brolucizumab is the only anti-VEGF treatment approved for wAMD that allows eligible patients to start on q12w dosing intervals immediately after the loading phase. Feedback from UK clinical experts has also indicated that there is an expectation in clinical practice that treatment with brolucizumab will result in fewer injection numbers compared with existing treatment options (Appendix B8.3).

1.2 Extrapolation of the q12w and q8w proportions from the HAWK and HARRIER trials is unlikely to accurately reflect anticipated real-world usage of brolucizumab

In order to estimate the long-term use of brolucizumab as a fixed dosing regimen, the ERG extrapolated q12w and q8w dosing proportions from the HAWK and HARRIER trials at the end of Year 2. HAWK and HARRIER both prohibited dosing re-extensions; following a q8w need, patients could not return to a q12w dosing schedule. This was done in order to accurately ascertain the proportion of patients who were maintained exclusively on a q12w regimen.

Feedback from UK clinical experts unanimously indicated that it is realistic to assume that patients would be considered for extensions to q12w from q8w throughout their journey based on disease activity at each visit, as stated on the finalised SmPC (Appendix B8.3). Experts noted that this is how wAMD is already managed in clinical practice and there is no reason why the approach would be different with brolucizumab (Appendix B8.3).

In HAWK and HARRIER, the majority of patients with a q8w need were identified immediately after the loading dose phase, and patients with no q8w need in the initial q12w cycle had high probabilities of being maintained on a q12w regimen to Week 48 (85% and 82% for HAWK and HARRIER respectively) (Figure 3.4 in the company submission).[2] [redacted] of patients with no q8w need at Week 48 in HAWK and HARRIER, respectively, were maintained on a q12w regimen to Week 96.[3, 4]

In UK clinical practice, some patients may initially require a more frequent treatment interval based on their individual needs. However, clinical experts have highlighted that these patients would be likely to re-extend, unlike the protocol of the HAWK and HARRIER trials (Appendix B8.3).

Therefore, extrapolating the q12w/q8w proportions from HAWK and HARRIER incorrectly assumes that all patients with a q8w need are effectively non-responders or treatment failures and would not be suitable for re-extension to a q12w regimen.

[redacted][3, 4]

Subgroup analysis of q12w/q8w patients must also be interpreted with caution, given that these analyses break the randomisation of the HAWK and HARRIER trials. This results in a subgroup of patients with a q8w need that have notably thicker CSFT at Baseline, who would be expected to be much harder to treat. In these patients, the treatment is not focused solely on achieving BCVA gains; instead, treatment aims to achieve resolution of retinal fluid, whilst maintaining stable BCVA.

Accounting for this limitation, a post-hoc comparison between brolucizumab and aflibercept patients in HAWK and HARRIER with a q8w need by Week 16 was conducted to more closely compare q8w cohorts between the two treatments. This analysis demonstrated that brolucizumab was associated with [redacted] compared with aflibercept (Figure 1). These results are supported by data from the OSPREY trial, which show that a higher proportion of brolucizumab patients (61%) compared to aflibercept (35%) achieved simultaneous intraretinal fluid (IRF)/sub-retinal fluid (SRF) resolution by Week 40 in a matched q8w cohort, suggesting a greater brolucizumab anti-VEGF effect.[5]

Figure 1: BCVA comparison for patients with a q8w need at Week 16 in HAWK and HARRIER

Abbreviations: BCVA, best corrected visual acuity; LS, least squares; q8, every 8 weeks; SE, standard error.
Source: Novartis Data on File[6]

Given this information, Novartis proposes that it is not reasonable to suggest that HAWK and HARRIER patients with a q8w need were treatment failures, and consequently, it is reasonable to assume that patients may be suitable for re-extension to a q12w regimen in clinical practice.

2. Real-world dosing of aflibercept and ranibizumab

The company base case cost-comparison analysis adopted a weighted average approach with regards to the dosing regimens for aflibercept and ranibizumab, based on pooled dosing frequencies derived from company market research survey data. The ERG considered there to be limitations with this approach and instead examined a dual base case considering only TREX and PRN regimens for aflibercept and ranibizumab. The ERG also noted that TREX and PRN regimens could be further extended towards q16w dosing intervals, and that this had not been accounted for.

As stated within the company submission, there is significant variability in anti-VEGF usage in clinical practice across the UK with a number of regimens in use; using the weighted average approach for the base case analysis is therefore considered the most clinically plausible reflection of real-world clinical practice, for the following reasons:

- Although TREX is a majority regimen in practice, as also reflected in the company weighted average approach, fixed dosing regimens have a clear and widespread role in UK clinical practice and cannot be disregarded (Section 2.1).
- The company market research survey provides an informative estimate of UK clinical practice, accounting for significant variability across 50 clinicians and over 5,000 patients. It is reasonable to suggest that this is a more accurate representation of UK clinical practice compared with the ERG dual base case (Section 2.2).
- Limited data exist for the use of q16w intervals; uptake of q16w dosing intervals in the UK is extremely limited and clinicians are not comfortable extending past q12w with aflibercept and ranibizumab (Section 2.3).

2.1 The ERG base case does not reflect the role of fixed dosing regimens or the significant variability in the wAMD treatment landscape

The ERG adopted a dual base case that considered the use of TREX and PRN regimens for aflibercept and ranibizumab alone. Feedback from UK clinical experts sought during the development of this response indicated that TREX is the most commonly adopted dosing regimen, and we note that approximately 50% of patients receive TREX regimens in the company market research survey (Appendix B8.2).

With regards to the use of PRN regimens, however, UK clinical expert feedback highlighted that the use of PRN regimens is both limited and declining; real-world effectiveness of PRN regimens has been observed to be inferior to TREX regimens, and monitoring visits without treatment are an inefficient use of clinical resources (Appendix B8.1). We therefore believe that a comparison assuming that all patients on aflibercept and ranibizumab receive PRN dosing is entirely inappropriate, and this scenario is not explored further within this response.

In contrast to the ERG assumptions, the UK clinical expert feedback sought during the development of this response highlighted that fixed dosing regimens are used in UK clinical practice and have a clear role in the treatment paradigm, citing that better planning can be achieved with simpler, fixed regimens (Appendix B8.1). These regimens are used particularly in the earlier years of treatment, with one clinician suggesting that in Year 1, mainly fixed regimens are used (Appendix B8.1). It was also noted that aflibercept regimens are used more frequently than fixed dosing regimens compared with ranibizumab (Appendix B8.1). Finally, clinical experts highlighted the substantial variability in dosing regimens adopted in clinical practice across the UK.

2.2 Results from the company market research survey have been validated by UK clinical experts as representative of clinical practice, given the substantial variability in dosing regimens adopted in clinical practice across the UK

Firstly, Novartis acknowledges the limitations identified with the company market research survey by the ERG, including the lack of disaggregated data, and the potentially ambiguous survey wording.

Unfortunately, disaggregated data from the company market research survey are not available to Novartis and therefore cannot be shared, as previously highlighted to the ERG. However, as part of this response, we are able to provide additional aggregated data detailing a breakdown of the responses to both the dosing regimens, and the clinicians' response to the initial survey screening questions (Appendix A). It is hoped that these additional data will allay some of the ERG's concerns about the conduct of the survey.

The ERG noted concerns regarding the exclusion of fixed dosing responses of q12w/q8w for ranibizumab and q12w dosing for aflibercept in the weighted analysis. Unfortunately, it was not possible to include these regimens into the NMA due to a lack of clinical data available, and as such, they were excluded from the weighted analysis. However, the estimates reported were very small, representing [redacted] and [redacted] of responses for ranibizumab q12w/q8w and aflibercept q12w regimens respectively.

Novartis acknowledge that the ERG's suggested wording of "remaining on anti-VEGF treatment" could have been a more general question to pose in the survey, to avoid the exclusion of patients treated with dosing intervals longer than q12w. However, as discussed in detail below, many clinical experts are not comfortable extending dosing intervals beyond q12w with aflibercept or ranibizumab and highlighted that the uptake of q16w dosing intervals is extremely limited (Appendix B8.1). Therefore, this is likely to be a very minor limitation.

Furthermore, the clinicians highlighted that treatment regimens vary substantially across the UK, and that the use of a market research survey was a positive step towards the estimation of an

accurate representation of clinical practice (Appendix B8.2). Reflective of this nationwide variation, the responses from the clinicians varied to some extent, but on balance, the UK clinician expert feedback was generally in support of the survey results and suggested that they were sufficiently representative of clinical practice in the UK (Appendix B8.2).

Consequently, the weighted analysis represents the more appropriate approach for the base case cost-comparison analysis, in light of substantial variability in clinical practice in the UK. In contrast, the ERG base case solely examining TREX and PRN based regimens cannot be considered the most plausible representation of UK clinical practice.

2.3 Potential uptake of q16w dosing intervals

The ERG notes that the injection frequency estimates considered in the report do not consider the possibility that aflibercept and ranibizumab flexible dosing regimens are being extended to q16w in clinical practice and that this possibly needs to be considered.

However, there is very limited clinical evidence to support the use of q16w dosing intervals for aflibercept and ranibizumab. The AURA study, examining real-world usage of variable ranibizumab regimens, found that visual outcomes were improved when associated with increased injection and monitoring frequencies.[7]

Clinical experts have reiterated this view and highlight that, in the UK, there is extremely minimal uptake of q16w dosing, with most clinicians not comfortable extending past q12w with aflibercept or ranibizumab. Clinical experts highlight concerns that beyond 12 weeks, patients would not be receiving effective anti-VEGF protection (Appendix B8.4).

In summary, there is very limited evidence to suggest that aflibercept and ranibizumab administered at q16w dosing intervals should be considered relevant comparators in the cost-comparison analysis.

3. Year 3+ dosing intervals

A key difference between the company and ERG base case economic analyses relates to the approach adopted to estimate the number of injections required in Year 3+ for brolucizumab and the relevant comparators. There are significant concerns around the ERG's preferred approach, for the reasons detailed below.

3.1 The ERG aflibercept and ranibizumab dosing frequencies are likely optimistic (lower cost) estimates compared with UK clinical practice

The company base case assumed injection frequency estimates would remain constant between Year 2 and Year 3+ across all treatment regimens. This is a pragmatic approach to overcome the paucity of data on injection frequencies in Year 3+, and results in plausible estimates that are reflective of clinical practice. In contrast, the ERG approach to estimating Year 3+ injection frequencies is associated with more substantial limitations and results in injection frequencies for Year 3+ that are not clinically plausible and would be associated with a substantial impact on visual outcomes that are subsequently not captured within the cost-comparison analysis.

The ERG base case used the methodology adopted in NICE clinical guideline 82 (NG82) to estimate the number of injections required in Year 3+ onwards for aflibercept and ranibizumab TREX and PRN regimens (detailed in full in Table 1).[8]

- Initially, a Year 3+ estimate for ranibizumab PRN (3.7 injections per year) was derived from the age-related macular degeneration (ARMD) database. The difference between the Year 2 estimates for ranibizumab PRN and regimens of interest were then taken from

clinical trials either directly comparing the two regimens, or indirectly by using an additional regimen to link between the two. The ratio between the two Year 2 estimates for the regimens of interest was then calculated. Finally, the same ratio was applied to the ranibizumab PRN value for Year 3+ in order to calculate the Year 3+ estimate for the regimen of interest.

- In order to estimate the Year 3+ injection frequency for aflibercept PRN, the VIEW 1 and 2 trials were examined. In Year 2, the ratio between aflibercept PRN and ranibizumab PRN estimates was calculated as 0.88 (4.9/5.6). This multiplier was applied to the ranibizumab PRN estimate (3.7) to estimate the aflibercept PRN value for Year 3+ as 3.2. No trials directly compared ranibizumab PRN with ranibizumab or aflibercept TREX regimens, so the ranibizumab q4w regimen was used as an intermediate, allowing ranibizumab PRN and TREX regimens to be compared via the CATT and TREX-AMD trials. Finally, this comparison (between ranibizumab PRN and ranibizumab TREX) was used in conjunction with the RIVAL trial to allow an indirect comparison between ranibizumab PRN and aflibercept TREX regimens to be made.

Table 1: Long-term number of treatments per year – variable dosing regimens

Trial	Trial Arms		Mean number of injections in year 2		Formula for relative frequency	Relative frequency vs Rani PRN	Formula for estimated mean injection frequency
CATT VIEW 1&2	Rani PRN	-	-	-	Reference from ARMD database	-	3.7
VIEW 1&2	Afli PRN[a]	Rani PRN	4.9	5.6	(4.9/5.6) = 0.88	0.88	0.88*3.7 = 3.2
CATT[b]	Rani q4w	Rani PRN	22.4	12.6	(22.4/12.6) = 1.78	1.78	N/A
TREX-AMD	Rani TREX	Rani q4w	8.5	12.5	(22.4/12.6)*(8.5/12.5) = 1.21	1.21	1.21*3.7 = 4.5
RIVAL	Afli TREX	Rani TREX	7.3	8.0	(22.4/12.6)*(8.5/12.5)*(7.3/8) = 1.10	1.10	1.10*3.7 = 4.1

Note: The CATT trial was used to indirectly compare between ranibizumab PRN and ranibizumab TREX regimens via the ranibizumab q4w regimen. Ranibizumab TREX was then used to link aflibercept TREX to ranibizumab PRN.
[a]Afli PRN was obtained by pooling Afli 2q4w → PRN and Afli 2q8w → PRN from VIEW 1&2.
[b]For CATT, the number of injections between baseline and two years was used because different populations were analysed at one and two years.
Abbreviations: PRN: pro re nata dosing regimen; qXw: one injection every X weeks; TREX: treat-and-extend dosing regimen.

The NG82 methodology is associated with substantial limitations, and results in a steep decline in injection numbers between Year 2 and Year 3+ for both aflibercept and ranibizumab TREX and PRN regimens (Table 2).

Table 2: Injection frequencies used in the ERG base case

	Brolucizumab	Afli TREX	Rani TREX	Afli PRN	Rani PRN
Year 1	6.7	9.7	9.5	7.1	7.1
Year 2	4.8	7.3	8.2	5.0	5.6
Year 3+	5.7	4.1	4.5	3.2	3.7

Abbreviations: PRN, pro re nata; TREX, treat and extend.

UK clinical experts have indicated that this decline is not representative of clinical practice, and that generally, injection numbers will remain constant or only experience a small decline between Year 2 and Year 3 (Appendix B8.4). As a result, the ERG's estimates are highly optimistic (lower cost) scenarios and effectively assume that all patients are either able to successfully maintain a q12w interval in Year 3+ or discontinue treatment altogether. Clinical experts also highlighted that this decline would also be associated with a substantial reduction in efficacy, a notion which is supported by a number of published studies (Appendix B8.3).[9, 10]

Barthelmes *et al*. (2013) has highlighted that TREX regimens do not always achieve a q12w injection frequency, demonstrating that only 24% of patients receiving an aflibercept TREX regimen were able to achieve a mean injection frequency longer than q11w in Year 2 (14% over the two year study).[11] The AURA study has identified that patients treated in the UK had both increased injection frequencies and improved visual outcomes compared with other countries worldwide, while the SEVEN-UP study has highlighted that close clinical monitoring and ongoing treatment continue to be important for long-term wAMD outcomes after Year 2.[9, 10]

Critically, feedback from UK clinical experts highlighted that the ranibizumab PRN value derived from the ARMD database was likely significantly influenced by service capacity issues at the time and resulted in poor vision outcomes (Appendix B8.4). As a result, using the ARMD value of 3.7 to derive injection frequencies in Year 3+ for all regimens results in low injection number estimates that are unlikely to accurately reflect clinical practice and anti-VEGF treatment need (Appendix B8.4).

In conclusion, the NG82 methodology is heavily influenced by service capacity issues and produces optimistic, low-cost estimates that would be associated with poor visual outcomes in clinical practice. It is therefore reasonable to suggest that the company base case assumption is the more reasonable approach to overcome the lack of Year 3+ data for aflibercept and ranibizumab.

3.2 The ERG mean estimate of 5.7 brolucizumab injections in Year 3+ has significant limitations and does not accurately reflect anticipated real-world usage

The company base case estimated that patients would receive an average of 4.76 brolucizumab injections in Year 3+, assuming that this estimate would remain constant with the mean injection frequency observed across Year 2 in the HAWK and HARRIER trials. As highlighted above, this assumption was made given the lack of data for brolucizumab usage in Year 3+ and was considered a pragmatic solution in the absence of alternative suitable methods. This value is likely a conservative (higher cost) estimate, given that brolucizumab is expected to be used as a variable dosing regimen (Section 1.1) and estimates in Year 3+ could plausibly be lower than in Year 2 (Section 1.2).

In contrast to both the company base case and the approach adopted for aflibercept and ranibizumab, the ERG took a very conservative view for brolucizumab and calculated the Year 3+ estimate from the number of injections required in HAWK and HARRIER at the end of Year 2. The concerns and limitations of this extrapolation have previously been outlined in Section 1.2. This resulted in a mean number of 5.7 injections for brolucizumab in Year 3+. This value incorrectly assumes that all patients in the HAWK and HARRIER trials with q8w need were effectively treatment failures, and does not take into account the fact that the HAWK and HARRIER trials prevented patients from re-extending to a q12w dosing regimen. This estimate also results in an increase in injections numbers between Year 2 and Years 3+; this lacks face validity and is not aligned with the management of wAMD in clinical practice.

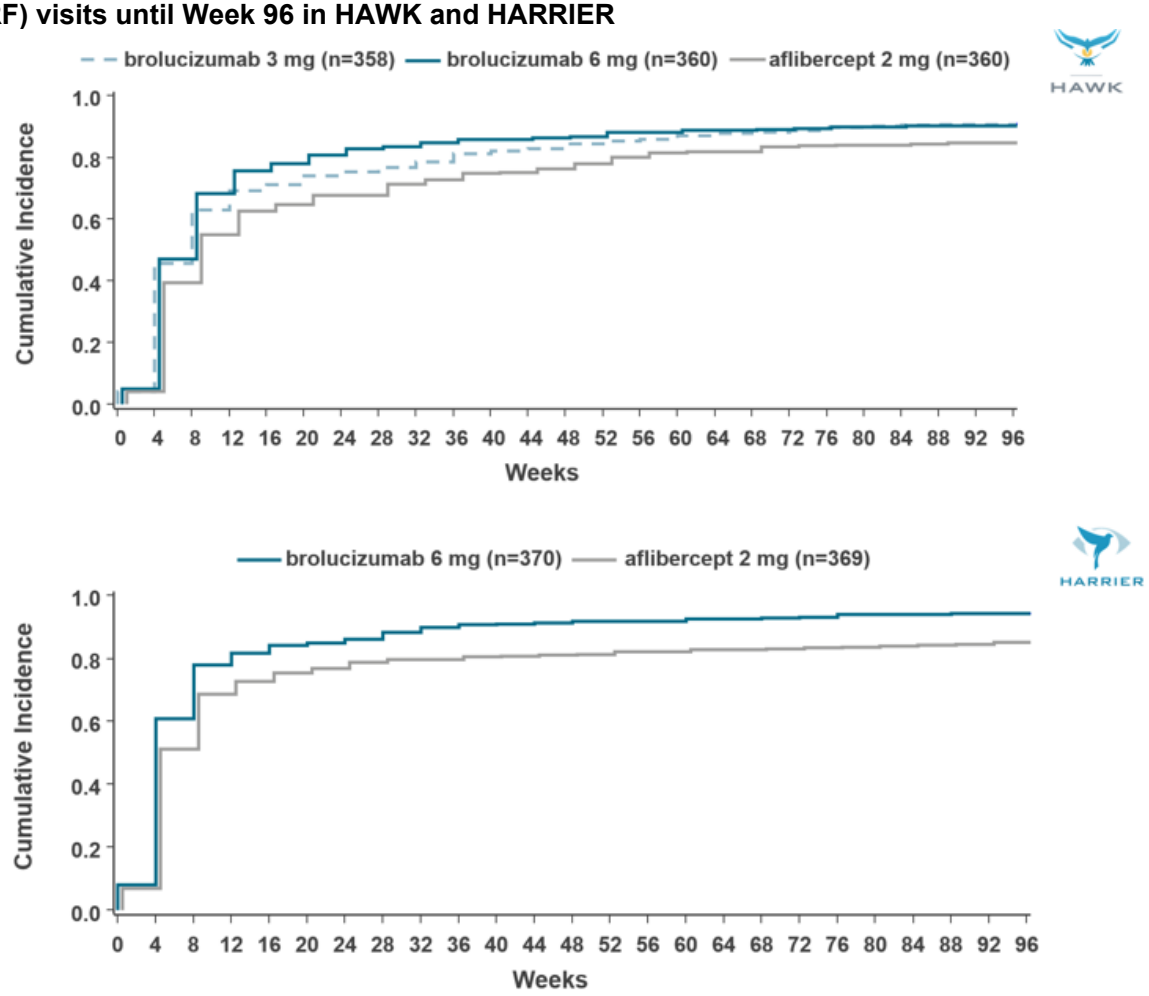
Feedback from all UK clinical experts consulted during the development of this response confirmed that patients with a q8w need would be considered for extension to a q12w regimen

based on disease activity, additionally highlighting that there is no reason to suggest that the injection frequency for brolucizumab will increase after Year 2 (Appendix B8.3). Furthermore, UK clinical experts unanimously selected the company base case estimate of 4.76 injections for brolucizumab in Year 3+ as more clinically plausible compared with the ERG estimate of 5.7 injections, noting that Year 3+ estimates will be the same or lower than Year 2; there is no expectation of an increase from Year 2 (Appendix B8.3).

Additionally, some experts highlighted that the number of brolucizumab injections would be expected to decrease in Year 3+ compared with the 4.76 injections recorded in Year 2 (Appendix B8.3). In the company submission, Novartis also proposed an alternative conservative scenario of 4.00 injections each year for all treatments in Year 3+; some experts noted that although 4.00 injections for brolucizumab could be considered clinically plausible, the estimates for the comparators would be higher (Appendix B8.4).

Furthermore, experts highlighted the HAWK and HARRIER results that showed a higher proportion of patients treated with brolucizumab experience sustained dryness (≥2 consecutive fluid [IRF and SRF] free visits) and were stable at the end of Year 2 compared with aflibercept (Figure 2).

Figure 2: Cumulative incidence of sustained dryness (≥2 consecutive fluid free (IRF and SRF) visits until Week 96 in HAWK and HARRIER



Abbreviations: IRF, intraretinal fluid; SRF, sub-retinal fluid
Source: Regillo et al., 2019[12]

The importance of fluid management was demonstrated in the UK by Chakravarthy *et al.* (2020), identifying that patient eyes with at least two visits with absence of IRF or SRF demonstrated

significantly higher VA gains compared with eyes with fewer clinic visits with absence of fluid.[13] These findings are supported by post-hoc analyses of the CATT and IVAN randomised controlled trials, which demonstrated that higher variation in foveal centre point retinal thickness was associated with significant reduction in measures of visual function.[14]

As a result of this evidence, the consensus from clinical experts is that the decline in injection frequency between Year 2 and Year 3+ could be expected to be greater for brolucizumab compared with aflibercept (Appendix B8.4). Consequently, the company base case estimate of 4.76 injections for brolucizumab in Year 3+ should be considered the more appropriate estimate for the cost-comparison model.

3.3 The comparison between a conservative estimate for brolucizumab fixed dosing regimen and optimistic TREX and PRN regimens for aflibercept and ranibizumab does not accurately represent a true cost-comparison analysis for brolucizumab, and lacks face validity

The company base case uses a consistent assumption to calculate the Year 3+ dosing frequencies for brolucizumab, aflibercept and ranibizumab, for the reasons outlined above. The resulting estimates give rise to a reasonable cost-comparison analysis between the three treatments that is reflective of clinical practice.

In contrast, the ERG methodology differs significantly between brolucizumab compared with aflibercept and ranibizumab. If the ERG approach to estimating injection numbers for aflibercept and ranibizumab is adopted, clinicians highlighted that, in the absence of a more reasonable calculation, the same approach should be applied to brolucizumab.

It is not possible to exactly replicate the NG82 approach for brolucizumab due to a lack of trial data on flexible brolucizumab regimens; however, a pragmatic approach may be used whereby the mean proportional decrease observed between Year 2 and Year 3 for aflibercept and ranibizumab is applied to the Year 2 frequency for brolucizumab.

This results in 2.64 injections for brolucizumab for Years 3+ in the ERG TREX scenario, an estimate that is likely to be substantially optimistic (lower cost) compared with expected clinical practice. However, this highlights that the steep decline between Year 2 and Year 3+ estimates that results from the NG82 methodology is unlikely to accurately reflect clinical practice and results in unrealistic, optimistic (lower cost) estimates that do not reflect optimal outcomes for patients in clinical practice.

In conclusion, the ERG base case combines an optimistic (lower cost) scenario for aflibercept and ranibizumab with a conservative estimate (higher cost) for brolucizumab, an approach which lacks face validity and is unlikely to accurately reflect real-world UK clinical practice (Section 3.3). Applying the ERG methodology to brolucizumab results in a higher validity approach, however the resulting estimates are still unlikely to be reflective of clinical practice. The company approach should therefore be considered the most appropriate, providing the best representation of the expectations in clinical practice.

3.4 Clarification on the dedicated monitoring visits for PRN based on the SALUTE trial

Finally, we note the ERG derives different numbers of dedicated monitoring visits for PRN dosing regimens from NG82 compared to those of the company, despite both referencing the SALUTE trial. For completeness, it is likely that this difference arises because the company submission assumes that 12.7 monitoring visits for PRN regimens are fixed and are unrelated to the number of injections required; this value is derived from NG82. The ERG instead calculates the number of additional monitoring visits required and adds this to the number of injection visits.

4. Company base case

Novartis maintains that the weighted analysis of dosing regimens represents the more appropriate approach for the base case cost-comparison analysis and as such, the results of the company base case are repeated here. The company base case is more appropriate for the following reasons:

- The weighted analysis of dosing regimens facilitates the use of both fixed and flexible dosing regimens. This analysis more accurately reflects the substantial variability in clinical practice in the UK and the clear and widespread role of fixed dosing regimens. In contrast, the ERG does not consider fixed regimens.
- Maintenance of the Year 2 injection frequency of 4.76 for brolucizumab into Year 3+ is the most plausible approach to take in the company base case and clinical expert opinion indicates that this is more plausible compared with 5.7 (as per the ERG base case). Furthermore, brolucizumab should be considered a variable dosing regimen, based on the final EMA-approved SmPC posology wording.[1] Although a paucity of data means that a lower estimate would be unsubstantiated, it is reasonable to assume that the value of 4.76 remains a conservative estimate compared with anticipated usage in clinical practice (Appendix B8.3).
- The company base case assumes that Year 2 injection numbers will continue for Year 3+ for aflibercept and ranibizumab. We consider this is more appropriate than the estimate based on the ARMD database and ranibizumab PRN, which is not reflective of UK clinical practice and has resulted in clinically implausible estimates (Appendix B8.4). Clinical experts have highlighted that estimates used in the ERG base case would be associated with a substantial loss of efficacy for ranibizumab and aflibercept.

The company base case results are presented in Table 3 below.

When adopting the company base case cost-comparison assumptions, brolucizumab remains cost saving over a lifetime time horizon provided the net price of aflibercept is not below [redacted]. This would represent a [redacted]. Any net price for aflibercept that is higher than [redacted] would result in brolucizumab being associated with cost savings versus aflibercept.

Table 3: Company submission base case results (with brolucizumab and ranibizumab provided at net prices; aflibercept provided at list price)

	Brolucizumab 6 mg LP→q12/q8w	Aflibercept weighted[a]	Ranibizumab weighted[a]
Drug costs	[redacted]	£53,515	[redacted]
Admin costs	[redacted]	£5,060	[redacted]
OCT costs	[redacted]	£5,383	[redacted]
FFA costs	[redacted]	£207	[redacted]
AE costs	[redacted]	£0.00	[redacted]
Total costs	[redacted]	£64,164	[redacted]
Incremental costs	-	[redacted]	[redacted]

[a]In the base case analyses, a weighted average approach was adopted with regards to the treatment regimens for aflibercept and ranibizumab based on market share data on the use of each regimen. Scenario analyses for each individual regimen were also conducted.
Abbreviations: AE: adverse events; FFA: fundus fluorescein angiography; LP: loading phase; OCT: ocular coherence tomography; qXw: one injection every X weeks.

Scenario analysis 1: ERG (TREX) base case with company Year 3+ injection frequency for brolucizumab

As highlighted above, we believe the maintenance of the Year 2 injection frequency of 4.76 represents a plausible estimate for the number of injections required with brolucizumab in Year 3+. A scenario analysis has therefore been conducted on the ERG (TREX) base case analysis to include 4.76 injections for brolucizumab in Year 3+. All other assumptions of the ERG (TREX) base case remain the same.

The results of this analysis are presented in Table 4, and demonstrate that brolucizumab remains cost saving over a lifetime time horizon provided the net price of aflibercept is not below [redacted], despite this scenario including very conservative (lower cost) estimates for the comparators. This would represent a [redacted]. Any net price for aflibercept that is higher than [redacted] would result in brolucizumab being associated with cost savings versus aflibercept.

Table 4: ERG (TREX) base case with company Year 3+ injection frequency for brolucizumab (with brolucizumab and ranibizumab provided at their net prices; aflibercept at list price)

	Brolucizumab 6 mg LP→q12/q8w	Aflibercept TREX	Ranibizumab TREX
Drug costs	[redacted]	£39,598	[redacted]
Admin costs	[redacted]	£3,791	[redacted]
OCT costs	[redacted]	£3,565	[redacted]
FFA costs	[redacted]	£207	[redacted]
AE costs	[redacted]	£0.00	[redacted]
Total costs	[redacted]	£47,162	[redacted]
Incremental costs	-	[redacted]	[redacted]

Abbreviations: AE: adverse events; FFA: fundus fluorescein angiography; LP: loading phase; OCT: ocular coherence tomography; qXw: one injection every X weeks.

Scenario analysis 2: ERG (TREX) base case with ERG assumptions applied to Year 3+ injection frequency for brolucizumab

A second scenario analysis has been conducted on the ERG base case whereby the ERG's approach to estimating the Year 3+ injection frequency for aflibercept and ranibizumab has also been applied to brolucizumab.

The results of this analysis are presented in Table 5, and assuming the similar approach for brolucizumab results in 2.64 injections in years 3+. As discussed previously, whilst this estimate is likely optimistic (lower cost), clinician feedback has suggested that this is more valid method to directly compare brolucizumab with the ERG base case, despite the significant limitations associated with this approach.

The results demonstrate that brolucizumab remains cost saving over a lifetime time horizon provided the net price of aflibercept is not below [redacted]. This would represent a [redacted]. Any net price for aflibercept that is higher than [redacted] would result in brolucizumab being associated with cost savings versus aflibercept.

Table 5: ERG (TREX) base case with ERG preferred approach also applied to Year 3+ injection frequency for brolucizumab (with brolucizumab and ranibizumab provided at their net prices; aflibercept at list price)

	Brolucizumab 6 mg LP→q12/q8w	Aflibercept TREX	Ranibizumab TREX
Drug costs	[redacted]	£39,598	[redacted]
Admin costs	[redacted]	£3,791	[redacted]

OCT costs	[redacted]	£3,565	[redacted]
FFA costs	[redacted]	£207	[redacted]
AE costs	[redacted]	£0.00	[redacted]
Total costs	[redacted]	£47,162	[redacted]
Incremental costs	-	[redacted]	[redacted]

Abbreviations: AE: adverse events; FFA: fundus fluorescein angiography; LP: loading phase; OCT: ocular coherence tomography; qXw: one injection weeks

5. Conclusion

In conclusion, the company base case represents the most plausible cost-comparison between brolucizumab, aflibercept and ranibizumab. The ERG base case combines a very optimistic (lower cost) scenario for aflibercept and ranibizumab with a conservative estimate (higher cost) for brolucizumab, an approach which lacks face validity and is unlikely to accurately reflect real-world UK clinical practice.

We would like to reiterate the following key points:

- Weighted comparator regimens as per the company base case reflect the use of several regimens in clinical practice, and facilitate the use of both fixed and flexible dosing regimens (Section 2). Although TREX represents the majority regimen, which is also reflected in the weighted company analysis, the continuing role of fixed regimens cannot be disregarded (Section 2.1). Additionally, the ERG base case compared with PRN only regimens is entirely inappropriate due to the limited and declining use of PRN regimens in practice (Section 2.1).

- The ERG injection number estimates for Year 3+ for brolucizumab (5.7) lack face validity as they result in an increase in injection numbers between Year 2 and Year 3+; this is not reflective of the management of wAMD in clinical practice (Section 3.2). The driver of the ERG estimate is the assumption that patients with a q8w dosing need will never re-extend to q12w dosing; this inability to re-extend was part of the HAWK and HARRIER trial protocols, but is not reflective of expected real-world clinical management (Section 1.2). The ERG estimate is based on the number of injections required from HAWK and HARRIER trial data at the end of Year 2, rather than the average number of injections from Year 2 as per the company base case. There are a number of limitations with this assumption (see Section 1.2 and Section 3.2). We hope that the final EMA-approved SmPC posology wording, and the unanimous feedback from clinical experts provides reassurance that using the average number of injections from Year 2 (4.76) in Year 3+ is more appropriate.

- The ERG injection number estimates for Year 3+ for aflibercept and ranibizumab result in very steep drops between Year 2 and Year 3+; these declines are not reflective of clinical practice and are likely to result in a drop in vision outcomes (Section 3.1). These steep reductions in injection numbers results from using real world (ARMD) ranibizumab PRN data to estimate all other regimens, despite ranibizumab PRN use having been significantly influenced by service capacity issues within this dataset (Section 3.1).

As such, the base case presented as part of the company submission remains the most reasonable approach for the cost-comparison analysis for this appraisal.

6. References

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16. Novartis Data on File. Additional Clinical Expert Feedback. 2020.

7. Appendix A: Additional company market research survey data

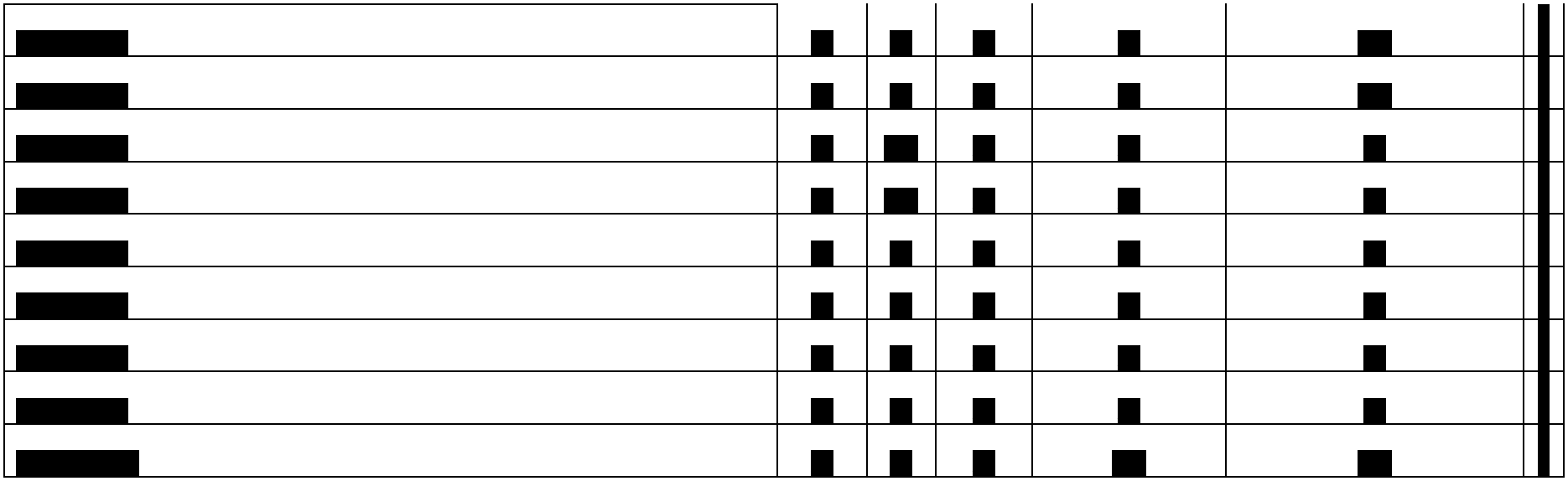
[redacted]

Abbreviations: AMD, age-related macular degeneration; PRN, pro re nata
Source: Novartis Data on File[15]

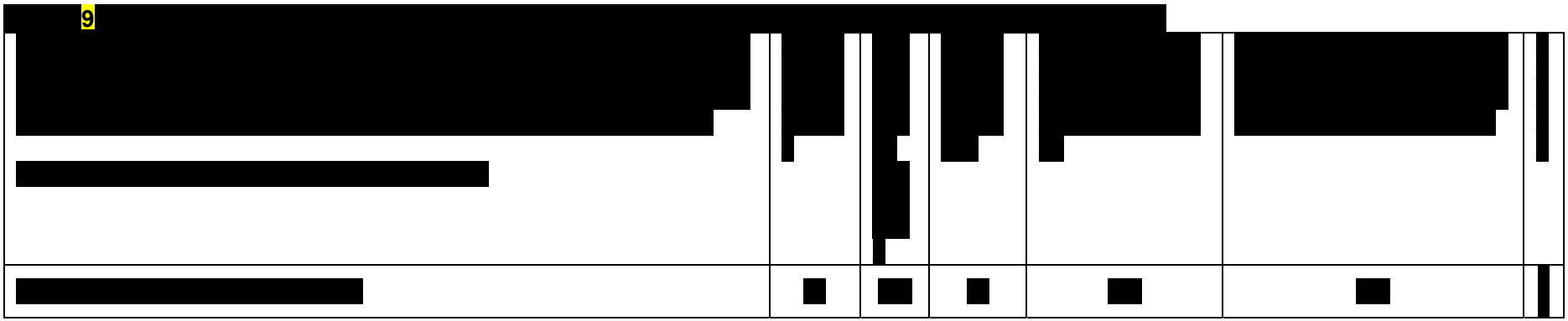
[redacted]

Abbreviations: AMD, age-related macular degeneration; PRN, pro re nata
Source: Novartis Data on File.[15]

[redacted]

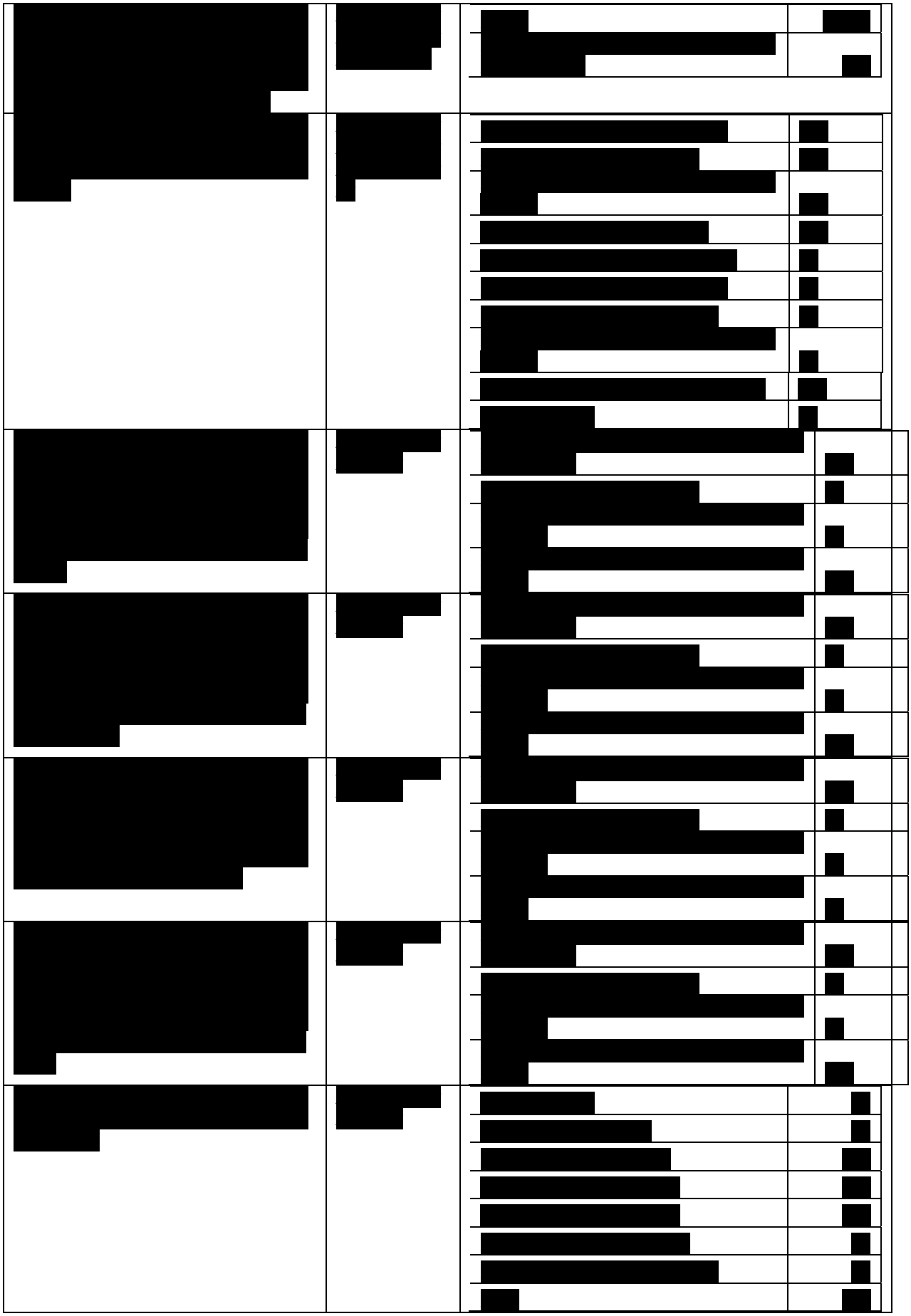


Abbreviations: AMD, age-related macular degeneration; PRN, pro re nata
Source: Novartis Data on File.[15]



Abbreviations: AMD, age-related macular degeneration; PRN, pro re nata
Source: Novartis Data on File.[15]

Table 10: Screening responses from the company market research survey



[redacted]

8. Appendix B: Clinical expert responses

The clinical expert responses described in the main body of the document are presented within this appendix. The responses from eight clinicians have been collated in this response for clarity, but the individual questionnaire responses per clinician are provided within the reference pack accompanying this response.[16] All experts are independent clinical experts practicing within the National Health Service (NHS), with vast experience in delivering retinal services in the UK. The questions were put to the experts individually, over the phone or in person. The notes were then transcribed and shared with the experts for approval. In some cases, the clinicians made additional changes to the wording of the responses.

8.1 Clinical expert opinion on dosing regimens used in UK clinical practice

The ERG assumes that only Treat-and-extend dosing (TREX) and Pro re nata dosing (PRN; 'as needed') regimens are used in clinical practice for the comparators aflibercept and ranibizumab, TREX being the majority regimen, and do not take any fixed regimens into consideration:

- **Is this reflective of practice across the UK?**
- **Is it realistic to assume that fixed regimens are not used in the UK?**

Clinician 1: TREX is the majority regimen, followed by PRN but some centres across the UK use fixed dose regimens. Fixed regimens have a place in clinical practice because the simplicity of the regimen can allow for better planning. The use of PRN is declining because a visit without treatment essentially displaces a treatment slot and is not an efficient use of resources. The real world experience of PRN has been inferior to the real world experience of TREX.

Clinician 2: Not realistic to assume no fixed regimens, some centres use fixed regimens Majority TREX use.

Clinician 3: It is not realistic to assume no fixed regimens, many centres use fixed dosing especially in the 1st 2 years of treatment as this reduces the burden on performing OCT scans. The majority regimens are fixed dosing and TRE in the first two to three years. PRN regimen or monitor and extend tend to be used in year 4 and beyond.

Clinician 4: TREX is a majority regimens, approximately 50% but fixed regimens are also widely in practice. In year 1 of treatment, mainly fixed regimens are used.

Clinician 5: This is unrealistic because a significant number of clinicians use fixed dosing, especially for aflibercept; around 30-40% would be on fixed q8w regimens.

Clinician 6: This assumption may be reasonable for ranibizumab, but fixed regimens are still commonly used for aflibercept in the first year of treatment.

Clinician 7: The majority regimen is TREX but fixed regimens cannot be disregarded, especially for aflibercept in the 1st year. There is very limited PRN use, and usually beyond years 3/4 of treatment.

Clinician 8: TREX is evolving as the majority regimen, often patients transition from fixed dosing as a loading phase, to individualised TREX dosing and eventually PRN within a long term monitoring phase. However some services still follow the original label for Eylea, using fixed 8 weekly dosing after loading in year 1 – some then continue this beyond year 1, in which case fixed dosing is occurring with q8 treatments. Finally, services with very limited capacity eg for

OCT assessments may decide to fix dose for extended periods to avoid the infrastructure needed to assess regularly.

8.2 Clinical expert opinion on the company market research survey

Novartis conducted a network meta-analysis (NMA) to pool data identified for aflibercept and ranibizumab in the clinical systematic literature review, weighting the different treatment regimens based on market share data on the use of each regimen. The market research survey included responses from 50 retinal specialists across the UK, who were asked the percentage of maintenance patients receiving ranibizumab or aflibercept that were using each of the following regimens, after the initial loading dose phase: q4w, q8w, q12w*, PRN, TREX, Other.

The regimens included in the economics model, and associated market share weights are:

Regimen	Weighting based on Novartis market research
Aflibercept	
Afli 2q4w (Fixed)	[redacted]
Afli 2 LP→q8w (Fixed)	[redacted]
Afli 2 LP→q8w→PRN	[redacted]
Afli 2 LP→TREX	[redacted]
Ranibizumab	
Rani 0.5q4w (Fixed)	[redacted]
Rani 0.5q4w→PRN	[redacted]
Rani 0.5 LP→PRN	
Rani 0.5TREX	[redacted]

***q12w was not included in the overall weighted regimen because no trial data was available for inclusion in the NMA; however, only [redacted] respondents reported using aflibercept q12w and [redacted] ranibizumab q12w**

- **Is this sufficiently representative of practice across the UK?**
- **If not, what proportions would you estimate are reflective of <u>national practice</u> (not your own clinical practice)?**

Clinician 1: Yes, the % included present a realistic national picture, with TREX as the majority regimen. For patients on long term treatment beyond 2 years PRN numbers could potentially be higher.

Clinician 2: PRN use likely to be lower, and TREX use higher

Clinician 3: Treatment regimens vary across the country and there is no robust evidence about proportions so a market research survey is a positive step. In general, would expect to see higher proportion of fixed dosing for aflibercept, and lower proportion of fixed dosing for ranibizumab.

Clinician 4: Yes

Clinician 5: Yes this is a broadly fair representation of national practice.

Clinician 6: The fixed regimen % for ranibizumab is likely to be lower than estimated, and slightly higher for aflibercept

Clinician 7: For aflibercept, one would expect to see higher TREX compared with fixed regimens, and similarly for ranibizumab would expect to see less PRN use than estimated.

Clinician 8: Yes, for aflibercept. For ranibizumab, I would have expected less fixed dose regimen use, but as previously this may reflect services with very stretched resources to assess eyes where long periods or fixed dosing are regarded as the only option

8.3 Clinical expert opinion on the assumptions in the economic analysis

In the economic model, Novartis assumes in the base case that the average number of injections received for years 2 from HAWK/HARRIER can be applied to years 3+, that is, 4.76 injections for brolucizumab. The ERG however considers that the proportions of patients on q8w increase throughout year 2 and therefore apply the HAWK/HARRIER week 92 proportions on q12w dosing and q8w dosing to estimate the average number of injections received for years 3+, resulting in 5.7 injections.

The trials do not permit patients to re-extend to q12w if they receive q8w, and the ERG assume that this will be replicated in practice. We believe that in clinical practice that patients will be able to re-extend from q8wk to q12wk if clinically appropriate.

- **Does this reflect your expectations of the use of brolucizumab in clinical practice?**

Clinician 1: Yes, this is the expectation and it will be unrealistic to assume that patients will not re-extend. The company assumption of average number of injections in year 2 is reasonable

Clinician 2: Yes, significant numbers will re-extend. This expectation is supported by the numbers of patients with 2 to 3 consecutive dry visits who would definitely re-extend to q12w in practice.

Clinician 3: Yes, this is very much expected in practice and aligns with how the condition is managed in clinical practice. There is no biological reason why patients on q8w would not re-extend to q12w if clinically appropriate. This would have an effect of reducing mean number of injections in years two and three.

Clinician 4: Patients will be re-extended in clinical practice

Clinician 5: It is expected that patients will be re-extended to q12w. This is not seen in the trials because the study design did not permit re-extension irrespective of subsequent performance. However, in clinical practice, it is expected that extensions and re-extensions will occur.

Clinician 6: Yes patients will re-extend in practice and in clinical practice using TREX q10w would also be an option.

Clinician 7: Yes, there will be a likely -extension in clinical practice as for other anti-VEGFs (TREX), and there is sufficient evidence from the trials that brolucizumab can be extended to q12w, and clinicians would attempt to possibly extend beyond q12w.

Clinician 8: There is a strong expectation that patients will extend from q8w to q12w brolucizumab with time in real-world practice. This is because there is increasing recognition amongst clinicians that TREX is the optimal dosing regimen as it allows individualized care and yet is proactive which is beneficial to the patient and service. Clinicians are aware that RWE supports the superiority of TREX to PRN. The principle of TREX is to achieve optimal disease control with minimal dosing ie to proactively extend the interval between injections. This fits with reducing patient burden and protecting service resources. It is therefore more likely, in my

opinion, that clinicians using brolucizumab would keep trying to extend the interval between injections. I agree that the phenomenon seen in HAWK/HARRIER is due to the design of the protocol which does not allow extension to q12 once a decision to dose once at q8 has been made and this would not fit with real world TREX practice which is compliant with brolucizumab posology.

- Which estimate (4.76 or 5.7) do you consider to be more plausible for the brolucizumab injection numbers in years 3+?

Clinician 1: 4.76. Brolucizumab is expected to have a lower treatment and patient visit burden; it is not anticipated that injection numbers for brolucizumb will increase from year 2 to year 3.

Clinician 2: 4.76 is the most likely scenario; estimates will not increase from years 2 to years 3+.

Clinician 3: 4.76, or fewer

Clinician 4: 4.76

Clinician 5: 4.76, assuming the average number of injections from year 2 is more reasonable

Clinician 6: 4.76, but would expect this to be even lower closer to 4 injections because in clinical practice q8w would be extended back and PRN would be likely used for particularly good responders with even fewer injections. A greater number of injections than ranibizumab and aflibercept is not consistent with available efficacy data.

Clinician 7: 4.76, because in practice of proactive treatment, the average numbers in year 3 are likely to decline not increase compared to year 2.

Clinician 8: 4.76, because treatment burden is expected to decline rather than increase with long term care. As a conservative scenario it may remain steady over time.

8.4 For the comparators, aflibercept and ranibizumab, Novartis assumes in the base case that year 2 injection numbers will continue for years 3+. The ERG disagrees and uses the method adopted in NICE Guideline 82. This approach uses data from Age-related Macular Degeneration (ARMD) database for year 3 for ranibizumab PRN which estimates the number of injections to be 3.7. Year 3 data were not available for the other variable dosing regimens; this approach compared the proportion between each dosing regimen at year 2 with the ranibizumab PRN year 2 frequency and applied the same proportion to Year 3+.

This approach results in a substantial decline in injections numbers for aflibercept and ranibizumab from years 2 to years 3, but not for brolucizumab:

	Brolucizumab		**Afli TREX**	**Rani TREX**		**Afli PRN**	**Rani PRN**
Year 1	6.7		9.7	9.5		7.1	7.1
Year 2	4.8		7.3	8.2		5.0	5.6
Year 3+	5.7		4.1	4.5		3.2	3.7

- **Is this decline from years 2 to years 3 for aflibcercept and ranibizumab reflective of clinical practice in the UK?**

Clinician 1: No. Using real world data is associated with challenges and needs to be interpreted alongside clinical trial data. Capacity to deliver has often influenced real world data. The number of injections remain relatively constant, any declines will be small.

Clinician 2: A decline from years 2 to years 3 for aflibercept and ranibizumab is not unrealistic, but this will be driven by the number of patients who stop treatment (approximately 40%). The reason to stop treatment also relates to capacity issues and therefore vision is impacted. The ranibizumab PRN data is older data reflective of a time when services were struggling with demand; around 3 injections a year is potentially reflective of a failing regimen and realistic clinical concern

Clinician 3: No, these estimates are quite low and decline from year 2 to year 3 is not expected to be so steep. In my practice very few patients on Afli and Rani are sufficiently stable on q12 injections before year 4.

Clinician 4: No, this decline is not reflective of clinical practice

Clinician 5: No, although there may some decline in injection numbers in practice, it is not so drastic especially in the context of maintaining vision. The FRB! report confirms that fewer injections result in vision loss.

Clinician 6: The drop in year 3 for TREX regimens is more than anticipated, would expect around 5 injections at least for TREX regimens. The number for PRN are extremely low and I would be concerned about visual outcomes in these patients.

Clinician 7: No, this drop is not reflective of clinical practice and is likely to be reflective of the modelling approach taken by the ERG where real world PRN data is extrapolated; the ranibizumab PRN data reflects under treatment and corresponding clinical outcomes will be poor as was noted in the RLE study in UK.

Clinician 8: No, the decline is steeper than expected particularly with PRN dosing. Using real-world data is problematic in Europe because it is hampered by adequate capacity, particularly a problem for prn due to the number of assessment visits needed. European RWE such as AURA and the Medisoft EMR publications report undertreatment with prn and not optimal care (visual acuity outcomes in these studies reflect this). Data from other better resourced healthcare systems (eg Australian FRB! Data – suggests a similar number of injections in year 3 for Ranibizumab and Aflibercept reported as 5 injections during that year for both drugs (Bhandari et al Ophthalmology 2020: 127)

- **If this approach is considered reasonable should it also apply to brolucizumab?**

Clinician 1: Although not ideal because of the challenges described above, if this approach is applied to other regimens it should be consistently applied to brolucizumab because its durability is expected to be at least as good if not better.

Clinician 2: Yes. Estimates for brolucizumab in years 3 are expected to be lower than for aflibercept and ranibizumab; by the end of year 2 more patients on brolucizumab will be dry and stable and this will drive numbers even lower in years 3 and beyond

Clinician 3: Yes.

Clinician 4: Yes, if the above approach is used it should also be applied to brolucizumab

Clinician 5: Yes, the same yardstick should apply as brolucizumab will be used the same way in clinical practice. In fact, the expectation is that brolucizumab will last longer, and therefore require less injections in years 2-3.

Clinician 6: Yes

Clinician 7: No, this approach should not be applied to any treatment because it is not an appropriate application of evidence, since clinical practice has changed/ evolved from PRN to more TREX.

Clinician 8: The approach is not reasonable based on the inaccuracy of RWE for PRN protocols and a measure of therapeutic need. However if it is deemed essential to use this flawed approach then yes all drugs should be assessed with the same algorithm

- **If the injection numbers decrease to the levels described above for years 3+ is there a corresponding impact on efficacy?**

Clinician 1: Yes, efficacy will be sacrificed.

Clinician 2: Yes, particularly if reduction in injection numbers relates to capacity constraints.

Clinician 3: Yes, the numbers are a sharp drop and are likely to have an impact on vision.

Clinician 4: Yes, these numbers may be reflective of under treatment and this will impact vision.

Clinician 5: Definitely, visual outcomes will worsen, and this is supported by experience in current practice as well as evidence from AURA, SEVEN-UP studies

Clinician 6: Yes, in particular for the PRN regimens the numbers are too low and may represent under treatment.

Clinician 7: Yes, clinical outcomes will – decline as was observed in the RLE studies.

Clinician 8: Yes, vision outcomes would not be adequate. Recent meta-analysis of data with Ranibizumab and Aflibercept suggest that with individualised dosing each extra injection deemed necessary for disease control produces an extra letter of vision improvement (Spaide R AAO 2019)

- **The ERG considers that the numbers estimated above for aflibercept and ranibizumab could be even lower if q16w dosing is considered. What is the uptake of q16w dosing for aflibercept and ranibizumab in practice?**

Clinician 1: Q16w dosing uptake is low. Most clinicians are not comfortable extending to q16w. There is a concern that patients beyond 12 weeks would not be receiving anti-VEGF protection.

Clinician 2: Extremely minimal uptake; driven by lack of clarity on the pathway (for example, once moved to q16w would patients be moved back or would they stay on q16w for the long term) and the lack of supportive data.

Clinician 3: Extremely limited q16w uptake in practice.

Clinician 4: Unable to comment fully due to lack of experience with this, but in general no knowledge of it being used in UK clinical practice

Clinician 5: There is no uptake of q16w dosing, as the experience is that most patients will not be able to extend beyond q12w without a compromise on outcomes. In reality, clinical experience indicates that some eyes require 4-6 weekly injections of aflibercept or ranibizumab. Only a few may be extended to q16w currently. However, the majority cannot be extended to more than q10w - q12w intervals. Emerging data suggests more than 60% require q10w or more frequent treatments.

Clinician 6: There is very little experience in practice of getting patients to q16w and keeping them there without any negative impact on outcomes. There is very low uptake in practice.

Clinician 7: It is very unusual and very infrequent to achieve q16w extension in clinical practice, most clinicians are restricting extension to q12w where successful extension is possible to that duration.

Clinician 8: There is currently very limited usage due to lack of experience in practice, issues with being able to pick up reactivation of disease in a timely manner and also to appropriately monitor the 2nd eye. Over time, if q16w usage increases, this confidence to extend the interval may well also apply to brolucizumab.

- **An alternative scenario put forward by Novartis based on clinical expert feedback assumes that all 3 regimens are associated with the same number of injections (4 per year) from years 3+. Is this reasonable from a clinical perspective?**

Clinician 1: The company base case approach is more reasonable

Clinician 2: This will be a conservative scenario for brolucizumab because expectation is that injections numbers will be lower with brolucizumab.

Clinician 3: No, the numbers for brolucizumab are expected to be lower than for aflibercept and ranibizumab.

Clinician 4: Assuming 4 injections in years 3+ for brolucizumab seems appropriate, will be higher for aflibercept and ranibizumab

Clinician 5: 4 injections for brolucizumab seems reasonable but estimates are likely to be higher for aflibercept and ranibizumab and may be as high as 5-6.

Clinician 6: This would be a more reasonable model than a greater number of brolucizumab injections.

Clinician 7: An estimate of 4 injections per year is reasonable for brolucizumab but possibly can be higher for aflibercept and ranibizumab.

Clinician 8: Although brolucizumab has demonstrated better fluid resolution, this is not unreasonable in the context of limited comparative trial evidence beyond year 2

8.5 Clinical expert opinion on fluid resolution in clinical practice

The ERG cites the FLUID study, stating that it provides evidence that a more relaxed TREX regimen tolerating some sub retinal fluid was comparable in clinical effectiveness to a more intensive TREX regimen aiming to resolve all subretinal fluid accumulation and required fewer injections (15.8 vs 17) in the first two years.

- **What is your opinion on the importance of fluid resolution to maintaining patients in clinical practice?**

Clinician 1:

**Please note that, due to time constraints, it has not been possible to obtain a sign-off from Clinician 1 for this question. This response can be followed up if required.*

Clinician 2: I do believe and all expert panels I have attended or contributed to believe that to dry the retina is beneficial. It is worth noting that the numbers of injection numbers in both arm is way above the real world and other studies that the ERG have quoted.

Clinician 3: Majority of clinicians treat to dry because this is considered important for outcomes. The FLUID study is not directly translatable into practice, and both arms in the FLUID study had high injection numbers. The message from FLUID is that visual acuity can be maintained by very frequent injections even though there is persistent SRF. It should not be interpreted as supporting the practice of reducing injection frequency to allow recurrence of SRF in those cases that have responded previously.

Clinician 4: The approach in practice is to treat fluid. The only reason to tolerate fluid may be if there is atrophy underneath in which case treatment stopping rules would apply.

Clinician 5: Fluid is detrimental to outcomes and indicates eventual degeneration of the retina. That is confirmed by the recent combined analysis of the CATT and IVAN OCT 'fluid data' (Chakravarthty et al, 2019 EURETINA), and a UK EMR cohort data (Chakravarthy U et al, 2020 Eye (Lond). 2020 Feb 17. doi: 10.1038/s41433-020-0799-y. Epub ahead of print). There is no tolerance for fluid in clinical practice.

Clinician 6: The aim in clinical practice is to clear fluid, and the levels of fluid seen in the FLUID study relaxed TREX regimen would not be tolerated in clinical practice. Of note, the overall visual outcomes in the FLUID study were poor.

Clinician 7: There is evidence available that shows that presence of retinal fluid results in worse outcomes for patients (IVAN, CATT). The aim in practice is to treat to dry the retina. Furthermore defining a level of tolerable fluid consistently is challenging to apply in clinical practice.

Clinician 8: In practice, fluid is treated as an indicator of active disease in patients with nAMD. This approach has evolved from a large number of RCTs where the presence of fluid of any type indicated disease activity and was treated by more frequent injections. It may be that SRF is a biomarker for a "milder" form of nAMD and hence its presence carries a better prognosis but that does not necessarily mean that the presence of SRF should be ignored. The FLUID study is a single RCT with an arbitrary threshold of a 200um measurement of SRF – clinicians generally feel that they would not ignore increasing SRF particularly accompanied by visual loss even if the fluid measured less than 200um. Whilst the findings of FLUID are interesting and merit further studies for clarification, this study alone will not necessarily lead to any change in practice.

