Evidence Review Group's report

Title: Brolucizumab for treating wet age-related macular degeneration

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Date completed	*24/07/2020 with addendum added*

Source of funding: This report was commissioned by the NIHR Systematic Reviews Programme as project number 13/05/26.

Declared competing interests of the authors

Samer Elsherbiny declared that he had received speaker and conference fees from Novartis, Bayer, Alimera Sciences and Alcon unrelated to brolucizumab. All other authors declared that they have no competing interests.

Acknowledgements

We are grateful to Professor Norman Waugh (Warwick Medical School, University of Warwick) for sharing his subject expertise in this topic area.

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.

This report should be referenced as follows:

Chen, Y-F., Cummins, E., Osokogu, O., Tsertsvadze, A., Brown, A., Patel, M., Elsherbiny S, Clarke, A., Sutcliffe, P. Brolucizumab for treating wet age-related macular degeneration: A Fast Track Appraisal. Warwick Evidence, 2020.

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 *w*as 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]

* 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	[redacted]	[redacted]	[redacted]
SA01. Baseline age 65	[redacted]	[redacted]	[redacted]
SA02. 50% female	[redacted]	[redacted]	[redacted]
SA03. Discount rate 0%	[redacted]	[redacted]	[redacted]
SA04. FEI developing wAMD 7.5%[1]	[redacted]	[redacted]	[redacted]
SA05. Bilateral treatment multiplier	[redacted]	[redacted]	[redacted]
SA06. AFLI 2mg q4w	[redacted]	[redacted]	[redacted]
SA07. AFLI 3mg q4w -> PRN	[redacted]	[redacted]	[redacted]
SA08. AFLI 2mg LP -> q8w	[redacted]	[redacted]	[redacted]
SA09. AFLI 2mg LP -> q8w -> PRN	[redacted]	[redacted]	[redacted]
SA10. AFLI 2mg LP -> TREX	[redacted]	[redacted]	[redacted]
SA11. RANI 0.5mg LP -> PRN	[redacted]	[redacted]	[redacted]
SA12. RANI 0.5mg LP -> PRNX	[redacted]	[redacted]	[redacted]
SA13. RANI 0.5mg PRN	[redacted]	[redacted]	[redacted]
SA14. RANI 0.5mg TREX	[redacted]	[redacted]	[redacted]
SA15. RANI 0.5mg q4w	[redacted]	[redacted]	[redacted]
SA16. RANI 0.5mg q4w -> PRN	[redacted]	[redacted]	[redacted]
SA17. Discontinuation NMA fixed effects	[redacted]	[redacted]	[redacted]
SA18. Discontinuation NG82 App. J	[redacted]	[redacted]	[redacted]
SA19. Inject/Monitor NMA fixed effects	[redacted]	[redacted]	[redacted]
SA20. Inject/Monitor Yr 3+ piecewise NMA	[redacted]	[redacted]	[redacted]
SA21. Additional Year 1 BROL Injection	[redacted]	[redacted]	[redacted]
SA22. Inject/Monitor NMA expert opinion	[redacted]	[redacted]	[redacted]
SA23. 36.8% Day case admin (NG82)	[redacted]	[redacted]	[redacted]
SA24. TA294 assumptions	[redacted]	[redacted]	[redacted]
SA25. TA294 costs and assumptions	[redacted]	[redacted]	[redacted]
SA26. AEs included: 96 week baseline RE	[redacted]	[redacted]	[redacted]

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 (%) Baseline CST (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Week 92 dosing[2]	q12w	q8w	q12w	q8w
N (%) 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]