# Faricimab for treating diabetic macular oedema

**Produced by**        Southampton Health Technology Assessments Centre (SHTAC)

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treatment with anti-VEGF treatment, including aflibercept, over time in different countries for AMD; and Novartis (manufacturer of ranibizumab) in relation to broluzicumab in AMD.

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Information reported in Table 2.

**Rider on responsibility for report**
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# 1 Summary of the ERG's view of the company's FTA case

## 1.1 The technology is pharmacologically similar to the comparators

In the current appraisal faricimab is intended for treating the eye condition diabetic macular oedema (DMO). Faricimab is a humanised bispecific antibody that acts on two distinct pathways, angiopoietin-2 (Ang-2) and vascular endothelial growth factor A (VEGF-A). These pharmacological pathways are aimed at reducing vascular leakage, neovascularisation and inflammation (CS section 1.3.3).

The two chosen cost comparators, aflibercept and ranibizumab, target all isoforms of VEGF-A. However, aflibercept binds to VEGF-A with a higher affinity than ranibizumab, and additionally targets VEGF-B and placental growth factor.[1]

The ERG's interpretation (confirmed by all four of our clinical experts) is that all three drugs are similar in terms of targeting VEGF-A, but faricimab is distinctive in targeting Ang-2. The company suggest that faricimab's dual mechanism of action translates to extended treatment intervals up to every 16 weeks, with efficacy and safety comparable to aflibercept (CS section 1.3.3). Three of our experts considered that extended treatment intervals are desirable in clinical practice. Two experts independently expressed the opinion that that while the Ang-2 action of faricimab may reduce inflammation, this remains to be demonstrated in clinical practice.

## 1.2 The selected comparators are appropriate

The company have positioned faricimab as a first-line treatment for people with vision impairment due to DMO and a central retinal thickness (CRT) ≥ 400 μm (CS Figure 2). The clinical experts advising the ERG agreed with the company's positioning of faricimab in the clinical pathway as a first-line therapy (CS Table 1 and CS section B.1.3.2). As stated in CS section B.1.3.2, NICE recommend both aflibercept and ranibizumab for people with a visual impairment caused by DMO and a CRT of ≥ 400 μm.[2, 3] The ERG's clinical experts agreed that aflibercept and ranibizumab are the most appropriate comparators for faricimab for treating visual impairment due to DMO in people with a CRT of ≥ 400 μm. The other treatments specified in the NICE scope either would be used off-label in people whose treatment eye has a CRT between 200 and 400 μm (bevacizumab), or as a second-line treatment (dexamethasone intravitreal implant and flucinolone acetonide intravitreal implant). Our clinical experts also stated that laser photocoagulation is now not generally used in practice, as better alternatives are available. Two experts commented that it is mainly used now for DMO that does not involve the centre of the retina and one noted it is also used in pregnant women. Another expert disagreed that laser is mainly used where there is non-central involvement, noting that macular

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laser therapy is a treatment option for people with DMO and a CRT < 400 μm. They stated that laser is a relevant comparator for faricimab for the CRT < 400 μm patient subgroup.

The CS states that market share data from January to April 2021 indicate that ███████████████████████████████████████████████████ (CS section B.1.3.2) but the company do not provide a reference to the source of these data or explain how these figures were obtained. The ERG's clinical advisors' estimates of the proportion of patients treated with aflibercept are higher (80% to 95%) than those stated by the company. Accordingly, the ERG's clinical experts provided lower estimates of the proportion of patients treated with ranibizumab (15% to 5%). Three of the ERG's experts agreed that treatment for DMO would be started with aflibercept or ranibizumab if a person's vision was better than 6/9 but if vision was below 6/9 aflibercept was considered more effective (based on the DRCR Protocol T trial[4]) and hence preferable. However, the fourth clinical expert questioned whether this is a standard practice.

We conclude, based on clinical expert advice, that the company's selected comparators of aflibercept and ranibizumab adequately represent NICE recommended treatments for treating visual impairment due to DMO in terms of efficacy, safety and cost for people with CRT of ≥ 400 μm.

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

### 2.1  Population

The NICE scope specifies the relevant population is people with visual impairment because of DMO. This is consistent with the expected marketing authorisation for faricimab, the population section of the company decision problem in CS Table 1 and the clinical effectiveness data presented in the CS. However, in the comparator section of CS Table 1 and in Figure 2 of the CS, faricimab is positioned as a first-line treatment option for patients with vision impairment due to DMO and central retinal thickness (CRT) ≥400μm. This aligns with the previous appraisals for the two chosen comparators of this cost-comparison (see section 2.2 below) and our clinical experts' opinions.

### 2.2  Comparators

The comparators in the company's Decision Problem are consistent with those in the NICE scope and are considered appropriate by the ERG and clinical experts (see section 1.2 above)

### 2.3  Outcomes

The outcomes specified in the company's decision problem are aligned with those in the NICE scope with the following two exceptions:

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1. The NICE scope specifies cataract surgery as an outcome but this is not included in the company decision problem. According to the company's response to clarification question A2, ocular adverse events, including cataracts were captured in the RHINE and YOSEMITE trials, but cataract surgery was not.

2. The NICE scope specifies disease severity as an outcome but this is not included in the company decision problem. According to the company's response to clarification question A2 the severity of DMO is captured in the change in Diabetic Retinopathy Severity Score (DRSS), which is an outcome in the pivotal clinical trials included in the submission (see section 3.1.2). Two of the ERG's clinical experts independently agreed that the DRSS is a standard tool for measuring disease severity in clinical practice. However, a third expert noted that the DRSS measures severity of diabetic retinopathy, not specifically severity of DMO. The ERG understand that "disease severity" is a broad outcome that could encompass other outcomes already included such as visual acuity and CRT which each contribute different information on disease severity.

# 3 Summary of the ERG's critique of clinical effectiveness evidence submitted

## 3.1 Clinical evidence submitted by the company

### 3.1.1 The company submission

The CS comprises a main evidence submission document (Document B), an evidence submission summary (Document A) and appendices to Document B. The CS includes two phase III company-sponsored trials comparing the efficacy of faricimab against aflibercept: YOSEMITE[5] and RHINE.[6] The company provided the primary clinical study report (CSR) for each trial as well as a meeting presentation reporting year one results from the trials.[7] The company state that phase III trials comparing faricimab against ranibizumab are not available (CS section B.3.9) and therefore network meta-analyses (NMAs) were conducted to assess the similarity of the efficacy and safety of faricimab versus ranibizumab (described in section 3.4 below).

### 3.1.2 Trial design

CS sections B.3.2 and B.3.3 provide details of the design and methodology of the YOSEMITE and RHINE trials. Participant flow is described in CS Appendix D.1.2. The trials had identical designs and included a mix of treatment-naïve patients (approximately 78%) and previously-treated patients (approximately 22%) (CS section B.3.3.3). Most analyses are based on the intention-to treat (ITT) population with results for a per protocol analysis provided to support noninferiority inferences for the primary outcome. As noted in section 2.1 above, the company's intended position of faricimab is as a

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first-line treatment for people who have CRT ≥400 μm. However, this is not consistent with the trial populations which included people with any CRT and some whom had received prior therapy. Implications for the external validity of the trials are discussed in section 3.2.3 below.

The treatment groups evaluated in the trials (described in detail in CS section B.3.3.1) were faricimab Q8W (once every eight weeks), faricimab PTI (personalised treatment interval) and aflibercept Q8W. In the PTI group, faricimab dosing could be extended, reduced or maintained at 4-week increments within the range Q4W to Q16W. The dosing schedule in the faricimab PTI arm reflects that in the faricimab draft Summary of Product Characteristics (SmPC), while the dosing schedule in the faricimab Q8W arm does not. The aflibercept dosing schedule reflects that specified in the aflibercept SmPC and as such is an appropriate comparison.

Outcomes in the YOSEMITE and RHINE trials are reported during the first year of treatment. The primary outcome was mean change from baseline in best-corrected visual acuity (BCVA) (CS section B.3.6.1). The company used a noninferiority margin of > -4 letters for this outcome for assessing noninferiority of faricimab against aflibercept, which we agree is appropriate. The company defined change in the primary outcome at 1 year in the YOSEMITE and RHINE trials as the average of the week 48, 52 and 56 visit data, rather than using the week 52 results. Reasons are given in clarification response A3 (c) which we believe are appropriate. For brevity, in the present report we refer to the primary outcome being the mean change from baseline in BCVA at 1 year.

Secondary outcomes included change in Diabetic Retinopathy Severity Scale (DRSS); the proportion of patients gaining, and the proportion avoiding losing, ≥10 or ≥15 letters of vision on the ETDRS (Early Treatment Diabetic Retinopathy Study) scale; change in health-related quality of life (HRQoL) assessed using the NEI VFQ-25 instrument; mean change in central retinal thickness (CRT); the proportion of patients with absence of intraretinal fluid and with absence of DMO; and adverse events. Note that the definition of CRT varies slightly across trials of DMO therapies; in the YOSEMITE and RHINE trials CRT refers specifically to the circular area 1 mm in diameter centered around the mid point of the fovea, which the CS refers to as the central subfield thickness.

Data from the YOSEMITE and RHINE trials were pooled for the efficacy analyses, due to their identical design (CS section B.3.6) and we agree that this is appropriate.

Clinical efficacy outcomes which informed the previous NICE appraisals of aflibercept (TA346) and ranibizumab (TA274) are summarised in CS Table 4. Outcomes which inform the economic analyses for the appraisals of aflibercept, ranibizumab and faricimab are shown in Table 1 below. In the

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present report we briefly summarise all the key efficacy and safety outcomes reported by the company.

**Table 1. Clinical efficacy and safety outcomes which inform the economic analyses of aflibercept, ranibizumab and faricimab for treating DMO**

| Outcome | Included in aflibercept TA346 cost-utility model | Included in ranibizumab TA274 cost-utility model | Reported in current company evidence synthesis [a] | Included in current cost-comparison model |
|---|---|---|---|---|
| Mean change in BCVA based on ETDRS letters | Yes | Yes | Yes | Yes |
| Probabilities of gaining or avoiding loss of 10 or 15 ETDRS letters | Yes [b] | No | Yes | No |
| Mean change in HRQoL) | Yes (EQ-5D) | Yes (EQ-5D) | Yes (NEI VFQ-25) | No [c] |
| Frequency of injections | Yes [b] | No | No [d] | Yes [d] |
| Ocular adverse events | Yes | Yes | Yes | No [c] |
| Non-ocular adverse events | No | Yes | Yes | No [c] |

ETDRS: Early Treatment Diabetic Retinopathy Study
[a] Source: YOSEMITE [5] and RHINE [6].
[b] This was derived from from a network meta-analysis in TA346.
[c] Assumed the same for faricimab, aflibercept and ranibizumab so excluded from the cost comparison model (CS section 4.2.1).
[d] CS section 4.2.8 states injection frequency was derived from pooled data from the YOSEMITE and RHINE trials although this outcome is not reported in the company's clinical outcomes section (CS section B.3.6).

CS section B.2.2 states that key drivers of the cost-effectiveness analysis in the aflibercept appraisal (TA346) were "the model time horizon, the relative efficacy for both aflibercept and ranibizumab, the cohort starting age and the number of ranibizumab injections at year 1". However, we note that according to the Committee papers and ERG report for TA346[3] the aflibercept cost-utility model was sensitive particularly to HRQoL and injection frequency.

### 3.1.3    Key clinical efficacy results from the pivotal trials

The key clinical efficacy results for the pooled ITT population across YOSEMITE and RHINE were:

- **Primary outcome: Adjusted mean change from baseline in BCVA at 1 year:** Noninferiority of faricimab was demonstrated for both faricimab Q8W and faricimab PTI when compared against aflibercept Q8W in the pooled ITT population (difference: 0.7 letters (95% CI: -0.4, 1.7) and 0.6 letters (95% CI: -0.4, 1.7), respectively) (CS section B.3.6.1). Results of the per protocol analysis (CS Table 10) ██████████████████████████████████████████████.

- **Key secondary outcomes:**

    o **Change in DRSS:** Both faricimab Q8W and PTI regimens were statistically ████████████ aflibercept Q8W (CS Table 12) (consistent with per protocol analysis reported in section 5.3.1 of the clinical study reports).

    o **Proportions of participants gaining or avoiding loss of ≥15 or ≥10 letters in BVCA from baseline at 1 year:** ██████████████████████████████████████████ gained or avoided losing ≥15 or ≥10 letters (CS section B.3.6.2).

    o **Health-related quality of life:** There was ███████████████████████████████████ between the faricimab and aflibercept treatment arms in change from baseline in the NEI VFQ 25 composite score at 1 year. There was also ████████████████████████████████████████████ between the pooled trials arms in the proportion of participants achieving a ≥4-point improvement from baseline (the ████████████████████████████████████████) (CS Table 18).

    o **Change in CRT:** Both faricimab Q8W and PTI regimens were ████████████ aflibercept Q8W, with █████████████████████████████████████████████ in CRT in the faricimab groups (CS Table 16).

    o **Proportion with absence of DMO (CRT<325 μm):** This was ██████ in both faricimab Q8W and PTI regimens than aflibercept Q8W but not tested statistically.

    o **Proportion with absence of intraretinal fluid:** This was statistically ██████ for both faricimab Q8W and PTI regimens than aflibercept Q8W (CS Table 17).

- **Subgroup analyses:** Of the subgroups specified to be of interest in the NICE scope, the company provided results for previous treatment history (whether or not participants had received prior intravitreal anti-VEGF therapy) and baseline visual acuity (BCVA of ≥ 64 letters and ≤63 letters) (CS Appendix E) (see also discussion of the treatment-naïve subgroup in section 3.2.3). The mean change from baseline in BCVA at 1 year in these subgroups ██████████████████████████████████████████████.

## 3.2 Critique of the clinical effectiveness evidence submitted

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### 3.2.1　Company searches for clinical evidence

The company's searches for clinical effectiveness evidence were initially performed up to October 2020 and updated in September 2021 (CS Appendix D). Systemic therapies (non-biologic and biologic) specified in the NICE scope were included apart from fluocinolone acetonide. This omission is inconsequential, as fluocinolone acetonide was not included in the company's decision problem (see section 2). The search identified a total of 26 studies for inclusion in network meta-analyses (see section 3.4.1 below) including the two pivotal phase III randomised controlled trials (RCTs) of faricimab versus aflibercept, YOSEMITE and RHINE. The ERG consider the searches and selection criteria to be appropriate. According to the company's responses to clarification questions A10 to A14 and A20, and the ERG's scrutiny of other relevant recent systematic reviews and meta-analyses on DMO,[8-19] we believe that all relevant published trials for the company's NMAs were identified.

### 3.2.2　Internal validity of faricimab trials

The company assessed the RHINE[6] and YOSEMITE[5] trials as being of moderate-to-high quality, using the NICE quality appraisal checklist (CS section B.3.5 and CS Appendix D.1.3). The ERG independently assessed the quality of the trials using the NICE checklist. Based on our assessment, we considered the trials to be well conducted and of a low risk of bias. The only exception to this was footnotes to CS Tables 13 and 14 state that missing data were not imputed in the ITT analyses of the gaining or not losing ≥15 letters in the study eye BCVA in the individual. The extent of missing data and reasons for missingness are unclear for these outcomes and there is therefore an unclear risk of attrition bias for these outcomes (although they do not directly inform the economic model).

The company stated it was 'unclear' if there was adequate blinding to participant allocation in the RHINE trial[6] (CS Table 8). We note that the RHINE[6] and YOSEMITE[5] trials were both double-masked (CS section B.3.2). The trials' clinical study reports,[5,6] show that the same masking procedures were used in both trials. From the information provided in the clinical study reports, we considered that care providers, participants and outcome assessors had been adequately masked to the participants' treatment allocations. We note

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████████████████████████████████████████████████████. We regarded the risk of bias from this to be low.

Both trials were adequately powered, with planned sample sizes reached (CS B.3.4.3 and CS Appendix D.1.2). We consider the statistical methods used in the trials to be appropriate.

**ERG conclusion:** Overall, we consider the trials to have been well designed and conducted with low overall risk of bias (except for an uncertain risk of attrition bias for the change in ETDRS letters outcomes which do not directly inform the economic model).

### 3.2.3 External validity of faricimab trials

**Relevance of the trials to people with DMO and CRT≥400 μm**

NICE recommend the comparators aflibercept and ranibizumab for treatment of DMO specifically in people who have CRT ≥400 μm. As discussed in section 3.1.2 of this report, participant eligibility for the YOSEMITE and RHINE trials was not restricted to people who had a CRT ≥ 400 μm and the company have not presented subgroup analyses for this population in the CS. They also did not report the number and proportion of participants who had a CRT ≥400 μm at baseline. The company state in CS section B.4.2.3 that the trial was not stratified at randomisation by a CRT of </> 400 μm and therefore conducting post-hoc subgroup analyses would break randomisation. We agree that there would be limitations to the subgroup analyses, but we believe that provision of these analyses would have provided a useful validation of the company's assertion, based on clinical expert advice they received that the efficacy and safety of faricimab in people with a "CRT > 400 μm [sic]" (CS section B.4.2.3) would be similar to the overall trial population of people with any CRT.

In a clarification response (17 [a]) the company provided the number of participants in these subgroups which shows that 30-35% of the ITT populations in the YOSEMITE and RHINE trials had baseline CRT <400 μm. The company also provided efficacy results for the CRT ≥400 μm subgroup for the primary outcome (i.e. mean change in best-corrected visual acuity [BCVA] score at 1 year) for the YOSEMITE and RHINE trials (clarification A17 [b]). Based on these data, faricimab appears to be ████████████████████████████████████ in improving BCVA in the target population who have DMO and CRT ≥400 μm. However, we note that the subgroup analysis may be underpowered statistically for confirming noninferiority of faricimab. The company did not provide CRT ≥400 μm subgroup analyses for any of the other outcomes assessed. One of the ERG's four clinical experts expressed concern that relatively limited evidence has been provided for the target population with CRT ≥400 μm given that this is the population for whom NICE recommend the comparator therapies and is the population for which the company are positioning faricimab.

**Relevance of the trials to treatment-naïve patients**

The company's positioning of faricimab is as a first-line therapy (CS Table 1). Approximately 78% of patients in the YOSEMITE and RHINE trials were treatment-naïve whilst approximately 22% had received prior DMO therapy (CS section B.3.3.3). The company present mean change in BCVA results for the treatment-naïve subgroup in CS Table 10. Note that this was a pre-specified subgroup

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and a relatively large sample size was obtained by pooling the data across the two identical pivotal trials. The mean difference in change from baseline in BCVA between both faricimab Q8W and PTI and aflibercept Q8W in the treatment-naïve subgroup was

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██████ (CS section 3.6.1). The company did not report the treatment-naïve subgroup results for other outcomes, apart from the change in DRSS, where the results were ████████ those of the ITT analysis (CS section B.3.6.2 and CS Appendix E). Given the relatively large size of the treatment-naïve subgroup the ERG believe that the conclusion of noninferiority of faricimab against aflibercept in the treatment naïve population is appropriate for these two efficacy outcomes.

**Other aspects of the trials relevant to clinical practice**

The ERG's clinical experts noted that the baseline characteristics of the participants included in the RHINE and YOSEMITE trials are generally representative of the patients seen in clinical practice, except that patients in clinical practice usually have worse diabetic control than those in the trials. Baseline HbA1c across the YOSEMITE and RHINE trial arms ranged from ████ to ████ which is lower than would be seen in clinical practice (this was also noted for the pivotal trials in the aflibercept technology appraisal TA346 which had a similar HbA1c range[3]). The clinical experts also noted that there was a higher proportion of people of a Hispanic ethnicity than seen in NHS practice, but that this difference is unlikely to be clinically important and that racial diversity was generally well reflected in the trials.

Two of the ERG's clinical experts commented that the initial aflibercept dosing regimen specified in the aflibercept SmPC (as applied in the YOSEMITE and RHINE trials) may not be precisely followed in NHS practice; one of these experts suggested eye units use six initial 4-weekly aflibercept doses in line with the DRCR Protocol T trial,[4] with subsequent monitoring then guided by patient response rather than the five recommended in the aflibercept SmPC. However, the remaining two experts considered that the SmPC dosing is reflective of aflibercept use in clinical practice.

One of our experts noted that the faricimab draft SmPC states

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████████████████████████████████.[5, 6]

**ERG conclusion on external validity:** Whilst the YOSEMITE and RHINE trials demonstrate noninferiority or superiority of faricimab compared to aflibercept across a range of clinical efficacy

outcomes there is uncertainty as to how well these results apply to the target subgroup of people who have CRT ≥400 μm.

## 3.3 Critique of the evidence on safety submitted by the company

Safety data were pooled from the YOSEMITE and RHINE trials, up to week 56 (N = 1887; CS section B.3.10). The company also provide faricimab safety summary data from the phase II BOULEVARD study (CS Appendix F). However, the ERG consider that the evidence from this study is not relevant for this appraisal because the ranibizumab treatment arm was dosed at 0.3 mg which is not used in NHS clinical practice and all the drugs were administered Q4W for a treatment period of 20 weeks, followed by an observational period of up to 16 weeks, which does not reflect the posology in the farcimab draft SmPC.

### 3.3.1 Comparative safety for faricimab versus cost comparators

Pooled adverse event frequencies for faricimab 6.0 mg Q8W, faricimab 6.0 mg PTI and aflibercept 2.0 mg Q8W arms of the YOSEMITE and RHINE trials up to week 56 are as follows:

- The incidence of one or more adverse events, and one or more serious adverse events (SAEs), were comparable across treatment arms (see CS Table 22 for more details).

- The incidence of participants withdrawing from the study due to adverse events (AEs) was low, but more frequent in the faricimab arms compared to aflibercept (███, ███ and ███ in the faricimab Q8W, faricimab PTI, and aflibercept arms, respectively).

- The incidence of participants withdrawing from the study treatment due to adverse events was low and similar between the treatment arms (███, ███ and ███ in the faricimab Q8W, faricimab PTI, and aflibercept arms, respectively).

- The incidence of at least one ocular adverse event occurring in the study eye was comparable across treatment arms (37.3%, 35.6%, and 34.4% in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arms, respectively), with the exception (≥2% difference in any treatment arms) of vitreous floaters (███, ███, and ███ in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arms, respectively). These vitreous floaters were reported to be mainly mild and all non-serious (CS section B.3.10.3).

- The incidence of at least one ocular SAE, ocular AEs of special interest, intraocular inflammation events, drop in visual acuity (VA) score ≥30, endophthalmitis, and rhegmatogenous retinal detachment (all in the study eye), were overall low. However, incidence in the faricimab arms was more frequent, in some cases more than double that, of aflibercept (see Table 2 below).

**Table 2 Ocular adverse events**

| Ocular AEs[a] | Faricimab Q8W | Faricimab PTI | Aflibercept Q8W |
|---|---|---|---|
| Serious ocular adverse event | 2.4% | 3.0% | 1.3% |

| Ocular AEs of special interest[b] | 2.4% | 2.7% | 1.0% |
|---|---|---|---|
| Intraocular inflammation | ■ | ■ | ■ |
| Drop in Visual Acuity (VA) score ≥30 | ■ | ■ | ■ |
| Endophthalmitis | ■ | ■ | ■ |
| Rhegmatogenous retinal detachment | ■ | ■ | ■ |
| PTI: personalised treatment interval. Source: This table incorporates information from CS Tables 22 and 25. [a] event occurred in study eye [b] Included: drop in VA score ≥30, associated with severe intraocular inflammation, intervention required to prevent permanent vision loss, suspected transmission of infectious agent by study drug | | | |

Two of the ERG's clinical experts commented that careful monitoring of adverse events will be important, given the experience with brolucizumab for AMD in which intraocular inflammation emerged during post-market monitoring. One expert considered that the incidence of vitreous floaters could be an early indicator of safety concerns, although within the 1-year data available so far these floaters were not classed as serious events.

**ERG conclusion on safety:** There are no immediate safety concerns apparent in the YOSEMITE and RHINE trials. Some specific ocular adverse events were more frequent in the faricimab arms than in the aflibercept arm but frequencies were low (≤3%).

### 3.4 Critique of the Network Meta-Analyses (NMAs) submitted by the company

As noted above (section 3.1.1) no RCTs have directly compared faricimab against ranibizumab. The company therefore conducted NMAs to enable this comparison.

### 3.4.1 Inclusion criteria for the NMAs

**Inclusion criteria**

The company's inclusion and exclusion criteria for their NMAs are provided in CS Appendix Table 1. The criteria are broadly consistent with the NICE scope except that the comparator broculizumab (which is not licensed for DMO) was included in the search strategy and inclusion criteria, without an explanation. However, no studies of broculizumab were included in the NMAs. The ERG consider the eligibility criteria to be broadly appropriate, except that we question whether it is appropriate to include steroid therapies in NMAs that compare effects of anti-VEGF therapies (for explanation see below in this section).

**Study selection process**

The company's selection process for including trials in their NMAs is outlined in CS Appendix D1.1 but contains ambiguities, including a lack of explanation of the company's NMA "feasibility assessment" and the reasons for excluding studies from the NMAs. Most of the ambiguities were resolved by the company's clarification responses.

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The company's approach to developing the NMAs does not discuss other published potentially relevant evidence networks. The NMA for the NICE aflibercept appraisal TA346 contains studies which are missing from the faricimab NMAs but which the ERG for TA346 considered relevant for indirect comparison of aflibercept versus ranibizumab (e.g. [20, 21]). We could not locate specific reasons within the CS or clarification responses for excluding these studies.

Despite these limitations the ERG's clinical experts were not aware of any relevant studies that are missing from the company's NMAs, so it appears likely that all relevant evidence has been included.

## Network characteristics

The NMA networks included RCTs which had arms comparing faricimab, aflibercept, ranibizumab, bevacizumab, dexamethasone, laser photocoagulation therapy and/or placebo/sham. We note that these therapies would not all be used in practice as first-line treatments (see section 1.2 above). The trials included the following anti-VEGF dosing regimens:

- dosing at fixed intervals, usually in 4-monthly increments, Q4W or Q8W;
- dosing as needed (pro re nata; PRN);
- treat and extend (T&E): in which the treatment interval is extended if the patient's response is satisfactory (as applies in the faricimab PTI regimen, within the range Q4W to Q16W).

**Inclusion of steroids as comparators:** In their Cochrane Review, Virgili et al.[9] considered that "steroids may be compared with anti-VEGF drugs but this needs a different approach, specifically patient subgroups and timing, and their inclusion could lead to violation of similarity in a review aiming to compare different anti-VEGF drugs". The ERG's four clinical experts concurred independently that it may be preferable to exclude steroids from the NMAs, for reasons including: steroids are a second-line therapy; steroids may be more effective in specific subgroups of people (those with chronic DMO and those who do not respond to anti-VEGF therapies); the dosing intervals and waning of steroid effects differ from those of anti-VEGF therapies; steroids have different side-effects to anti-VEGF therapies (e.g. inducing cataracts); steroids are recommended by NICE only in pseudophakic patients. The ERG therefore believe that a sensitivity analysis would be appropriate to investigate the impact of excluding the dexamethasone trial arms from the NMAs.

**Inclusion of different ranibizumab doses:** Six of the trials included in the NMAs (Eichenbaum 2018,[22] DRCR-T,[4] REACT,[23] RESOLVE,[24] ROTATE,[25] TREX-DME[26]) used a ranibizumab dose of 0.3 mg which is lower than that used in UK NHS clinical practice (0.5 mg) and was considered not relevant to clinical practice in the NICE appraisal of aflibercept (TA346).[3] The company pooled these two doses in their NMAs, based on an observation that at 24 months in the RIDE and RISE trials[27] the

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mean change in BCVA did not differ between the doses (clarification response A21). (NB RIDE and RISE were not included in the company's NMAs as they did not report relevant 1-year outcomes). However, the company do not provide any relative efficacy or safety evidence for the 0.3 mg versus 0.5 mg doses for any of the outcomes that they evaluated in their NMAs. Three of the ERG's clinical experts agreed independently that the 0.3 mg ranibizumab dose may have the potential to introduce bias in the analyses and should have been analysed separately or excluded from the NMAs, although the fourth expert believed pooling the 0.3 mg and 0.5 mg doses would likely be inconsequential for the efficacy and safety outcomes. The ERG believe that a sensitivity analysis would be appropriate to determine the impact of pooling the 0.3 mg and 0.5 mg ranibizumab doses in the NMAs.

**ERG conclusion on the NMA inclusion criteria:** The inclusion of the 0.3mg dose of ranibizumab and the steroid dexamethasone in NMAs may not be appropriate. The impact of these trial arms on the NMA results should be investigated in sensitivity analyses.

### 3.4.2    Quality assessment of trials included in the NMAs

The company provided risk of bias assessments for each of the trials included in the NMAs (CS Appendix D1.3). In response to clarification question A15 the company provided explanations for each of their risk of bias judgements and provided a sensitivity analysis to investigate the effect of excluding high risk of bias studies.

It was not feasible for the ERG to check all the company's risk of bias judgements. For 14 of the 26 included trials we were able to compare the company's judgements against risk of bias judgements made by the authors of other recent systematic reviews[9, 10, 12, 15, 16, 28, 29] including two Cochrane Reviews[9, 29]. One ERG reviewer then checked the remaining 12 trials. We found some differences between the company, ERG and other review authors in assigning low, high and unclear risks of bias to the individual bias domains within trials (a full table of these comparisons is available from the ERG on request). However, this has little impact on the overall study-level risk of bias classification, i.e. the company, ERG and other authors were generally consistent in identifying the same trials as being at overall high risk of bias.

The company did not assess the potential risk of bias relating to between-eye correlations where more than one eye per patient was included in analyses. Five of the trials included in the NMAs included more than one eye per patient but did not report any adjustment for between-eye correlations (footnote d in Table 4 below). The company did not adjust for any correlations between eyes in their NMAs (clarification response A19) and did not record this as a source of bias or imprecision.

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**ERG conclusion:** The company's approach for assessing the risk of bias appears appropriate, except that the potential for bias due to inter-individual correlations between eyes was not assessed and therefore the potential influence of this on the NMA results is uncertain.

### 3.4.3 NMA modelling approach

The company's Bayesian statistical approach to the NMA methods is explained only superficially in CS section B.3.9.3 but can be ascertained from the WinBUGS statistical code provided in clarification response A24. The company conducted six NMAs which in total included 26 studies identified during the study selection process (listed in Table 3), for the following outcomes:

- Mean change in BCVA at 1 year: 22 studies; random effects model (CS Figure 12)
- Mean number of injections in year 1: 11 studies; random effects model (CS Figure 14)
- Mean change in CRT at 1 year: 24 studies; random effects model (CS Figure 16)
- Proportion of patients gaining or not losing ≥10 or ≥15 letters at 1 year: 22 studies; random effects model (CS Figure 18). Note that for this outcome the company were unable to find an appropriate prior distribution to adequately estimate the between-study heterogeneity and therefore this outcome should be interpreted with caution (clarification response A26).
- All-cause discontinuation up to 1 year: 14 studies; fixed effects model (CS Figure 20)
- Ocular adverse events up to 1 year: 11 studies; fixed effects model (CS Figure 22).

**ERG conclusion:** The overall modelling approach is appropriate except that the company do not provide an explanation for using fixed-effects models for two outcomes. A random effects model would have been preferable for all outcomes, given that model fit was similar for the fixed and random effects models (clarification response A26). In addition to the NMAs the company conducted meta-regression analyses; these are discussed below in sections 3.4.4 and 3.4.5.

### 3.4.4 Heterogeneity assessment

The company discuss several limitations of the NMA analyses (CS section B.3.9.5) but do not mention clinical heterogeneity, i.e. the variation of baseline characteristics of participants across the trials included in the NMAs. CS section B.3.9.3 states that meta-regressions were conducted "to assess whether treatment effects were influenced by patient characteristics" but no information on the methods or results of these analyses is provided in the CS.

In response to clarification question A16 (d) the company explained that two meta-regressions were conducted, to adjust for baseline variation in BCVA and baseline variation in CRT (acknowledging that these are correlated variables). The company do not explain why these two specific moderator variables were selected and not others. The meta-regressions were run for the primary outcome only

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(change in BCVA). Results of these meta-regression analyses are provided in clarification response Tables 24 and 25. However, the ERG have concerns about the statistical approach employed for these meta-regressions, discussed in section 3.4.5 below.

In clarification response 16 (a) the company suggest baseline visual acuity and intraretinal fluid morphology are prognostic factors. The ERG heard from our clinical experts that systematic factors including poor diabetic control (high HbA1c), hypertension, renal disease and dyslipidaemia can all make DMO worse. Duration of DMO, baseline visual acuity, macular thickness and macular ischaemia are also prognostic factors for DMO, although macular ischaemia is difficult to measure and define consistently.

The company provided an Excel table of trial baseline characteristics in clarification response A16 (c) which the ERG have checked against the source publications. The key participant characteristics are summarised in Table 3 below. We note that many of the prognostic factors for DMO identified by our experts were not always reported in the trials and one of our clinical experts commented that this is one of the reasons why real-world treatment results are usually inferior. Two of the ERG's clinical experts considered that (within the limitations of data available), the factors summarised in Table 3 appear adequately homogeneous for the studies to be combined in NMA. However, one expert considered that it may not be appropriate to combine treatment-experienced and treatment-naïve people in the analysis since prior treatment may reflect a worse prognosis.

The NMA networks contain several further sources of potential heterogeneity in addition to those listed in Table 3. These include differences between trials in the way PRN treatment was provided (CS Appendix Table 13), in the way sham/placebo arms were administered (CS Appendix Table 14), in aflibercept loading doses (CS Appendix Table 15) and in the permitted laser or other rescue treatment use (CS Appendix Table 16). We note that the company also identified a difference between trials regarding whether they had adjusted for the rescue treatment or not (CS Appendix Table 16) but the company do not comment on whether these studies could have been analysed separately or what their influence on outcomes would be. It is unclear whether networks could be constructed to account for any of these differences and the company do not discuss this.

**ERG conclusion:** There are several baseline characteristics that could introduce heterogeneity in the NMAs, most of which were not adjusted for in the meta-regression analyses, although two clinical experts felt that the trials were broadly homogeneous across those baseline characteristics that were most frequently reported. A more systematic and explicit consideration of the factors that contribute to heterogeneity and which of them can or cannot be adjusted for would be helpful. In particular,

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clarification is needed on whether it is appropriate to combine treatment-naïve and treatment-experienced populations in the analysis.

### 3.4.5 NMA data and statistical procedures

The ERG were able to validate the statistical code by running selected analyses. Targeted checks of the NMA input data against the source publications identified only minor discrepancies which are likely inconsequential.

The company explained in clarification response A22 that there was no inconsistency between the direct and indirect evidence within their NMA for change in BCVA. The ERG agree with the company, although we note that consistency was not assessed for the other outcomes.

The ERG have two concerns relating to the meta-regressions reported by the company in clarification response A16 (d):

- Adjustment was made for only two baseline variables: BCVA and CRT. The company do not discuss whether any other factors could have been adjusted for, such as HbA1c or the duration of DMO which the ERG's clinical experts noted as prognostic factors (section 3.4.4 above).
- The company dichotomised the median values of the baseline BCVA and CRT (clarification response A16[d]). The ERG advise against dichotomising continuous data for several reasons including information loss and ignoring potential non-linearity.[54]

**ERG conclusion:** The company's "base case" NMA methods are appropriate. However, the ERG disagree with the statistical approach employed by the company for their meta-regression analyses to account for baseline heterogeneity in prognostic factors for DMO.

**Table 3 Baseline characteristics of participants in the 26 trials included in network meta-analyses**

| Trial<br><br>Means and medians in the table are across all arms within each trial | Mean [median] age, years | DMO treatment history (laser or anti-VEGF) | Mean [median] duration of diabetes, years | Mean [median] HbA1c % | Mean [median] time since DMO diagnosis, years | Mean BCVA letters | Mean [median] central retinal thickness μm | % pseudo-phakic | Total eyes/ patients |
|---|---|---|---|---|---|---|---|---|---|
| BEVORDEX [30, 31] | 60.9-62.2 | Prev trt | 16.7-19.5 | 7.7-8.4 | NR | 55.5-59.0 | 451-503 | 30 | 88/61 [a] |
| BOLT [32] | 63.5-64.9 | Prev trt | 13.5-14.8 | 7.5-7.6 | NR | 54.6-55.7 | 481-507 | 12-21 | 80/80 |
| Chatzirallis 2020 [33] | 64.4-64.8 | Trt naive | 11.1-12.1 | NR | NR | 56.3-58.9 | 424-430 | NR | 112/112 |
| DA VINCI [34, 35] | 60.7-64.0 | Mixed | NR | 7.9-8.1 | NR | 57.6-59.9 | 426-456 | NR | 221/221 |
| DRCR Protocol T [4, 36-38] | 60-62 | Mixed | [15-17] | [7.6-7.8] | NR | 64.6-66.3 | 403-460.5 [b] | 21-17 | 313/313 |
| Eichenbaum 2018 [22] | 60.4-64.5 | Mixed | NR | NR | NR | 29.2-32.5 | 455-471 | NR | 20/20 |
| ETDRS [39] [c] | NR [c] | NR [c] | NR [c] | NR [c] | NR [c] | NR [c] | NR [c] | NR [c] | 2998/1876 [d] |
| Fouda 2017 [40] | 55.1-56.6 | Trt naive | NR | NR | NR | Snellen decimal 0.17-0.18 | 465-472 | NR | 70/42 [d] |
| LUCIDATE [41] | [64.9-67.4] | Trt naive | [18-18.5] | 7.25-7.93 [e] | [1.75-2.67] calculated by ERG | 63.8-70.4 | 455-488 | 18-36 | 33/33 |
| MEAD 1 & MEAD 2 [42-44] | 62.3-62.5 | Mixed | 15.8-16.5 | 7.5-7.6 | NR | MEAD 1: 55.2-57.0 [b] MEAD 2: 55.9-56.8 [b] | MEAD 1: 453.7-486 [b] MEAD 2: 436.7-468.7 [b] | 24-29 | 1048/1048 |
| Ozsaygili 2020 [45] | 64.8-66.4 | Trt naive | [10.2-10.4] | 8.2-8.4 | NR | [46.3-47.5] | [576.5-615.2] | 54.0-60.4 | 98/62 [d] |
| REACT [23] | 62.5-63.8 | Prev trt | NR | NR | NR | 64.2-65.1 | 399-444 | NR | 27/27 |
| REFINE [46] | 58.6-59.0 | Mixed | NR [f] | 7.3-7.4 | 1.1-1.3 [f] | 58.2-59.6 | 473-475 | NR | 384/384 |

| Study | Age | Treatment | | | | | | | n/n |
|---|---|---|---|---|---|---|---|---|---|
| RESOLVE [24] | 62.8-65.0 | Mixed | 13.9-15.1 | 7.3-7.6 | 1.1-1.4 | 59.2-61.2 | 449-460 | NR | 151/151 |
| RESPOND [47] | 60.8-62.8 | Mixed | 16.5-18.5 | 7.6-7.8 | 1.6-2.1 | 61.9-64.8 | 422-458 | NR | 220/220 |
| RESTORE [48] | 62.9-64.0 | Mixed | 12.9-15.2 | NR | 1.6-2.0 | 62.4-64.8 | 412-427 | NR | 345/345 |
| RETAIN [49] | 63.0-64.5 | Mixed | NR | 7.8-8.0 | 2.5-2.6 | 61.7-64.7 | 433-481 | NR | 372/372 |
| REVEAL [50] | 60.7-61.5 | Trt naive | 11.2-11.3 | 7.4-7.5 | 1.2-1.5 | 58.4-58.8 | 395-430 | NR | 396/396 |
| ROTATE [25] | 68-69 | Prev trt | NR | NR | NR | 63.0-63.7 | 401-453 | NR | 30/22 [d] |
| TREX-DME [26] | 58.7-59.9 | Mixed | 13.6-15.8 | NR | NR | 64.1-65.1 | 434-480 | 20-23 | 150/116 [d] |
| VISTA [51, 52] | 61.7-63.1 | Mixed [c] | 16.5-17.6 | 7.6-8.1 | NR | 58.9-59.7 | 479-485 | NR | 466/466 |
| VIVID [51, 52] | 62.6-64.2 | Mixed | 14.1-14.5 | 7.7-7.8 | NR | 58.8-60.8 | 502-540 | NR | 406/406 |
| VIVID-East [53] | 57.6-59.3 | NR | 11.5-12.9 | 7.3-7.6 | NR | 55.1-57.1 | 520-528 | NR | 381/381 |
| RHINE [e] | ██████ | █████ | █ | █████ | █████ | ██████ | █████ | █████ | ███ |
| YOSEMITE [e] | ██████ | █████ | █ | █████ | █████ | ██████ | █████ | █████ | ███ |

NR: not reported; Prev trt: previously treated; Trt naïve: treatment-naïve.

[a] More than one study eye per patient included with adjustment made for between-eye correlation.

[b] ERG unable to locate source of data as reported in the company's data extraction table provided in clarification response A16 (c).

[c] EDTRS trial baseline characteristics are not included in the company's data extraction table (clarification response A16 [c]) and several publications for this trial were not provided by the company and are not accessible to the ERG; however, this trial is only included in the NMA of change in BCVA letter categories where it is an outlier in the network and unlikely to be influential (see CS Figure 18).

[d] More than one study eye per patient included but no adjustment for between-eye correlation reported.

[e] Data provided by ERG (company's data extraction table states these data were not reported).

[f] The paper does not state whether this is duration of diabetes or duration of DMO; the company extracted this as the duration of diabetes; the ERG believe it is the duration of DMO.

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### 3.4.6 NMA results

The company's NMA results are summarised in Table 3. The ERG regard these results illustrative only, since the company's NMAs pooled the 0.3 mg and 0.5 mg doses of ranibizumab which is not reflective of clinical practice. Note also that for the mean change in ETDRS letters outcome (i.e. the proportion of people gaining or not losing ≥10 or ≥15 letters) the company were unable to satisfactorily account for between-study statistical heterogeneity and suggest that these results should be treated with caution (clarification response A26).
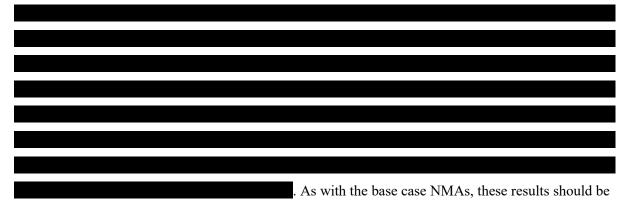
**Meta-regression on baseline BCVA and baseline CRT**

Results of the company's meta-regression analyses that included baseline BCVA and baseline CRT as covariates are provided in clarification response A25. The model fit statistics (clarification response Table 23) and treatment-by-covariate estimates (clarification response Table 24) suggest that the models accounting for baseline variation in BCVA and CRT

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**Sensitivity analyses excluding high risk of bias studies**

The company reran their NMAs for each of the six outcomes excluding studies which had been classified as being at high risk of bias (clarification response Figures 2 to 12).

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███████████████████████████████████. As with the base case NMAs, these results should be interpreted with caution, since 0.3 and 0.5 mg ranibizumab doses were pooled in the analyses.

**Baseline CRT ≥400 μm subgroup analysis**

The company identified six trials, including YOSEMITE and RHINE, which reported baseline CRT by subgroups <400 μm and ≥400 μm and they conducted a NMA using the CRT ≥400 μm subgroup for the mean change in BCVA to 1 year (clarification response Figure 14).

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█████████████████████████████████████████. The company suggest that the CRT

≥400 μm subgroup results show

███████████████████████████████████████████████████████████in terms of change in visual acuity, but they state that results must be interpreted with caution given that subgroups were not pre-specified, i.e. breaking randomisation (clarification response A17 [b]).

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█████████████████████████████████. Note also that one of the trials included in the subgroup analysis, DRCR-T, used the 0.3 mg ranibizumab dose which is not used in UK clinical practice.

**ERG conclusion:** The company's NMAs show that, across the five efficacy outcomes assessed, the PTI dosing regimen of faricimab was

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█████████████. For the one safety outcome assessed, odds of an ocular AE, faricimab was

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████████████████████████████. These NMA results are subject to uncertainties in the NMA methods discussed above which are summarised in section 3.5 below.

### 3.4.1 Consistency of NMA results with other evidence

As would be expected, the company's NMA results for the comparison of faricimab versus aflibercept (Table 4) are generally consistent with the results of the comparison of faricimab versus aflibercept in the YOSEMITE and RHINE trials which were included in the NMAs. It is not possible to validate the results of the NMAs for the comparison of faricimab against ranibizumab since no other evaluations of the relative effectiveness of faricimab against other anti-VEGF agents have been conducted, apart from the phase II BOULEVARD study, reported in CS Appendix 7. BOULEVARD included 0.3 mg ranibizumab, a dose not used in UK NHS practice. It may be possible to partially validate the NMAs against external evidence if an alternative comparator pair is selected, such as aflibercept versus ranibizumab, for which external trial and meta-analysis evidence exists, but the company have not reported NMA results for this comparison.

**Table 4 Summary of NMA results for 1-year outcomes**

| Faricimab PTI versus others ► Outcome | Faricimab 6.0 mg | Aflibercept 2.0 mg | | | | Ranibizumab 0.3 mg+ 0.5 mg pooled | | | Deferred laser | Data source |
|---|---|---|---|---|---|---|---|---|---|---|
| | Q8W | Q4W | Q8W | PRN | | Q4W | T&E | PRN | | |
| Mean difference change in BCVA | ■ | ■ | ■ | ■ | | ■[a] | ■[a] | ■[a] | ■ | CS Fig 13 |
| Mean difference number of injections | ■[b] | ■[b] | ■[b] | ■ | | ■[b] | ■ | ■ | ■ | CS Fig 15 |
| Mean difference change in CRT | ■ | ■ | ■[a] | ■[a] | | ■[a] | ■[a] | ■[a] | ■ | CS Fig 17 |
| Mean change in ETDRS letters [c] | ■ | ■ | ■ | ■ | | ■ | ■ | ■ | ■ | CS Fig 19 |
| Odds all-cause discontinuation | ■ | ■ | ■ | ■ | | ■ | ■ | ■ | ■ | CS Fig 21 |
| Odds ocular adverse events | ■ | ■ | ■ | ■ | | ■ | ■ | ■[d] | ■ | CS Fig 23 |

NA: comparison not available for this network; PTI: personalised treatment interval

[a] "Favoured" denotes that the mean difference is significantly higher than zero for faricimab PTI versus the specified comparator.

[b] "Favoured denotes that the mean difference is significantly lower than zero for faricimab PTI versus the specified comparator.

[c] This refers to the proportion of people gaining or not losing ≥10 or ≥15 letters.

[d] "Favoured" denotes that the odds ratio is significantly lower than 1.0 for faricimab PTI versus the specified comparator.

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## 3.5 ERG conclusions on the clinical effectiveness evidence

**Comparison of faricimab against aflibercept: YOSEMITE and RHINE trials**

The clinical evidence for faricimab compared to aflibercept is from pooled data from two identical phase III trials, YOSEMITE and RHINE, which appear well designed and executed with overall low risk of bias. The trial populations were comparable for faricimab and afibercept.

- The trials demonstrate noninferiority of the proposed dosing regimen of faricimab (Q4W-Q16W) compared to aflibercept Q8W for the primary outcome of the change in visual acuity in the ITT population as well as the change in DRSS score (a key secondary outcome which assesses severity of diabetic retinopathy, but is not specific to DMO) (section 3.1.3).
- Faricimab Q4W-Q16W was statistically superior to aflibercept Q8W for the change in CRT and was statistically not different to aflibercept for other outcomes assessed (section 3.1.3).
- The results are clinically plausible and consistent with the expected pharmacological mode of action of faricimab.
- However, the applicability of the trial results to the target population with CRT ≥400 μm is uncertain (section 3.2.3).
- The efficacy data presented by the company are for one year of therapy and may not reflect longer-term outcomes.

**Comparison of faricimab against ranibizumab: NMAs**

The company's NMAs were informed by a comprehensive literature review. The ERG consider the review to be at low risk of bias and unlikely to have omitted any relevant studies. The NMA modelling approaches are appropriate, based on NICE DSU recommended methodology, except for meta-regressions conducted by the company (see below). The company conducted a sensitivity analysis which demonstrated that results for the primary outcome were insensitive to the exclusion of studies with a high risk of bias.

The ERG have several concerns with the company's NMAs which we believe may render these analyses potentially unreliable for decision-making, unless the following issues can be addressed:

- The company's NMAs combined ranibizumab doses of 0.3mg and 0.5 mg but the 0.3 mg dose is not recommended nor used in NHS clinical practice and has the potential to introduce bias in efficacy or safety outcomes. A sensitivity analysis would be appropriate to determine the impact on clinical and safety outcomes of pooling these doses (section 3.4.1).
- Clinical experts considered it inappropriate to include steroid therapies in the NMAs. A sensitivity analysis would be appropriate to investigate the impact of including/excluding trials with dexamethasone arms from the NMAs (section 3.4.1).

- The company's NMAs combined treatment-naïve and treatment-experienced populations. Clarification is needed on whether this is appropriate (section 3.4.4).
- The ERG do not agree that the company have used appropriate statistical methods for their meta-regressions to account for between-study baseline heterogeneity in the NMAs (section 3.4.5).
- The applicability of the NMA results to the target population of people who have CRT ≥400 μm is uncertain (section 3.4.6).

**Safety of faricimab**
- The YOSEMITE and RHINE trials do not currently indicate any major safety concerns, although some specific ocular adverse events were more frequent in the faricimab arm(s) compared to the aflibercept arm (section 3.3.1).
- The company's NMA of aggregate ocular adverse events did not identify any safety concerns for faricimab relative to aflibercept or ranibizumab (Table 4).

# 4 Summary of the ERG's critique of the cost evidence submitted

## 4.1 Decision problem for the cost comparison

### 4.1.1 Population

The ERG agree that the population for the cost-comparison analysis should reflect that in the NICE recommendations for the comparators. In practice, the cost analysis uses input parameters estimated from trials with a broader population:

- The modelled cohort has a mean age of 62 years, with 60% male (CS Table 27), based on the pooled ITT populations of the YOSEMITE and RHINE trials. These patient characteristics are consistent with models for the comparator appraisals (TA346 guidance for aflibercept and TA274 guidance for ranibizumab[2]). In the company model, population characteristics only affect mortality rates, which has little impact on cost estimates.

### 4.1.2 Comparators

The analysis compares faricimab with aflibercept and ranibizumab. As stated in section 2.2 above, the ERG consider that these comparators are appropriate for the cost-comparison analysis.

## 4.2 Cost-comparison model

The company describe their cost-comparison model in CS section B.4.2.1. The model structure is illustrated in CS Figure 24 and described in CS section B.4.2.2, with the key assumptions given in CS Table 34. Whilst the company state that the general modelling approach and inputs were cross referenced with previous technology appraisals, they do not provide any comparison in the CS.

**ERG conclusion:** We view the company's modelling approach is reasonable. It shares general modelling features with previous technology appraisals (e.g. TA346).

## 4.3 Model parameters

### 4.3.1 Treatment effect

The treatment effect is modelled through treatment discontinuation. The annual probability of discontinuation for faricimab is obtained from the YOSEMITE and RHINE trials. For year 1, the annual probability is based on discontinuation probabilities observed in pooled year 1 data from the YOSEMITE and RHINE trials. In years 2 to 5, the company assumed the same probability of discontinuation, based on the annualised probability of discontinuation derived from patients' part way through the second year of the YOSEMITE and RHINE trials. For the comparator arms, the annual probability of treatment discontinuation was assumed to be equivalent to that of the faricimab arm in year 1 to year 5.

**ERG conclusions:** We have reservations about the company's assumption of the same probability of discontinuation in years 2 to 5. Advice from our clinical experts suggest that patients who discontinue treatment either due to efficacy (i.e. resolution of DMO) or lack of efficacy might experience recurrence or need to restart treatment. Furthermore, the probability of discontinuation in each of the following years is likely to be higher due to fewer injections. However, we have not conducted a scenario exploring this assumption due to data constraints.

With respect to treatment duration, the company assume a maximum duration of 5 years from baseline for the study eye for treatment with faricimab, ranibizumab and aflibercept. After this, 85% of those who were alive and on treatment are assumed to discontinue treatment. The remaining 15% remain on treatment beyond year 5 to reflect the fact that some people with DMO require long-term treatment. Expert clinical advice to the ERG is that the company's assumption aligns more with neovascular oedema than DMO. The ERG's clinical experts advised that, in DMO, the on/off treatment cycle could go back and forth. For example, a study by Elman et al.[55] indicates that at 5 years, 50% of people were still receiving treatment. Based on our clinical experts' advice and the

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study by Elman et al. we view the assumption that 50% of people who are alive would discontinue treatment after 5 years reflects clinical practice. The company have conducted a scenario analysis for this assumption (shown in CS Table 40) which indicated that at the patient access scheme (PAS) price for faricimab and list prices for the two comparators, ███████████████████████████████.

For those developing DMO in their second eye, a maximum treatment duration of 5 years from the point of DMO development in the second eye is assumed. The ERG's clinical experts suggested that this assumption may be reflective of patients with AMD, but not those with DMO. In clinical practice, 50% of those developing DMO in the second eye would still receive treatment at 5 years as observed in the DRCR Protocol T trial.[4]

The company conducted a range of scenario analyses where they explore the impact of alternative assumptions for treatment discontinuation:

- Varying the treatment duration between 3 and 10 years
- Varying the proportion of people discontinuing treatment after year 5
- Varying the positive discontinuation probabilities differently for faricimab, aflibercept ad ranibizumab after year 1 whereby it was assumed that ████ receiving faricimab and ████ receiving aflibercept would stop treatment after 1 year. These are based on the outcome in YOSEMITE and RHINE. The discontinuation proportion for ranibizumab was assumed equivalent to that applied for aflibercept.

**ERG conclusion:** We view that the company have provided a reasonable range of scenarios for treatment discontinuation. Across all their scenarios, ████████████████████████████████████████████████████████ (as shown in CS Table 40). Overall, we view that their scenario where 50% of people discontinue treatment after 5 years is more reflective of the UK clinical practice. We explore the impact of this assumption in conjunction with other ERG preferred assumptions in ERG additional analyses. These are discussed in Section 4.6 below.

### 4.3.2 Mortality

The model uses general population mortality rates, adjusted for the age and sex of the modelled cohort (England and Wales 2017-2019, ONS 2019). Furthermore, mortality was adjusted by applying a diabetes specific hazard ratio (HR 1.95, Preis 2009[56]) for the entire population as well as health state mortality risks from being blind and visually impaired (HR 1.5 and 1.2). These assumptions are consistent with the previous aflibercept appraisal (TA346[3]). The company do not assume an increase

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in mortality from bilateral disease. Furthermore, the annual mortality rate is assumed to be equivalent regardless of DMO treatment.

**ERG conclusion:** We agree with the company's assumptions.

### 4.3.3 Costs

- **Acquisition costs**

The company set out the dosing assumptions and list prices for the calculation of acquisition costs for faricimab and the comparators in CS Table 28.

- **Treatment Dosing**

In the model base case, the dosing regimen for faricimab aligned with the personalised treatment interval (PTI) arm in the YOSEMITE and RHINE trials and with the anticipated marketing authorisation for faricimab. This included a loading phase of 4 injections (one per month for 4 months). Dosing included a protocol-driven treat- and- extend regimen in which treatment intervals are adjusted based on individualised treatment response, measured by central subfield thickness (CST) and visual acuity. The dosing intervals in the PTI could extend up to every 16 weeks, in increments of 4 weeks.

For the comparator arms, the company assume treatment dosing is administered using a PRN regimen in which patients receive treatment in response to disease activity. Prior to commencing the PRN regimen, patients are assumed to receive five injections of aflibercept or ranibizumab (one per month for 5 months) in a treatment loading phase (aflibercept 2 mg LP → PRN, ranibizumab 0.5 mg LP → PRN). This is based on the treatment and monitoring schedule in the DRCR Protocol T trial,[4] which compared visual acuity loss for people receiving aflibercept, bevacizumab or ranibizumab.

The company explored alternative dosing regimens for the comparator treatments in their scenario analyses (e.g. ranibizumab on a treat and extend dosing regimen) by varying the frequencies of injections and monitoring visits. However, they did not explore the impact on the cost comparison of a treat and extend regimen for aflibercept. Their scenarios indicated that the changes in dosing regimen did not change the overall conclusions.

**ERG conclusion:** Following a treat-and-extend regimen in the first years of treatment is reflective of the UK NHS clinical practice. Therefore, we view the company's approach to the dosing regimen for faricimab is reasonable. We have conducted a range of exploratory scenario analyses on alternative dosing regimens for aflibercept and faricimab (see section 4.6).

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- **Healthcare resource use and costs**
  - **Diagnosis using optical coherence tomography**

The company's analyses assume that patients with DMO are diagnosed using optical coherence tomography (OCT). The cost of OCT, sourced from
the 2019/2020 NHS reference costs schedule, is applied:

- across all patients at cycle one
- in the first model cycle after patients develop DMO in their second eye and
- in subsequent injection and monitoring visits.

**ERG conclusion:** We agree that DMO diagnosis using OCT is reflective of UK NHS clinical practice. We noted an inconsistency in the OCT cost used in the company's analyses, which the company corrected as part of their response to clarification question B4. The correction did not have any significant impact on the overall results.

  - **Injection administration**

The company discuss their base case assumptions for estimating the annual mean number of injection administration visits in CS Section B.4.2.8 and CS Table 30.  Briefly, the frequency of injection administrations for faricimab in years 1 and 2 is derived from data pooled from the YOSEMITE and RHINE trials. The frequency of aflibercept and ranibizumab injections is informed by the results of the NMA assuming a PRN regimen in year 1. For year 2, both comparators used the number of injections received considering the DRCR Protocol T trial.[4]. Alternative assumptions about the injection administration visits for the two comparator treatments aflibercept and ranibizumab were explored by the company in scenario analyses (CS Table 39).

With respect to resource use, for their base case the company assume:

- Intravitreal (IVT) injections are administered in consultant-led outpatient appointments
- Additional resource use and costs associated with IVT injections would apply at each injection administration visit.
- The cost of an injection administration visit comprised of an outpatient consultant-led visit, an injection administration cost, and an OCT procedure.

**ERG conclusion:** We have several concerns with the company's assumptions, as follows:

- The number of injection administration visits assumed by the company do not reflect clinical practice and the existing evidence (Egan et al.[57]). Advice from our clinical experts suggests

that there are less than 9 injection administration visits in year 1 and fewer thereafter, reflecting NHS capacity limitations. We conducted a range of scenario analyses whereby the number of visits were varied between 6 and 8 in year 1 and between 2 and 4 in year 2 and are assumed to be similar across the DMO treatments. As discussed previously in Section 3.1.2, we note from the Committee papers and the ERG report for the aflibercept appraisal TA346[3] that the cost-utility model was particularly sensitive to injection frequency. The NICE guidance on the appraisal concluded that it is reasonable to conduct sensitivity analyses that included equal numbers of injections for aflibercept and ranibizumab in year 2. We explore this assumption in our scenario analyses (see section 4.6). We prefer to base the number of injection administration visits on the estimates from our clinical experts and TA346.

- In UK clinical practice, a majority of the IVT injections are administered by staff such as specialist nurses and optometrists. The company conducted a scenario analysis (CS Table 40) exploring the impact of non-consultant led outpatient visits; this increases the incremental costs versus aflibercept and ranibizumab by ████ and ████ respectively, compared to the base case results. We view this scenario better reflects UK NHS clinical practice.

- Furthermore, an OCT procedure is unlikely to be performed during an injection administration visit in the initial doses. Often vision testing and OCT are performed prior to an injection. We have conducted a scenario to explore this assumption (see section 4.6).


- **Monitoring visits**

The company detail their approach for estimating the monitoring visits in CS Section B.4.2.8 and in CS Table 32 (reproduced below in Table 8). They made the following assumptions:

  o In the faricimab arm, there are no additional monitoring visits in years 1 and 2. In year 3 and beyond, people in this arm would transition to a PRN type regimen where there will be separate monitoring visits. The total number of visits in year 3 and beyond is based on the total visit numbers observed for patients treated with aflibercept and ranibizumab in years 3-5 of the DRCR Protocol T trial.[4]

  o For those receiving the comparator treatment regimens, monitoring visits are applied in all years of the model as they are administered using a PRN regimen.

  o The cost of a separate monitoring visit comprised of an outpatient-led visit and an OCT procedure.


**ERG conclusion:** Our clinical experts viewed that faricimab would be administered in a similar way to the other anti-VEGFs. Therefore, faricimab is likely to have the same monitoring visits as the comparators. Secondly, the company's number of monitoring visits for aflibercept and ranibizumab appear to be lower than observed in UK clinical practice. We conducted scenario analyses varying the

number of these visits based on the previous appraisal TA346 and our experts' opinion, as shown in section 4.6.

- o **Bilateral treatment multipliers**

To account for additional costs for treating two eyes instead of one, the company use bilateral cost multipliers for the drug, administration, and monitoring costs in their base case analysis (see CS Table 33). Their assumptions for the cost multipliers are based on the NICE clinical guideline for AMD NG82 and previous technology appraisals for DMO (TA346) and AMD (TA672).

**ERG conclusion:** We have no concerns with these assumptions.

- o **Other: adverse events and miscellaneous**

In the company's analyses, adverse events are assumed to be equivalent across all the three treatments. We view this as a reasonable simplification based on the safety results from the YOSEMITE and RHINE trials where the incidence of AEs was comparable across the treatment arms (section 3.3.1). While the incidences of serious AEs were higher in both the arms of faricimab compared to that of the aflibercept arm, the company argued that these are unlikely to have a significant impact. We agree with the company as the overall frequency was low and therefore unlikely to influence the overall results.

The company model has the provision to include the wider societal impact of visual impairment and anti-VEGF treatment burden such as reduced productivity of the patients and that of the carer for disruption to their workday. These scenarios are explored in the company's scenario analyses (CS Table 40).

**ERG conclusion:** We agree with the company's approach to exclude adverse events from the cost comparison analyses.

## 4.4 ERG model checks

The ERG conducted a range of checks on the company's cost-comparison model. This included verification that all input parameters and model results matched the values cited in the CS and, where available, values in published sources. We also inspected formulae in the Markov trace and intermediate calculations ('white box' verification) and checked that changes to input parameters had a plausible impact on results ('black box' verification). Furthermore, the ERG re-ran all the company's sensitivity and scenario analyses.

We identified the following issues, although these do not affect the overall model conclusions.

- There is a small discrepancy in reporting the cost for retinal tomography which the company addressed as their response to clarification question B4.

- For five of the company's scenario analyses (shown below in Table 5) there are slight discrepancies in the results reported by the company and those obtained by the ERG.

**Table 5 Inconsistency in the cost comparison results obtained by the company and the ERG (PAS price for faricimab and list price for the comparators) (based on the company's revised model submission as part of the clarification response)**

| Scenario | | Incremental cost vs aflibercept | | Incremental cost vs ranibizumab | |
|---|---|---|---|---|---|
| | | Company | ERG | Company | ERG |
| Ranibizumab dosing regimen | LP→q4w | N/A | N/A | -£7,966 | -£7,976 |
| | LP→T&E | N/A | N/A | -£6,473 | -£6,484 |
| Aflibercept dosing regimen | LP→q4w | -£21,366 | -£21,382 | N/A | N/A |
| | LP→q8w | -£17,774 | -£17,658 | N/A | N/A |
| Treatment and monitoring setting costs | £89.13 | -£15,995 | -£15,955 | No discrepancy | |
| LP: Loading Phase; T&E: Treat and extend | | | | | |

## 4.5 Cost comparison analysis results

The company base case cost comparison results are presented in CS Table 35. The analyses are based on the PAS discount for faricimab and the list prices for the comparators. Uncertainty over model assumptions was assessed with one-way sensitivity analyses (presented in CS Figures 25-26) and scenario analyses (CS Table 40).

The cost-comparison analyses and their results reported in this report are conducted with the PAS discount for faricimab and the two comparators at list price. We present the cost-comparison results with the available PAS discounts for faricimab and ranibizumab and Commercial Medicines Unit (CMU) discount for aflibercept in a confidential addendum to this report.

## 4.6 ERG analyses

We summarise the results of the company's base case at the PAS price for faricimab and list price for the comparators in Table 5 below. These results are based on the company's revised submission provided in response to the ERG's clarification questions. The company also conducted a threshold analysis that explored the impact of varying the level of discounts for the comparators aflibercept and

ranibizumab (in CS Table 36). We present the cost comparison results for the company's assumption that the PAS prices for aflibercept and ranibizumab are ▮ and ▮ respectively in Table 6 below. In line with NICE methodological guidance for FTA cost-comparisons, the company did not report a probabilistic sensitivity analysis. All results are therefore deterministic.

**Table 6 Company's base case results – PAS price for Faricimab and comparators**

| Cost | Faricimab<br>6 mg LP → q16w/q12w | Aflibercept<br>2 LP → PRN | Ranibizumab<br>0.5 LP → PRN |
|---|---|---|---|
| **Mean total cost** | ▮ | £44,476 | £34,675 |
| **Incremental cost vs faricimab** | N/A | ▮ | ▮ |
| Source: Results from the cost-comparison model in Excel | | | |

**Table 7 PAS price for Faricimab and assumed discounts for ranibizumab and aflibercept at ▮ and ▮ respectively**

| Cost | Faricimab<br>6 mg LP → q16w/q12w | Aflibercept<br>2 LP → PRN | Ranibizumab<br>0.5 LP → PRN |
|---|---|---|---|
| **Mean total cost** | ▮ | ▮ | ▮ |
| **Incremental cost vs faricimab** | N/A | ▮ | ▮ |
| Source: Results produced by ERG from the company's model | | | |

### 4.6.1 Scenario analyses conducted by the ERG on the company's model

In addition to the company's scenario analyses, the ERG conducted a range of additional scenarios on the company's revised base case model, varying the annual mean number of injections and monitoring visits. These scenarios (ERG Scenarios 1 to 7) are detailed below in Table 8 and Table 9. Furthermore, we conducted a scenario assuming no OCT procedure is performed during an injection administration (ERG Scenario 8). The results of our analyses are summarised in Table 10.

**Table 8 Different dosing regimens**

| | Dosing regimen | Year 1 | Year 2 | Year 3+ |
|---|---|---|---|---|
| **Annual mean number of injections** | **ERG scenario 1 (exploratory scenario)** | | | |
| | Faricimab (6 LP → Q16W/Q12W [T&E] → PRN) | 6 | 2 | 2 |
| | Aflibercept (2 LP → PRN) | 6 | 2 | 2 |
| | Ranibizumab (0.5 LP → PRN) | 6 | 2 | 2 |
| | **ERG Scenario 2 (based on clinical experts' opinions and TA346)** | | | |

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| | | | | |
|---|---|---|---|---|
| | Faricimab (6 LP → Q16W/Q12W [T&E] → PRN) | 8.42 | 4.73 | 1.90 |
| | Aflibercept (2 LP → PRN) | 8 | 4 | 2.3 |
| | Ranibizumab (0.5 LP → PRN) | 8 | 4 | 2.3 |
| **Separate monitoring visits** | **ERG scenario 3 (based on clinical experts' opinions and TA346)** | | | |
| | Faricimab (6 LP → Q16W/Q12W [T&E] → PRN) | 4 | 2.3 | 1.7 |
| | Aflibercept (2 LP → PRN) | 4 | 2.3 | 1.7 |
| | Ranibizumab (0.5 LP → PRN) | 4 | 2.3 | 1.7 |

LP: loading phase; PRN pro re nata (administer as needed); T&E: treat and extend (increase dosing interval)
Numbers (e.g. as in "6 LP") reflect the loading phase dose in mg

**Table 9 Different combinations of injection and monitoring visits**

| Dosing regimen | Injections | | | Separate Monitoring visits | | |
|---|---|---|---|---|---|---|
| | Year 1 | Year 2 | Year 3+ | Year 1 | Year 2 | Year 3+ |
| **ERG Scenario 4: Aflibercept on a T&E regimen (assumed same as that of ranibizumab T&E regimen)** | | | | | | |
| Aflibercept (2 LP → T&E) | 9.53 | 5.40 | 2.17 | 3.13 | 3.90 | 1.83 |
| **ERG Scenario 5: No monitoring visits for aflibercept and ranibizumab in Years 1 & 2** | | | | | | |
| Faricimab (6 LP → Q16W/Q12W [T&E] → PRN) | 8.42 | 4.73 | 1.90 | 0 | 0 | 2.10 |
| Aflibercept (2 LP → PRN) | 9.20 | 5.00 | 2.37 | 0 | 0 | 1.63 |
| Ranibizumab (0.5 LP → PRN) | 9.40 | 5.40 | 2.17 | 0 | 0 | 1.83 |
| **ERG Scenario 6: Similar dosing regimens for faricimab and aflibercept** | | | | | | |
| Faricimab (6 LP → Q16W/Q12W [T&E] → PRN) | 6 | 2 | 2 | 4 | 2.3 | 1.7 |
| Aflibercept (2 LP → PRN) | 6 | 2 | 2 | 4 | 2.3 | 1.7 |
| Ranibizumab (0.5 LP → PRN) | 6 | 2 | 2 | 4 | 2.3 | 1.7 |
| **ERG Scenario 7: Injection dosing visits and monitoring visits based on clinical experts' opinions and TA346 (Scenario 2 + 3)** | | | | | | |
| Faricimab (6 LP → Q16W/Q12W [T&E] → PRN) | 8.42 | 4.73 | 1.90 | 4 | 2.3 | 1.7 |
| Aflibercept (2 LP → PRN) | 8 | 4 | 2.3 | 4 | 2.3 | 1.7 |
| Ranibizumab (0.5 LP → PRN) | 8 | 4 | 2.3 | 4 | 2.3 | 1.7 |
| **ERG Scenario 8: No OCT performed during injection procedure** | | | | | | |
| Injections and monitoring visits as per the company's base case | | | | | | |

LP: loading phase; PRN pro re nata (administer as needed); T&E: treat and extend (increase dosing interval)
Numbers (e.g. as in "6 LP") reflect the loading phase dose in mg

**Table 10 Results from the scenarios conducted by the ERG on the company's revised base case model (PAS price for faricimab and list prices for comparators)**

| | Incremental cost vs aflibercept | Incremental cost vs ranibizumab |
|---|---|---|
| Company base case | ██████ | ██████ |
| ERG scenario 1 | ██████ | ██████ |

| | | |
|---|---|---|
| ERG scenario 2 | ███████ | ███████ |
| ERG scenario 3 | ███████ | ███████ |
| ERG scenario 4 | ███████ | ███████ |
| ERG scenario 5 | ███████ | ███████ |
| ERG scenario 6 | █████ | █████ |
| ERG scenario 7 | █████ | █████ |
| ERG scenario 8 | ███████ | ███████ |

## 4.6.2    ERG's preferred assumptions

The ERG's preferred assumptions are as follows:

- The proportion of patients discontinuing treatment after 5 years is 50%

- Injection dosing visits and monitoring visits based on clinical experts' opinions and TA346 (section 4.6.1, ERG Scenario 7)

- Appointments for treatment and monitoring are non-consultant led (£89.13)

- No OCT procedure performed during an injection administration (section 4.6.1, ERG Scenario 8)

The cumulative results of the ERG's preferred assumptions are shown below in Table 11. The incremental cost for faricimab versus aflibercept ███████ from ███████ (company's revised base case) to ███████ (ERG's preferred case) and that for faricimab versus ranibizumab ███████ from ███████ to ███████.

**Table 11 Results from the ERG's preferred assumptions (PAS price for faricimab and list prices for comparators)**

| Analysis | Incremental cost vs aflibercept | Incremental cost vs ranibizumab |
|---|---|---|
| Company's base case | ███████ | ███████ |
| +  50% treatment discontinuation at 5 years | ███████ | ███████ |
| + Injection dosing visits and monitoring visits based on clinical experts' opinions and TA346 (ERG Scenario 7) | ███████ | ███████ |
| + Non-consultant led appointments for treatment and monitoring (£89.13) | ███████ | ███████ |
| + No OCT procedure for injection administration | ███████ | ███████ |
| ERG preferred case | ███████ | ███████ |

We also conducted two additional scenarios on the ERG preferred case:

- No monitoring visits for aflibercept and ranibizumab in years 1 & 2
- Similar dosing regimens for faricimab and aflibercept

The cost comparison results of these two scenarios are presented below in Table 12.

**Table 12 Scenarios conducted on the ERG's preferred model (PAS price for faricimab and list prices for comparators)**

| Analysis | Incremental cost vs aflibercept | Incremental cost vs ranibizumab |
|---|---|---|
| ERG's preferred case | ███████ | ██████ |
| No monitoring visits for aflibercept and ranibizumab in Years 1 & 2 | ███████ | ██████ |
| Similar dosing regimens for faricimab and aflibercept | █████ | █████ |

## 5   ERG conclusions on the cost comparison

- The model structure and key assumptions of the company's cost-comparison model are appropriate, and consistent with the previous NICE aflibercept appraisal TA346.
- The model assumes equal clinical efficacy for all three drugs. However, limitations in in the NMA comparing faricimab against ranibizumab (as discussed in section 3.5) mean that the appropriateness of assuming equal efficacy of faricimab and ranibizumab is uncertain.
- With the PAS price for faricimab and list prices for aflibercept and ranibizumab, faricimab is estimated to be ██████████ than the two comparators. This applies for the company's revised base case analysis and for all the company and ERG scenario analyses. Results with the PAS discounts for faricimab and ranibizumab and the CMU discount for aflibercept are shown in a confidential addendum to this report.
- For the ERG's preferred assumptions, while faricimab is estimated to be ██████████ than the two comparators (at the PAS price for faricimab and list prices for the comparators), there is a ████████ in the incremental costs of faricimab versus the two comparators compared to the company's revised base case results. For example, the incremental cost for faricimab versus aflibercept ██████████ by ████████ (█████████ in the company's revised base case versus ████████ in the ERG's preferred case) and that for faricimab versus ranibizumab ██████████ by ████████ (████████ in company's revised base case versus ████████ in the ERG's preferred case).
- The cost difference between faricimab and the two comparators is most sensitive to assumptions about different treatment regimens and the duration of maximum treatment.

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