



# Cost-Effectiveness of Faricimab in the Treatment of Diabetic Macular Oedema (DMO): A UK Analysis

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## Abstract

**Aim** The aim of this work was to evaluate the cost-effectiveness of faricimab against relevant therapeutic alternatives used in clinical practice for the treatment of diabetic macular oedema (DMO) in the UK.

**Methods** A state-transition (Markov) model, with health states based on visual acuity scores and treatment pathways, was developed to conduct cost-utility analysis of faricimab treat and extend (T&E) regimen versus ranibizumab pro re nata (PRN) and aflibercept PRN over a time horizon of 25 years. Comparison against bevacizumab PRN was considered in scenario analysis. Effectiveness data for faricimab was sourced from the pivotal YOSEMITE and RHINE double-blind randomised controlled trials, and from a network meta-analysis for comparators. Costs and (dis)utilities were taken from nationally published sources or literature. The base case included indirect costs (productivity gains, informal care) given the wider impacts of DMO on society. Sensitivity analyses were conducted.

**Results** In the base case, faricimab T&E dominated ranibizumab PRN and aflibercept PRN, being more effective and resulting in cost savings (between 0.16 and 0.36 mean QALYs gained, and £5483–9655 mean cost savings). In scenario analysis, faricimab was more effective but costlier compared with bevacizumab, with an incremental cost-effectiveness ratio (ICER) of £8898 per QALY gained. Considering only healthcare payer costs, the ICER of faricimab compared with ranibizumab PRN was £7991 per QALY gained and faricimab dominated aflibercept PRN.

**Conclusions** Faricimab T&E has the potential to reduce the burden of vision loss on society, giving people living with DMO greater independence and contributing to increased healthcare system capacity. At a threshold of £20,000, faricimab T&E is cost-effective compared with relevant comparators, and potentially cost saving.

## Key Points for Decision Makers

At a cost-effectiveness threshold of £20,000, faricimab treat & extend regimen (T&E) is cost-effective compared with flexible treatment regimens used in clinical practice in the UK.

Faricimab T&E has the potential to reduce the burden of vision loss on society, giving people living with DMO greater independence.

Given current capacity constraints in the UK health service, the reduced frequency at which faricimab T&E is administered and monitored could be valuable in reducing the burden placed on ophthalmology clinics in the NHS.

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## 1 Introduction

Diabetic macular oedema (DMO) is a complication of diabetes mellitus, resulting from damage to retinal capillaries in the eye. DMO can result in distortion and blurring of central vision, or in severe cases, irreversible sight loss. It is a leading cause of visual impairment, estimated to affect up to 13% of the 422 million people with diabetes worldwide [1–3]. Therefore, in the UK alone, upwards of 500,000 of the nearly 5 million people with a diagnosis of diabetes suffer from DMO, and healthcare resource use associated with DMO is estimated in excess of £100 million [4, 5]. Projections suggest that the prevalence of diabetes could reach 783 million people (uncertainty interval: 605–899 million) globally by 2045 [6]. Demand on ophthalmology services is therefore likely to increase further given that the incidence of DMO is increasing correspondingly.

Anti-vascular endothelial growth factor (anti-VEGF) intravitreal injections are the most common first-line therapy for centre-involving, vision-affecting DMO, which have superseded laser photocoagulation and corticosteroids as the standard of care [7]. In the UK, ranibizumab and aflibercept are anti-VEGF treatments licensed for the treatment of DMO. The National Institute for Health and Care Excellence (NICE) recommends their use in eyes with central retinal thickness of 400  $\mu\text{m}$  or more [8, 9]. Bevacizumab is an additional anti-VEGF sometimes used off-label but does not have marketing authorisation in DMO. Brolucizumab has recently been recommended by NICE, but was not used in the routine treatment of people with DMO in the UK at the time of the analysis [10], and use in routine practice is expected to be limited due to potential safety concerns [11].

Faricimab is a novel bispecific antibody targeting VEGF and angiopoietin-2, an antagonist cytokine of the angiopoietin-1 and Tie2 pathway. DMO is a multifactorial disease characterised by increased permeability of the retinal vasculature; therefore, novel targets beyond the VEGF pathway might promote vascular stability, extend treatment durability, and improve patient outcomes. The angiopoietin (Ang) and tyrosine kinase with immunoglobulin-like and epidermal growth factor homology domains (Tie) signalling pathway is a key regulator of vascular stability, and Ang-2 upregulation has been implicated in the pathogenesis of diabetic macular oedema and other retinal vascular diseases. As such, dual pathway inhibition via Ang-2 and VEGF-A blockade is a novel therapeutic strategy for the treatment of patients with diabetic macular oedema [12].

Phase III double-blind randomised controlled trials (YOSEMITE and RHINE) have demonstrated

non-inferiority in change from baseline in visual acuity (BCVA) for faricimab treat and extend (T&E) regimen compared with aflibercept administered every 8 weeks following a loading phase [12]. Faricimab was recently recommended as a first-line option in DMO by NICE [13].

As well as demonstrating clinical effectiveness, cost-effectiveness is an increasingly important part of the evidence base, informing the adoption of new pharmaceuticals both at national and local decision-making levels. A de novo state-transition (Markov) model was constructed to evaluate the cost-effectiveness of faricimab in the UK compared with flexible treatment regimens used in clinical practice. This paper details the model structure, input parameters, results and characterisation of uncertainty.

## 2 Methods

The model reflects a population of adults with DMO (62 years old, 60% men), 78% of which are anti-VEGF treatment-naïve, as per the intention to treat analysis of the pivotal YOSEMITE and RHINE randomised trials [12]. Base-case analyses compared faricimab treat and extend (T&E) with aflibercept pro re nata (PRN) and ranibizumab PRN. Given bevacizumab is not indicated in DMO but is occasionally used off-label, a comparison was performed as a scenario.

Evidence on the effectiveness of faricimab T&E compared with relevant comparators was derived from a network meta-analysis (NMA). NMA enabled the effectiveness of faricimab T&E from YOSEMITE and RHINE to be pooled and facilitated indirect comparisons with aflibercept PRN, ranibizumab PRN and bevacizumab PRN.

The model incorporated data on effectiveness, mortality, adverse events, health related quality of life (HRQoL) and costs (direct and indirect) to perform a cost-utility analysis. The analysis took a societal perspective, with a healthcare perspective used in scenario analysis.

### 2.1 Intervention and Comparators

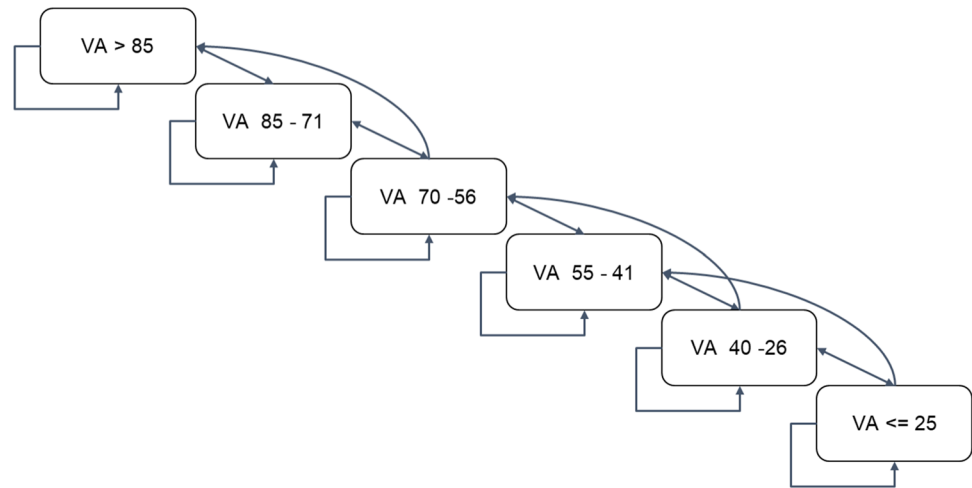
The modelled intervention and comparators and their respective regimens are summarised in Table 1. Faricimab is administered in a treat and extend regimen with a loading phase followed by flexible treatment intervals. This is likely to be standard of care rather than fixed dose, in line with the pivotal randomised trials. Aflibercept, ranibizumab and bevacizumab are administered every 4 weeks during an initial loading phase and then pro re nata thereafter, as required. These regimens reflect the recommended treatment approaches in the UK, including those from the UK expert panel on the use of aflibercept in the treatment of DMO (referred to as monitor and extend) [14]. An additional T&E

**Table 1** Intervention and comparator regimen descriptions and list prices

Treatment	Regimen	Administration	List price
Faricimab T&E	Loading phase: 6.0 mg every month for 4 months → T&E → PRN (year 3+)	IVI	28.8 mg vial = £857.00 [15]
Aflibercept PRN	Loading phase: 2 mg every month for 5 months → PRN	IVI	4.0 mg vial = £816.00 [16]
Ranibizumab PRN	Loading phase: 0.5 mg every month for 5 months → PRN	IVI	2.3 mg vial = £551.00 [17]
Ranibizumab T&E	Loading phase: 0.5 mg every month for 5 months → T&E		
Bevacizumab PRN	Loading phase: 1.25 mg every month for 5 months → PRN	IVI	100.0 mg vial = £242.66 [18]

IVI, intravitreal injection; PRN, pro re nata; T&E, treat and extend

**Fig. 1** Model structure—visual acuity health state categories. VA, visual acuity



ranibizumab comparator is included as a scenario, given that this alternative regimen is sometimes used in UK clinical practice and as data were available for this regimen to enable inclusion in the NMA. Data for high-dose (8 mg) aflibercept were not available at the time of analysis, and it is currently not licensed and not recommended by NICE for use in DMO in the UK.<sup>1</sup> Although brolocizumab has recently been recommended by NICE, it was not included in the analysis as it is not currently used in the routine treatment of people with DMO in the UK and its use is expected to be limited due to potential safety concerns [11].

## 2.2 Model Structure

The model structure is depicted in Figs. 1, and 2 and is designed to describe the natural course of the disease and development of DMO. The DMO cohort state-transition model includes a partial relaxation of the Markov assumption, as the model contains time-dependent probabilities (mortality) and treatment-related tunnel states to segment

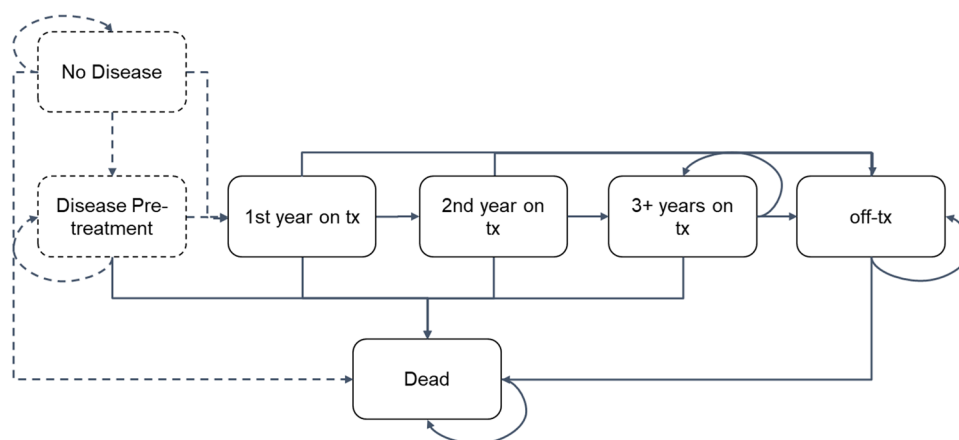
the cohort according to time on/off treatment. State-transition models are well suited for modelling chronic and degenerative diseases, explicitly allowing for time and treatment pathways to appropriately account for differences in costs and quality of life [19]. There is also precedence for the use of similar conceptual model in age-related macular degeneration (AMD), from UK guidelines which included extensive review of the existing literature to inform the modelling approach [20].

The model consists of 6 categories of vision-related health states determined by visual acuity (VA) score (> 85, 85–71, 70–56, 55–41, 40–26 and ≤ 25), where a lower score indicates worse vision (see Fig. 1). The score corresponds to letters correctly identified in a visual acuity test.

The model cohort is distributed across these health states at baseline [see Supplementary Material (Online Resource) Table A1] on the basis of the proportion of patients included in the YOSEMITE and RHINE clinical trials [12]. Each eye is modelled independently, assuming that all patients in the cohort have at least one eye with DMO, and 46.5% have DMO in both eyes at baseline. This was based on previous NICE appraisals and validated in consultation with three UK experts who provided input for all expert clinical inputs [9, 21]. The model differentiates

<sup>1</sup> Data on the effectiveness of the T&E regimen using aflibercept in treatment-naïve patients were not available for inclusion in the NMA.

**Fig. 2** Model structure – Treatment pathway health state categories. tx, treatment



Note: Dashed lines indicate health states and transitions that can only be made for patients with emerging involvement of the second eye

three periods following the clinical pattern typically observed for DMO:

**Year 1:** long loading phase where most vision improvements occur

**Year 2:** characterized by a stabilization of the disease and maintenance of vision gains previously achieved

**Year 3 and beyond:** reduced treatment intensity and long-term maintenance.

The condition of patients in the cohort can be stable, where they remain in the same visual acuity state, or they can transition between states (increased or decreased visual acuity). In Year 1 patients can move up two health states (e.g. VA 40–26 to VA 70–56) and down one health state (e.g. VA 70–56 to VA 55–41). In Year 2 patients can move up or down one health state and in Year 3 patients can move down up to two health states. This was based upon clinical patterns observed in clinical trials with long follow-up, including Protocol T [22], and reflects that patients are unlikely to regain vision in the long term. Non-treatment-related costs (i.e. determined by visual impairment) and utility values are assigned by VA health state category.

The visual acuity health states are combined with the treatment pathway states (see Fig. 2) to appropriately apply costs of treatment (acquisition, administration and monitoring), health state utilities and treatment related disutility values to the proportion of the cohort on/off treatment to reflect the impact of greater vision loss for those who discontinue treatment. The model assumed treatment duration of 5 years, with 15% of patients remaining on long-term treatment, which aligns with a retrospective cohort study [23] and was validated in consultation with UK clinical experts [21]. The dotted line indicates transitions that can only be made for patients with emerging involvement of the second eye.

## 2.3 Model Input Parameters

The model required estimation of key model input parameters including transition probabilities and treatment effectiveness, health state utility values, adverse events, direct costs and indirect costs.

### 2.3.1 Effectiveness

Transition probabilities between visual acuity states in the faricimab T&E arm were derived from pooled data from the YOSEMITE and RHINE trials [12] by fitting a multi-state model in R programming language (msm package). The best fitting model contained four states [see Supplementary Material, (Online Resource) Fig. A2], which were defined corresponding to a transition of one or two VA state increase, one VA state decrease or no transition: state 1, gain of at least 22.5 letters; state 2, gain of between 7.5 and 22.5 letters; state 3, between gain of 7.5 and loss of 7.5 letters (i.e. stable); and state 4, loss of 7.5 or more letters. In the first year, transitions depend on baseline visual acuity score given it is an important prognostic factor in treatment effectiveness. Thereafter, transitions are independent of baseline score.

Effectiveness data for model comparators was informed by an NMA, described in full elsewhere [24]. In brief, a systematic literature review was performed to identify randomised controlled trials containing relevant comparators (including placebo/sham to form networks) in patients with DMO older than 18 years. Outcomes include changes in baseline visual acuity, change in retinal thickness, injection frequency and adverse events. The NMA showed that faricimab T&E demonstrated superior or comparable efficacy in terms of visual acuity outcomes compared with the relevant comparator anti-VEGF treatment regimens for DMO after 1 year [25]. Therefore, effectiveness for year 1

**Table 2** Administration, monitoring and supportive care costs and sources

Input parameter	Resource use	Unit Cost	Source
<i>Administration costs</i>			
Consultant-led outpatient attendance	1 per admin	£101.8	National Schedule of NHS costs 2019/2020 WF01A Service code 130 [30]
Optical coherence tomography	1 per admin	£125.9	National Schedule of NHS costs 2019/2020 BZ88A [30]
Administration of injection	1 per admin	£55	NICE TA294 [29]
<i>Monitoring visit costs</i>			
Consultant-led outpatient attendance	1 per visit	£101.8	National Schedule of NHS costs 2019/2020 WF01A Service code 130 [30]
Optical coherence tomography	1 per visit	£125.9	National Schedule of NHS costs 2019/2020 BZ88A [30]
<i>Supportive care costs</i>			
One-off cost (VA ≤ 55)	1 per patient	£165.71	NICE NG82 [20] inflated to 2019/2020 prices [31]
Ongoing cost of vision aids (VA ≤ 55)	1 per month	£5.89	NICE NG82 [20] inflated to 2019/2020 prices [31]
Ongoing care costs (VA ≤ 25)	1 per month	£981.06	NICE NG82 [20] inflated to 2019/2020 prices [31]

NHS, National Health Service; NICE, The National Institute for Health and Care Excellence; VA, visual acuity

is based on YOSEMITE and RHINE for faricimab T&E and the NMA for all comparators. Beyond year 1, the second year treatment effect derived from YOSEMITE and RHINE for faricimab T&E is applied to all interventions during treatment [22].

Background mortality was informed by UK life tables, using data from Office for National Statistics for years 2017–2019, adjusted for increased mortality amongst a diabetic population and the impact of visual impairment [20, 26, 27].

### 2.3.2 Adverse Events

Treatment-related adverse event probabilities were informed by YOSEMITE and RHINE for faricimab T&E and applied for all interventions on the basis of the finding from the NMA of comparable adverse event results. Costs and disutility were taken from a UK guideline in nAMD [20] and are shown in Supplementary Material (Online Resource) Table A3.

### 2.3.3 Costs

Costs were presented in 2019/2020 prices and were made up of both direct healthcare payer costs to the UK National Health Service (NHS) and Personal Social Services (PSS), including ongoing supportive care, as well as indirect costs of DMO treatment (productivity impacts and informal care costs). Travel costs were not included given their negligible impact. In the base-case these wider personal and societal costs were included given their importance in relation to the impact of DMO on patients and society. A 2018 UK study estimated indirect costs of sight loss due to AMD, cataract, diabetic retinopathy, glaucoma and under-corrected refractive error of £5.65 billion, which was nearly double the value

of estimated direct healthcare costs [28]. A scenario analysis was also presented considering only NHS costs.

Acquisition costs (see Table 1) were taken from list prices available from the British National Formulary [15–18]. The proportion of patients receiving faricimab at 4, 8, 12 or 16 weekly doses after the loading phase in years 1 and 2 was informed by YOSEMITE and RHINE pooled data [12]. It was assumed that no additional monitoring is required between treatment visits during years 1 and 2 as per T&E regimen.

Frequency of administration for PRN regimens in year 1 was informed by the NMA [24], with the number of injections apportioned over the year. In year 2 and beyond, administration frequency and monitoring visits throughout treatment was informed by a randomised trial of the three comparator treatments and an extension cohort study (Protocol T) of the same group of patients. The same source was used to inform monitoring in the faricimab T&E arm after 2 years, where patients are likely to move to PRN regimen. To account only for additional monitoring costs, this was implemented in the model as the difference between number of visits and number of treatments. The resultant mean frequency of administration and monitoring visits are presented in Supplementary Material (Online Resource) Table A4, alongside the annual acquisition costs in year 1 to year 3 for each treatment.

Administration costs (see Table 2) were informed by a UK clinical guideline and a NICE technology appraisal in nAMD [20, 29]. Costs were composed of a consultant-led outpatient attendance, an optical coherence tomography (OCT) and a cost of the injection, where unit costs were informed by the National Schedule of NHS costs [30].

Supportive care costs (Table 2) were sourced from a UK guideline and were composed of low vision and blindness resources which fall upon NHS and Personal Social Services (vision-related depression, low vision rehabilitation,



**Table 3** Productivity and informal care costs and sources

Cost input parameter	Value	Source
<i>Productivity costs</i>		
Retirement age	66 years	UK Department Work and Pensions [34]
Mean salary	£38,131	ONS [35]
Employment level (population)	75.5%	ONS [36]
Employment level (vision loss)	48.6%	ONS [37]
Employment level (blind)	27.0%	Royal National Institute of Blind People [38]
Treatment-related absenteeism	1 day per visit	Assumption
<i>Informal care costs</i>		
Visual impairment costs	£267.21	Marques et al and ONS [35, 39]
Treatment-related costs	£37.48	Assumption and ONS [35]

ONS, Office for National Statistics

**Table 4** Health state utility scores by visual acuity and first/second eye

		Second eye – visual acuity score					
		> 85	85–71	70–56	55–41	40–26	≤ 25
First eye – visual acuity score	> 85	0.919	0.893	0.868	0.842	0.817	0.782
	85–71	0.893	0.808	0.783	0.758	0.732	0.697
	70–56	0.868	0.783	0.698	0.673	0.647	0.612
	55–41	0.842	0.758	0.673	0.588	0.562	0.527
	40–26	0.817	0.732	0.647	0.562	0.477	0.442
	≤ 25	0.782	0.697	0.612	0.527	0.442	0.326

hip replacement due to falls, residential and community care) and wider societal costs (housing and council tax benefit, social security and governmental tax allowances) [20]. Health states that encompass at least one eye with visual acuity of 55 letters or less incur costs associated with visual impairment. Cost associated with blindness are assigned to health states where both eyes have visual acuity of 25 letters or less. Costs were inflated to 2019/2020 costs using published inflation indices [31].

The costs of productivity losses/gains (see Table 3) were estimated using a human capital approach. Costs were computed on the basis of remaining productive working life years determined by the statutory state pension age (66 years), productivity for relative visual impairment and working years valued at the UK average market wages [34, 35].

Informal care costs for visual impairment were informed by data from a 2018 study in Portugal, which assessed informal care associated with vision loss [39]. Marques et al. reported a mean of 470 h per annum for the 39.6% of all interviewees who received some informal care. Therefore, informal care hours of 186 h per year ( $39.6\% \times 470$ ) were valued at UK average market wages [35]. The costs of informal carers taking time off work for treatment and monitoring visits were assumed to be 4 h, valued in the same way.

### 2.3.4 Utilities

Utility values (see Table 4) are based on a study by Czoski-Murray et al. conducted in the UK which estimated a regression model to relate visual acuity score and utility on the basis of time trade-off methods, including an age covariate [40]. A further adjustment was applied to account for better vision in one eye, partially compensating for worse vision in the other. Aligned with the approach in a guideline review conducted by NICE in nAMD [20], a scaling factor of 0.3 is used to estimate the impact of changes in the worse seeing eye on utility. A disutility for injections and adverse events was included in the model. It was assumed that 50% of patients experience a total loss of quality of life on treatment days, informed by the same UK guideline [20].

### 2.3.5 Cost-Effectiveness Analysis

The state transition model and cost-utility analyses were operationalised in Microsoft Excel©. The model adopted a 4-week cycle length, which is typically the shortest treatment period observed in clinical practice. Given the short cycle length, the impact of event timings within this period were considered negligible and therefore no half-cycle correction was applied. A discount rate of 3.5% was applied to costs and utilities according to UK guidelines [41]. Analyses

**Table 5** Base-case results – Faricimab T&E versus ranibizumab PRN and aflibercept PRN

Treatment	Costs (mean)	Δ costs versus faricimab T&E	LY (mean)	QALYs (mean)	Δ QALYS versus faricimab T&E	ICER versus faricimab T&E	NMB
Faricimab T&E	£37,136	–	11.83	7.56	–	–	£114,015
Ranibizumab PRN	£42,619	£5483	11.77	7.20	–0.36	Faricimab T&E is dominant	£101,389
Aflibercept PRN	£46,791	£9655	11.81	7.40	–0.16	Faricimab T&E is dominant	£101,156

ICER, incremental cost-effectiveness ratio; LY, life-years; NMB, net monetary benefit; PRN, pro re nata; QALYs, quality adjusted life-year; T&E, treat and extend

**Table 6** Base-case results—components of total costs

Treatment	Drug acquisition costs	Admin costs	Monitoring costs	AE costs	Supportive care costs	Productivity gains (versus no. treatment)	Informal care costs
Faricimab T&E	£25,968	£8217	£1858	£78	£4056	–£25,381	£22,341
Ranibizumab PRN	£18,636	£9172	£4165	£77	£5271	–£20,557	£25,854
Aflibercept PRN	£27,562	£9163	£4325	£78	£4546	–£22,992	£24,110

AE, adverse events; PRN, pro re nata; T&E, treat and extend

were run for cohort aged 62 years and with a time horizon of 25 years to ensure important differences in costs and effects were captured. Results were estimated for difference in quality adjusted life-years (QALYs), costs and net monetary benefit (NMB), with health benefits valued using the lower end of cost-effectiveness threshold adopted by NICE (£20,000 per QALY) [41]. Base-case results were based on a societal perspective and presented deterministically.

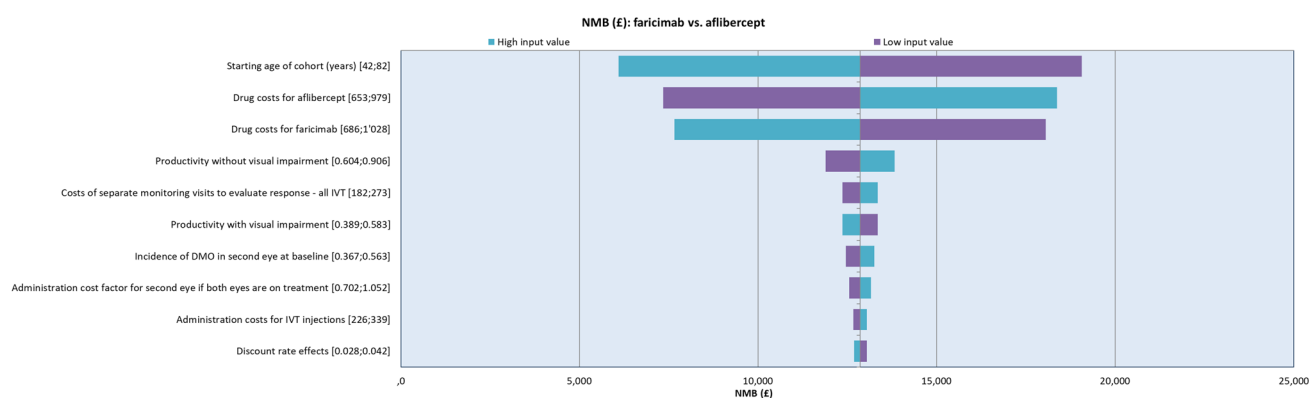
Deterministic and probabilistic sensitivity analysis (PSA, 1000 simulations) were conducted to characterise uncertainty and explore robustness of model results. Upper and lower bounds for deterministic sensitivity analysis (DSA) were informed by source material estimates of uncertainty, 95% confidence interval where available, or an arbitrary 20% of the mean value otherwise to reflect limited knowledge of uncertainty around mean values, and incremental NMB was used as the output. The distributions used in the PSA were based on parameter characteristics, and distributional shape was defined by observed data (i.e. alpha, beta, mean, standard error). The PSA inputs for visual acuity changes, treatment discontinuation and number of injections were implemented on the basis of sampling with replacement from the empirical distribution for trial-based data, or CODA outputs from the Bayesian NMA for comparators. Cost parameters used gamma distributions; proportions, probabilities and utility values used beta distributions. A normal distribution was used for all other parameters. A full table of model inputs not derived from NMA is given in Supplementary Material (Online Resource) Table A4, including characterisation of uncertainty. A healthcare payer perspective was presented in a scenario, as well as a comparison with bevacizumab

and ranibizumab T&E. Alternative health state utilities from a study by Brown and colleagues were presented in scenario [see Supplementary Material (Online Resource) Table A6], which were similarly used as sensitivity analysis in a recent NICE guideline [20, 42].

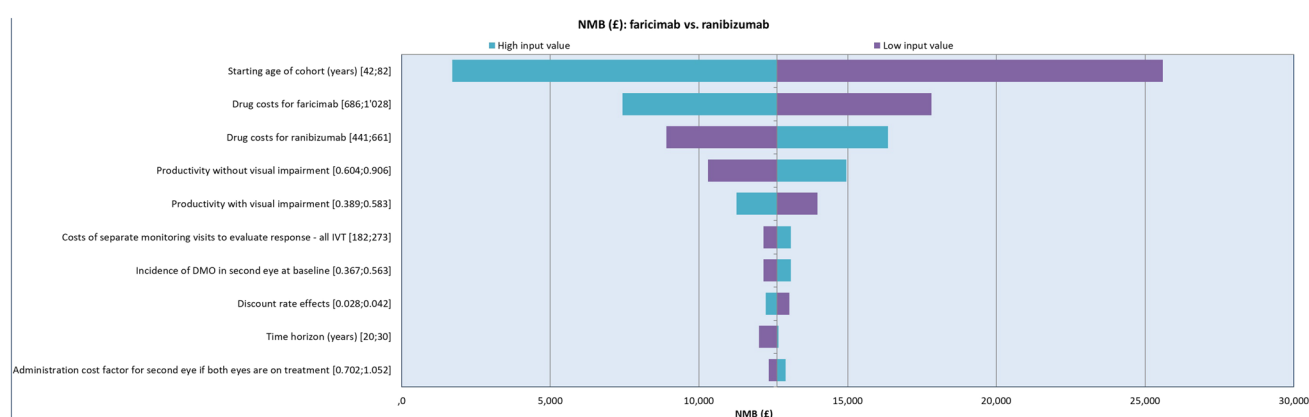
### 3 Results

Base-case results comparing faricimab T&E against ranibizumab PRN and aflibercept PRN over a lifetime are presented in Table 5. For both comparisons, faricimab T&E produced additional mean life years (LY) and QALYs, with most of the benefit captured in quality-of-life improvements. The mean benefit of faricimab T&E over comparators ranged from 0.16 to 0.36 QALYs. Faricimab T&E resulted in cost savings compared with ranibizumab PRN (£5483) and aflibercept PRN (£9655) and is therefore considered dominant.

A breakdown of the components of costs is given in Table 6. Drug acquisition, informal care and cost offsets from productivity gains are the largest components of the total cost estimates. Given that fewer monitoring visits are required, monitoring costs for faricimab T&E are approximately 50% of the other comparators (£1858 versus £4165 and £4325). Productivity gains from faricimab T&E compared with ranibizumab PRN and aflibercept PRN were £4824 and £2388, respectively. Faricimab T&E informal care costs (£22,341) were lower than ranibizumab PRN (£25,854) and aflibercept PRN (£24,110).



**Fig. 3** Tornado diagram - faricimab T&E vs aflibercept PRN. IVT, intravitreal; nAMD, neovascular age-related macular degeneration; NMB, net monetary benefit; PRN, pro re nata; T&E, treat and extend



**Fig. 4** Tornado diagram - faricimab T&E vs ranibizumab PRN. IVT, intravitreal; nAMD, neovascular age-related macular degeneration; NMB, net monetary benefit; PRN, pro re nata; T&E, treat and extend

## 4 Sensitivity and scenario analysis

Deterministic sensitivity analysis is summarised in the tornado diagrams shown in Figs. 3 and 4, which display the ten most sensitive parameters included in the analysis for comparisons against aflibercept PRN and ranibizumab PRN, respectively. Results were most sensitive to the starting age of the cohort, drug costs and productivity input parameters. All analyses suggested positive incremental NMB for faricimab T&E versus comparators.

Results of the probabilistic sensitivity analysis, jointly characterising uncertainty in all input parameters, are presented using cost-effectiveness acceptability curves (CEAC). It shows the probability of each regimen being the most cost-effective option at willingness to pay of £0 to £50,000 (see Fig. 5). Faricimab T&E has the highest likelihood of being the most cost-effective option across the range. At a willingness-to-pay threshold of £20,000 per QALY, the probability that faricimab T&E is cost-effective

compared with aflibercept PRN and ranibizumab PRN is 85%. At lower thresholds ranibizumab PRN displays a small probability of being most cost-effective (£5000: 24%; £10,000: 19%)

Results of scenario analyses comparing faricimab T&E against bevacizumab PRN and ranibizumab T&E and incorporating healthcare resource use costs only are presented in Tables 7 and 8, respectively. Results of the scenario analysis exploring alternative health state utility values by Brown and colleagues are presented in Table 9 [42]. Mean costs per patient are lower for bevacizumab PRN (£3478) and mean QALYs are also lower (– 0.39) compared with faricimab T&E, resulting in an ICER of £8898 per QALY gained or incremental net benefit (INB) of £4339, using cost-effectiveness threshold of £20,000 per QALY.

When only NHS costs are included, faricimab T&E still dominates aflibercept PRN (see Table 8). Patients in the faricimab T&E arm accrued more costs compared with ranibizumab PRN. However, given the QALY benefits, faricimab T&E would be considered cost-effective at a



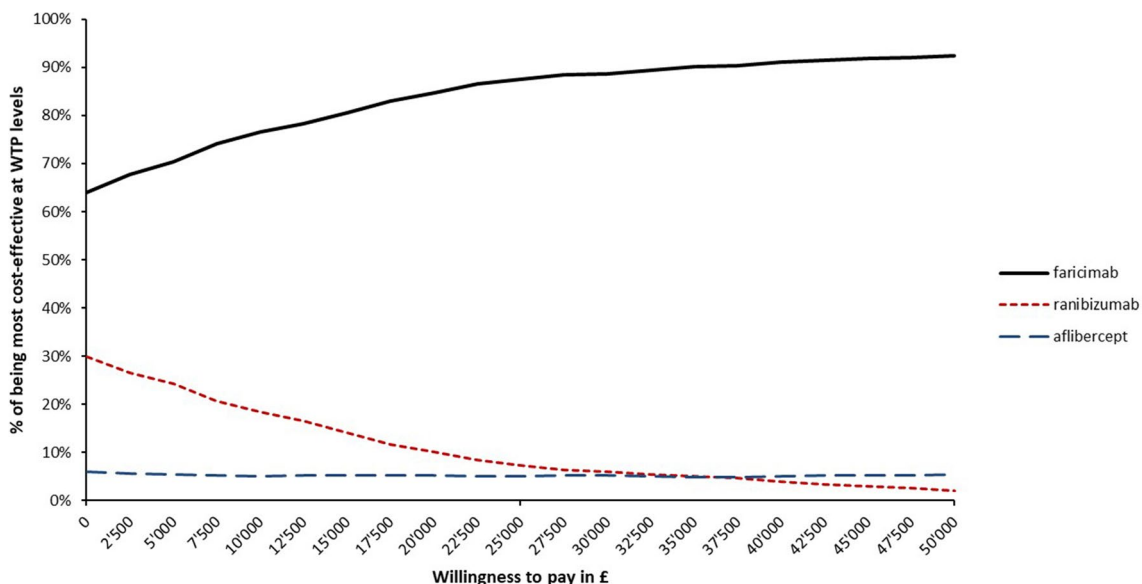


Fig. 5 Cost-effectiveness acceptability curves (CEAC). WTP, willingness to pay

Table 7 Scenario analysis – Faricimab T&E compared with bevacizumab PRN and ranibizumab T&E

Treatment	Costs (mean)	Δ costs versus faricimab T&E	LY (mean)	QALYs (mean)	Δ QALYS versus faricimab T&E	ICER versus faricimab T&E	NMB
Faricimab T&E	£37,136	–	11.83	7.56	–	–	£114,015
Bevacizumab PRN	£33,658	–£3478	11.77	7.17	–0.39	£8898	£109,676
Ranibizumab T&E	£42,614	£5478	11.77	7.20	–0.36	Faricimab T&E is dominant	£101,394

ICER, incremental cost-effectiveness ratio; LY, life years; NMB, net monetary benefit; QALYs, quality adjusted life years; PRN: pro re nata; T&E, treat and extend

Table 8 Scenario analysis – NHS costs only for faricimab T&E versus ranibizumab PRN, aflibercept PRN

Treatment	Costs (mean)	Δ costs versus faricimab T&E	LY (mean)	QALYs (mean)	Δ QALYS versus faricimab T&E	ICER versus faricimab T&E	NMB
Faricimab T&E	£40,176	–	11.83	7.56	–	–	£110,975
Ranibizumab PRN	£37,322	–£2854	11.77	7.20	–0.36	£7,991	£106,686
Aflibercept PRN	£45,674	£5498	11.81	7.40	–0.16	Faricimab T&E is dominant	£102,274

ICER, incremental cost-effectiveness ratio; LY, life-years; QALYs, quality adjusted life-years; NMB, net monetary benefit; PRN, pro re nata; T&E, treat and extend

Table 9 Alternative health state utility values—faricimab T&E versus ranibizumab PRN, aflibercept PRN

Treatment	Costs (mean)	Δ costs versus faricimab T&E	LY (mean)	QALYs (mean)	Δ QALYS versus faricimab T&E	ICER versus faricimab T&E	NMB
Faricimab T&E	£37,136	–	11.83	7.97	–	–	£122,218
Ranibizumab PRN	£42,619	£5483	11.77	7.57	–0.40	Faricimab T&E is dominant	£108,804
Aflibercept PRN	£46,791	£9655	11.81	7.79	–0.18	Faricimab T&E is dominant	£109,011

ICER, incremental cost-effectiveness ratio; LY, life-years; QALYs, quality adjusted life-years; NMB, net monetary benefit; PRN, pro re nata; T&E, treat and extend

threshold of £20,000 per QALY compared with ranibizumab PRN.

## 5 Discussion

National and local decision-makers are increasingly concerned with cost-effectiveness and the cost-saving potential of new interventions. A *de novo* model was constructed to conduct a UK cost-utility analysis of faricimab T&E compared with relevant alternatives. Analyses demonstrate that faricimab T&E is cost saving or cost-effective compared with aflibercept PRN, ranibizumab PRN and T&E and bevacizumab PRN at a cost-effectiveness threshold of £20,000 per QALY. Probabilistic analysis demonstrated that there is a high degree of certainty that faricimab T&E is cost-effective compared with ranibizumab PRN and aflibercept PRN. Scenario analysis versus bevacizumab PRN, which is not licensed for the treatment of DMO in the UK but occasionally used in clinical practice, suggests that although bevacizumab PRN is less costly, faricimab T&E would be considered a cost-effective option due to greater health gains.

Deterministic sensitivity analysis suggested that the age of cohort was the most sensitive parameter. This suggests that reducing the starting of age of treatment, for example, by improved diagnosis, could further increase the net monetary benefit from faricimab T&E substantially. This is driven by the productivity gains from the younger patient population and the relatively large bounds explored (ages 42 and 82 years). Furthermore, the analysis conservatively assumes an average retirement age of 65 years for the cohort. Given that the state pension age in the UK is set to rise in the future, the period over which productivity gains are estimated will also increase, leading to further increases in productivity gains and net monetary benefit.

The reduction of independence has been found to be a major concern for people with diabetic retinopathy, including people with DMO, with limitations in social activities and driving having a substantial impact [43]. Base-case analyses incorporating informal care costs and productivity gains suggest faricimab T&E produces cost savings in addition to improvements in quality of life against ranibizumab PRN and aflibercept PRN. These indirect costs have been shown to be an important part of the burden of DMO, in addition to the direct healthcare costs to the NHS [4, 28]. When only NHS and PSS costs are considered, faricimab T&E can still be considered cost-effective. In addition, administration and monitoring costs were lower for faricimab T&E than all alternatives.

Whilst several HTA agencies typically take a narrow healthcare perspective, there are other societal and healthcare impacts that provide value but are not routinely included in HTA decision-making. For health services that

have significant capacity constraints, such as ophthalmologic clinics, effective treatments which reduce healthcare resource requirements can alleviate some of these capacity issues [44]. Ophthalmology is the busiest outpatient speciality in the NHS [45] and there is a severe shortage of ophthalmologists to manage the increasing demand for services. This is likely to increase further given that the incidence of type 1 and type 2 diabetes is increasing, and the incidence of DMO is increasing correspondingly [28, 46]. The coronavirus disease 2019 (COVID-19) pandemic further exacerbated the strain on ophthalmic services; ophthalmology outpatient attendances in the UK fell from 7.9 million in 2019/2020 to 5.4 million in 2020/2021, a drop of 32% [45, 47]. This created a large backlog for ophthalmic care in the UK, with more than 600,000 patients awaiting ophthalmology treatment as of December 2021, including 27,000 patients who have been waiting for a year or more [48]. The reduced frequency at which faricimab T&E is administered and monitored offers a potential route for alleviating part of the burden on ophthalmology services [49].

This study presents the first model of its kind comparing faricimab for the treatment of DMO against relevant comparators and regimens in a UK setting, with faricimab effectiveness informed by pooled analysis of two large randomised controlled trials [12]. The model structure, and some of the key assumptions having precedence and clinical validation, have been used to inform UK national guidelines in a similar disease area [20]. Key input parameters, including comparator effectiveness and frequency of administration, were sourced from an NMA performed following a systematic review of the literature.

### 5.1 Limitations

There is some variation in clinical practice and adaptations in the use of treatments for DMO, with a general move away from PRN to T&E regimens. Analyses were conducted in line with pivotal trials YOSEMITE and RHINE and on the basis of UK clinical expert opinion on the use of comparator treatments. Analyses against other potential regimens using fixed monthly or bimonthly treatment could be performed, but were deemed of limited relevance in UK clinical practice as outlined above. [21] Similarly, analysis against brolocizumab was not included given the respective NICE appraisal highlighting that it may rather be used as a second-line treatment [10]. State-transition (Markov) models are appropriate for modelling chronic conditions and there is significant precedence for use in DMO [20]. However, other approaches, including individual patient simulation, may be able to better capture patient heterogeneity and have been explored in ophthalmology applications [50].

Direct clinical evidence was not available to compare faricimab T&E with ranibizumab and bevacizumab regimen.

For these comparators, data were informed by a Bayesian NMA of 26 studies [24]. This analysis suggests faricimab is superior to flexible dosing regimens on the basis of retinal thickness, and superior or equal in terms of BVCA (credible intervals include 0 only for aflibercept), with injection frequency numerically lower, reflecting some remaining uncertainty. However, these Bayesian methods are consistent with probabilistic sensitivity analysis, allowing this uncertainty to be jointly characterised by sampling with replacement from the empirical distribution or NMA CODA. PSA showed a high probability that faricimab is the most cost-effective option.

Health state utility values for visual conditions such as DMO pose some difficulties, with concerns about the performance of commonly recommended generic measures such as the EQ-5D [51]. The source for utility values was a study that applied a novel method by recreating visual acuity groups, using contact lenses and performing direct elicitation [33]. These visual acuity groups were able to directly map the health states used in the model. There has been criticism of the results of this approach, suggesting that it may underestimate the disutility associated with loss in visual acuity [52]. This may have the impact of consequently also underestimating the benefits of faricimab T&E relative to the comparator treatment regimens. A scenario analysis suggested results were not sensitive to use of alternative utility values.

All analyses were based on list prices. In practice, treatments may be offered in the UK at discounted prices, due to patient access schemes negotiated in parallel to NICE Technology Assessments. In addition, a vial of bevacizumab formulated for cancer treatment may be compounded by pharmacies into multiple doses for off-label intravitreal treatment. However, acquisition costs varied by  $\pm 10\%$  in sensitivity analysis and results were robust to changes.

## 6 Conclusion

Faricimab T&E can be considered cost-effective treatment for DMO compared with ranibizumab PRN and T&E, aflibercept PRN and bevacizumab PRN, whether using a societal or healthcare payer perspective for costs. The deterministic and probabilistic sensitivity analysis performed suggests results are robust to allowance for uncertainty.

Faricimab as a new treatment option has the potential to reduce the burden of vision loss on patients and on society, giving people living with DMO greater independence. Further, given the current capacity constraints in the health system and the expected increase in future demand for

ophthalmology services, the reduced frequency at which faricimab T&E is administered and monitored could be valuable in reducing the burden placed on ophthalmology clinics in the NHS.

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## Declarations

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**Conflicts of Interest** Christian Bührer is employed by and reports stock ownership in F. Hoffmann-La Roche Ltd. Tatiana Paulo and Marloes Bagijn are employees of F. Hoffmann-La Roche Ltd. Thomas Paling is an employee of Roche Products Ltd. Richard Gale has received financial support from consultancy support from Hoffmann-La Roche Ltd, Novartis and Bayer.

**Availability of Data and Material** All data used for this study are provided in the article or are publicly available as indicated by citations.

**Ethics Approval** Not applicable.

**Consent to Participate** Not applicable.

**Consent for Publication** Not applicable.

**Code Availability** The cost-effectiveness model was developed in Microsoft Excel 365 (Microsoft Corporation). Additional information about model programming is available from the corresponding author upon request.

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