Dexamethasone intravitreal implant for treating diabetic macular oedema in people without a pseudophakic lens

For public observers – AIC information redacted [redacted]

Technology appraisal committee C [05 July 2022]

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NICE

Purpose of this appraisal

Part review of Technology appraisal (TA) guidance TA349

- Part review of TA349 (published July 2015), which included people with both pseudophakic and phakic DMO
- TA349 recommends dexamethasone intravitreal implants as an option for treating DMO that is insufficiently responsive to available therapies if the implant is to be used in an eye with an intraocular (pseudophakic, or artificial) lens
- In TA349, DEX700 was not cost effective compared with watch and wait in people who do not have a pseudophakic lens, and with DMO that does not respond to non-corticosteroid treatment or for whom such treatment is unsuitable
- The company reports that there is now a change in the most appropriate comparator for part of this population due to changes in clinical practice, and additionally, that there is new RWE for dexamethasone
- Therefore, this part-review of TA349 is for people with phakic lenses
- Current technology appraisal guidance in development for people with visual impairment due to DMO include Brolucizumab [ID3902] and Faricimab [ID3899]

Abbreviations: DMO, diabetic macular oedema; DEX700, Dexamethasone 700 μg; TA, technology appraisal; RWE, real world evidence

Background on Diabetic macular oedema

DMO is the most common cause of visual impairment in diabetes mellitus

Causes

- Diabetic macular oedema (DMO) occurs as a result of changes in retinal blood vessels
- Disruption of the blood–retinal barrier allows fluid to leak from blood vessels in the macula, leading to fluid accumulation and thickening of the macula

Epidemiology

- 3.9 million people have been diagnosed with diabetes in the UK as of 2019
- Approximately 7% of people with diabetes may have DMO in England, of whom 39% have clinically significant macular oedema (CSMO)
- DMO is more common in people of African–Caribbean and South Asian family origin

Diagnosis and classification

- DMO may be detected during an annual eye screening visit
- Most vision loss occurs when DMO involves the centre of the macula (CSMO) and is regarded as the threshold for treatment

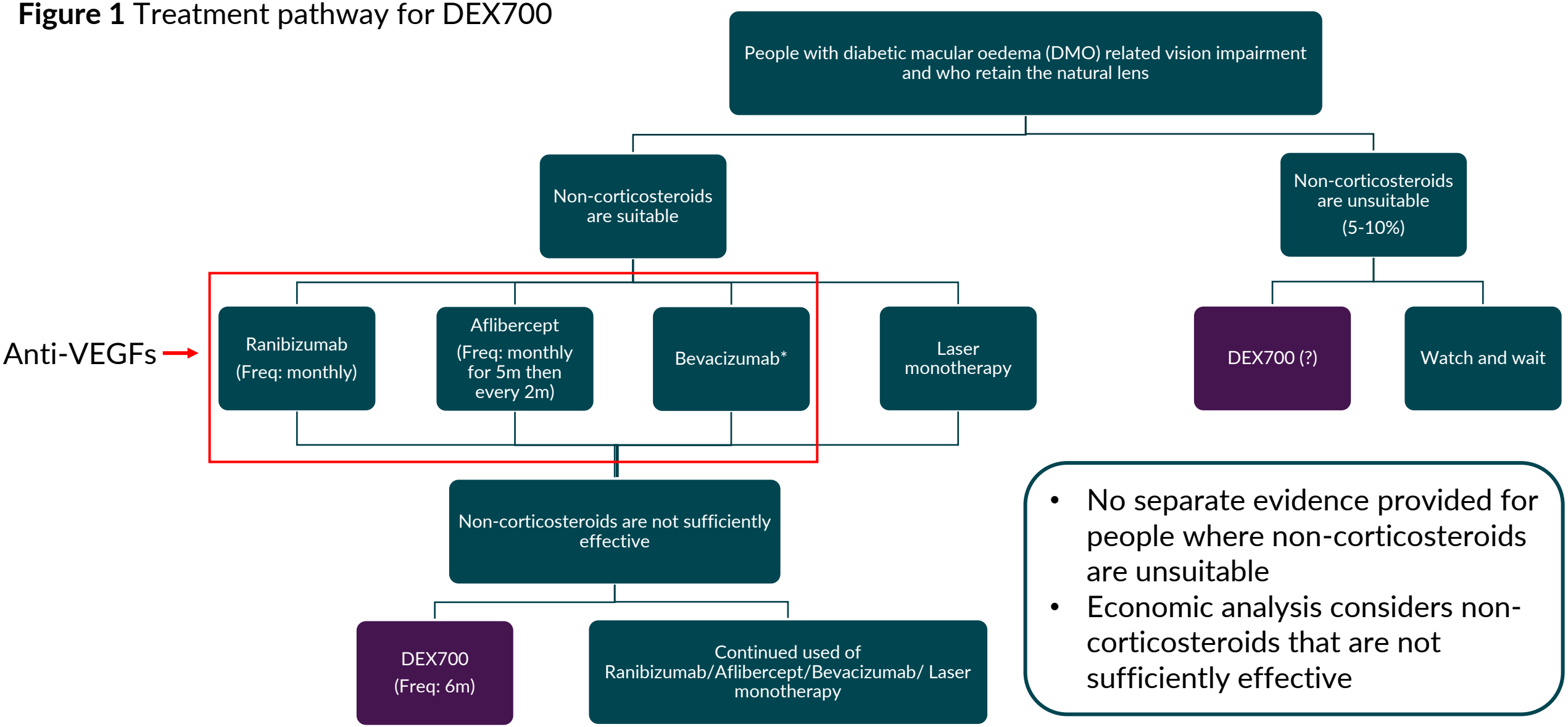
Symptoms

Symptoms include dark spots or gaps in vision, vision loss, difficulty reading and blurred vision

Abbreviations: DMO, diabetic macular oedema; CSMO, clinically significant macular oedema

Treatment pathway and proposed position

Figure 1 Treatment pathway for DEX700



- No separate evidence provided for people where non-corticosteroids are unsuitable
- Economic analysis considers non-corticosteroids that are not sufficiently effective

*Bevacizumab does not currently have a marketing authorisation in the UK and is not recommended by NICE

Abbreviations: DEX700, Dexamethasone 700 µg; DMO, diabetic macular oedema; Freq, frequency; M, months

Perspectives on living with DMO

Need for less frequent and painful treatment

NICE thanks Macular Society and patient expert for their contributions

- DMO disrupts the activities of every day life and has a profound impact on emotional and mental health
- Number of people with DMO is increasing. Substantial additional treatment burden on patients and carers in addition to managing diabetes
    - NHS eye services are under-resourced to meet their needs
    - Optimism that longer acting drugs can alleviate the problem
    - Welcome measures that reduce the need for attendance at eye clinics for an invasive, distressing and sometimes painful treatment
- People with a natural lens who do not respond to anti-VEGF now have the opportunity for treatment that meets their needs and preferences

"[Survey] responders felt less able to manage their eye health and DMO compared to their diabetes" "Regular trips to the hospital for check-ups, having to arrange holidays etc around treatment. Painful treatment."

"Within 14 months of diagnosis I lost my beloved job and the following year my driving license. The loss was so quick and sudden it took me 6 months to regain any feeling of self worth.

Abbreviations: DMO, diabetic macular oedema; anti-VEGF, anti-vascular endothelial growth factor

Clinical perspectives

Unmet need for a treatment option for anti-VEGF treatments in DMO

NICE thanks the Royal College of Ophthalmologists and Clinical Experts for their contributions

- Unmet need for this technology in:
  - phakic eyes that are unresponsive to intravitreal anti-VEGF therapies
  - people for whom intravitreal injections of anti-VEGF therapies are unsuitable
- Intraocular pressure increases after dexamethasone implants in people with diabetes are less frequent than in the eyes of people who don't have diabetes
- Efficacy of dexamethasone implants in DMO is not affected by the lens status
- For people with diabetes, a significant number have eyes with cataracts at baseline (pre-treatment with the technology); clinical trial data reflects this
- Outcomes of cataract surgery in phakic eyes treated with dexamethasone implants are excellent and comparable to eyes that have not been treated with the technology
- Eye services are under pressure: this is capacity sparing

"The new treatment will lead to better resolution of DMO, and visual acuity improvements, less frequent hospital visits, and patient satisfaction compared to current care"

"The aim of treatment with dexamethasone implant is to reduce the macular oedema and stop progression of visual loss in DMO"

Abbreviations: DMO, diabetic macular oedema; anti-VEGF, anti-vascular endothelial growth factor

Equality and Innovation considerations

Equality considerations

- There are no known relating to the use of DEX700 that have been identified or are anticipated

Innovation (from company submission)

- Substantial unmet clinical need for people with phakic eyes and DMO where non-corticosteroids are not sufficiently effective or non-corticosteroids are unsuitable. DEX700 has potential to address the unmet need
- DEX700 requires less frequent injections. A therapy requiring less frequent injections reduces treatment burden, improving adherence and quality of life
- DEX700 has potential to free up resources and reduce the burden on the healthcare system whilst providing clinical benefit

Dexamethasone 700 µg (DEX700) intravitreal implant (Ozurdex, AbbVie)

Table 1 Technology details

Marketing authorisation (MHRA)	"Indicated for the treatment of adult patients with: • visual impairment due to diabetic macular oedema (DMO) who are pseudophakic or who are considered insufficiently responsive to, or unsuitable for non-corticosteroid therapy" • MHRA licence approved July 2010, label renewed March 2015
Mechanism of action	• Dexamethasone is a corticosteroid that reduces the levels of multiple inflammatory mediators • DEX700 is an injectable intravitreal implant that delivers active treatment to the eye through a solid polymer drug delivery system
Administration	• One intravitreal implant in an applicator containing DEX700 at approximately 6-month intervals
Price	• £870 per one intravitreal implant of 700 µg or £1,740 per annum (unilateral treatment/ one unit assumed to treat one eye) • One implant is given at approximately 6-month intervals (model assumes a maximum of 5 years) • No confidential commericial arrangements in place

Abbreviations: DMO, diabetic macular oedema; MHRA, Medicines and Healthcare products Regulatory Authority; DEX700, Dexamethasone 700 µg intravitreal implant in applicator; DMO: diabetic macular oedema

Decision problem

Table 2 Population and comparators from the scope

	Final scope	Company	ERG comments
Population	People with phakic lenses and DMO that is insufficiently responsive to, or is unsuitable for, non-corticosteroid treatment	Although the submission does consider the full population outlined in the final scope, the economic analysis only considers insufficient responders as there is no relevant additional evidence available to model this specific population beyond the data that was presented in TA349	DEX700 data from the MEAD trials does not reflect patients with [redacted] (Issue 1)
Comparators	• Laser photocoagulation alone • Watch-and-wait • Aflibercept • Bevacizumab* • Ranibizumab	Economic analysis only considers anti-VEGF therapies on basis of UK clinical feedback	Clinical evidence for the efficacy of laser alone compared with DEX700 not provided in the company submission

*Bevacizumab does not currently have a marketing authorisation in the UK and is not recommended by NICE

Abbreviations: DEX700, Dexamethasone 700 µg intravitreal implant in applicator; anti-VEGF, vascular endothelial growth factor

Clinical effectiveness

NICE National Institute for Health and Care Excellence

Key clinical trials*

Trials for DEX700

Table 3 Clinical trial designs and outcomes

	MEAD-010	MEAD-011
Design	Phase 3, multicentre, masked, randomised, sham-controlled	
Population	Patients ≥18 years of age with type 1 or 2 DM who had fovea-involved macular oedema associated with diabetic retinopathy (phakic and pseudo-phakic) and had been previously treated with medical or laser therapy	
Intervention	DEX700; DEX350	
Comparator(s)	Needleless applicator system (Sham)	
Duration	36–39 months	
Primary outcome	Mean BCVA average change from baseline	
Key secondary outcomes	Proportion of patients receiving treatment, treatment discontinuation rates, rate of cataract surgery, AE rates (including elevated intraocular pressure)	
Locations	59 study centres in 10 countries	72 study centres in 14 countries
Used in model?	Yes	

*Company conducted ITCs; evidence sourced from SLR and the UK RWE audit however ERG considers caution drawing conclusions based on the results of these ITCs. Details in the backup slide 36

Abbreviations: DM, diabetes mellitus; DEX700, intravitreal implant in applicator; ITC, indirect treatment comparison; RWE, real world evidence DEX350, 350 µg intravitreal implant in applicator; BCVA, Best-corrected visual acuity; AE, Adverse event

Results from MEAD trials (1)
Best corrected visual acuity (measured using ETDRS method)

Figure 2 Change in BCVA from baseline to 39 months

Table 4 Change in BCVA from baseline to 39 months

	DEX700 (n=)	SHAM (n=)	p-value
Mean BCVA average change, n(%)			

- ETDRS letters: ETDRS charts present a series of 5 letters of equal difficulty per row, with standardized spacing between letters and rows; (total of 14 lines/70 letters)
- Company's expert panel considered in the mean change in BCVA from baseline between months
- Beyond month BCVA , which the company reported coincided with the timing of cataract extraction surgery in the DEX700 patients

Abbreviations: BCVA, Best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study

Key issue 1: Generalisability of results from MEAD trials

Uncertainty around generalisability to UK practice

Background

- ERG concerned data from MEAD does not reflect population whose disease had an insufficient response to [redacted] and the population has [redacted] than expected in the NHS
- [redacted] for the DEX700 ([redacted]) and sham arms ([redacted]) and a LOCF approach used to account for missing data

Company response

- MEAD trials most appropriate source of evidence and impact of differences unlikely to favour efficacy of DEX700
- MEAD underestimates efficacy of DEX700 in phakic patients as baseline characteristics tend to be poorer than those observed in UK clinical practice
- Sham arm of MEAD overestimates efficacy of continued anti-VEGF use in insufficient responders to anti-VEGF treatment vs observed UK RWE, therefore underestimates the expected relative difference between DEX700 and continued use of anti-VEGF therapy in insufficient responders

ERG comments

- Uncertainty around generalisability of results from MEAD trials to UK clinical practice remains
- Company provided no detail on methodology for identifying RWE studies, so potentially not fully representative of all relevant published RWE
- Concerned that LOCF approach biases sham and DEX700 arms and not possible to predict the direction of bias

Abbreviations: Dexamethasone 700 µg intravitreal implant in applicator; LOCF, Last observation carried forward; anti-VEGF, anti-vascular endothelial growth factor; RWE, real-world evidence; vs, versus

Cost effectiveness

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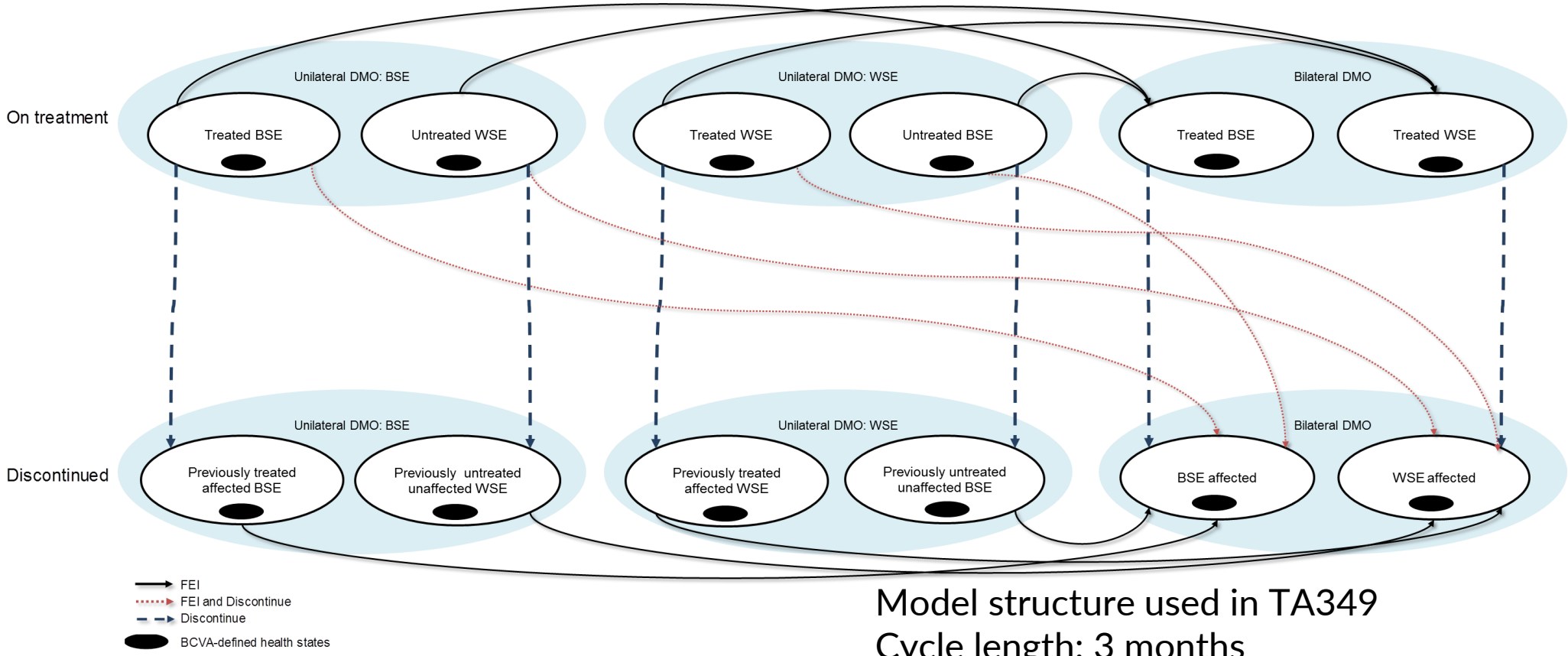
Company's model overview
Markov cohort state-transition model

Visual acuity (BCVA): 6 states (10 letter increments)
DMO: Unilateral (BSE) / Unilateral (WSE) / Bilateral
Treatment: on/off

Figure 3 Model structure



Model structure used in TA349
Cycle length: 3 months
Time horizon: 40y with starting age 61 (ERG favoured 10y)
Costs/health outcomes discounted at 3.5%pa

Abbreviations: DMO, diabetic macular oedema; BSE, Best-seeing eye; WSE, Worst-seeing eye; FEI, Fellow eye involvement; BCVA, Best-corrected visual acuity

How company incorporated evidence into model

Evidence from MEAD trials, UK RWE audit, and previous utility study

Table 5 Input and evidence sources in the company base case model

Input	Assumption and evidence source
Baseline characteristics	Pooled DEX700 arms of phakic patients in the MEAD trials
Comparator	Composite comparator Ranibizumab ([redacted]), Aflibercept ([redacted]) - based on UK RWE audit (scenario analyses for each therapy alone)
Intervention efficacy	Y1-3 Based on dosing and efficacy observed from the phakic DMO patients in the DEX700 arms of the pooled MEAD trials Y4-5 extrapolated from MEAD trials (transitions for m33-36)
Comparator efficacy	Y1-5 Sham arm of MEAD trials, extrapolated for Y4-5
Natural history	Y5+ DMO natural history from TA274 (alternative TA613)
Discontinuation	Intervention: MEAD trials (constant rate projected after 39m); anti-VEGF none, but reduced injection frequency over time (TA613)
Utilities	Czoski-Murray *et al.* 2009 study (ERG preferred in TA349)
Costs and resource use	MIMS, NICE DSU report, BNF, eMIT, NHS reference costs
Discounting	3.5% for costs and health effects

Abbreviations: BNF, British National Formulary; Dexamethasone 700 µg intravitreal implant in applicator; DMO, diabetic macular oedema; DSU, Decision Support Unit; eMIT, the drugs and pharmaceutical electronic marketing tool; RWE, Real-world evidence; MIMS, Monthly Index of Medical Specialities; PSSRU, Personal Social Services Research Unit

Key issue 2: Time horizon (1)*

Time horizon considered for the economic analysis

Company

- Company adopted a lifetime time horizon (40 years) consistent with NICE TA613 and TA346

ERG comments

- Mean BCVA increases from Year 25 for unilateral DMO in the BSE and bilateral DMO (Figure 4) as the company applied additional mortality due to blindness in revised base case
- ERG maintains that a shorter time horizon (10 years) should be used as the company's long-term modelling assumptions are too simplistic
- Some experts suggested convergence in BCVA might occur 7-10 years following cessation of treatment

*Slides 38-9 in back-up slides cover issue 2 in more detail

Figure 4 Mean BCVA in treated eye(s) over modelled time horizon: revised company base case (generated by the ERG)

Is a lifetime horizon too long to capture the costs and consequences of DEX700 and comparator treatments?

Abbreviations: DEX700, Dexamethasone 700 µg intravitreal implant in applicator; BCVA, Best-corrected visual acuity; BSE, best-seeing eye; WSE, worst-seeing eye

Key issue 3: Changes in BCVA resulting from DEX700

Changes in BCVA resulting from DEX700 treatment in Years 4 and 5

Background

- 3-monthly transition probabilities in Years 4 and 5 were assumed to equal the last transition probability matrix estimated from MEAD in company's base case analysis

Company response

- Upward trend in visual acuity outcomes from the end of MEAD
- Company retained assumption that the last transition probability matrix from MEAD can be applied in each 3-month cycle during Years 4 and 5 for those who continue to receive DEX700

Clinical expert

- Expected that DMO eyes that are optimally treated will maintain vision, however, vision will deteriorate in eyes that receive suboptimal treatment with DEX or other therapies
- Expected that BCVA should not decline in years 4 and 5 if optimally treated. Any deterioration due to cataract would have been corrected previously by cataract surgery

ERG comments

- Considers the changes in BCVA resulting from DEX700 treatment in Years 4 and 5 to still be a key area of uncertainty and therefore maintains its preferred assumption that DEX700 maintains vision in Years 4 and 5

Abbreviations: DEX700, Dexamethasone 700 µg intravitreal implant in applicator; BCVA, Best-corrected visual acuity

Key issue 6: Natural history of vision

The natural history of vision in eyes with DMO

Background

- Natural history data were taken from Mitchell et al. 2012 (3-month probability of gaining or losing at least 10 letters of BCVA of 3.5% and 4.5%, respectively
- ERG considered the source to reflect outdated practice and include a population with diabetic retinopathy that may not have had DMO
- ERG's clinical experts considered the 3-month probability of gaining at least 10 letters of BCVA of 3.5% to high

Company response

- Company identified a 3-month probability of gaining or losing at least 10 letters of BCVA of 2.5% or 3.5% in TA274, respectively and assumes this in revised base case
- TA274 may have greater clinical plausibility, as the assumption that no patient would experience any improvement in vision lacks clinical plausibility and is not consistent with what was observed in the WESDR study, what was accepted in TA274, and data from the sham arm from MEAD and the UK RWE

ERG comments

- TA613 committee accepted a 3-month probability of gaining or losing at least 10 letters of BCVA of 0% or 3.5%, respectively (and was conducted after TA274)
- Overall the ERG maintains that the most appropriate natural history estimates are those accepted in TA613

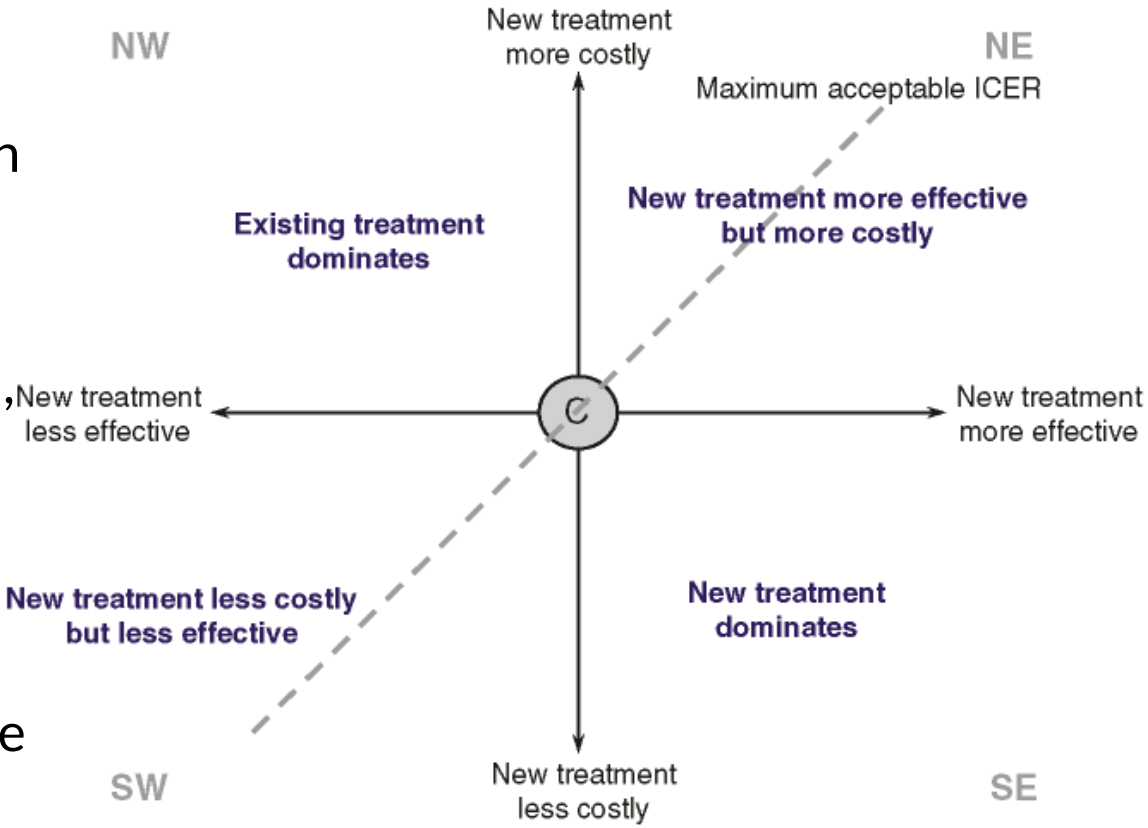
What is the most appropriate source of natural history estimates for decision making?

Abbreviations: BCVA, Best-corrected visual acuity

Decision-making with south west quadrant ICERs

- South-west quadrant ICERs are presented as costs saved per QALY lost
- The higher the ICER, the more cost is saved per QALY lost, so high ICERs are better here and the commonly assumed decision rule of accepting ICERs below a given threshold is reversed
- This is reflected in decision making in previous appraisals with south-west quadrant ICERs (e.g. TA433, TA561)
- Positive recommendations are made when the costs saved are sufficient to cover the QALY loss
- Usually, south-west quadrant ICERs have led to positive recommendations when ICERs are substantially above £30,000 per QALY lost

Figure 5 The incremental cost effectiveness plane



Abbreviations: QALYs, Quality-adjusted life years; ICER, incremental-cost effectiveness ratio

Decision-making with net-monetary benefit

Table 6 Summary of Net monetary benefit and ICERs

	Equation	Output	Meaning
ICERs	Incremental costs (£)/ Incremental benefits (QALYs)	ICER value	Extra cost per extra unit of benefit
Net monetary benefit	(Incremental benefits x threshold) – incremental cost	Costs	Value of an intervention in monetary terms at a given willingness-to-pay threshold

- Net monetary benefit can be presented as an additional consideration to support decision-making in appraisals involving south-west quadrant ICERs
- Positive net monetary benefit implies that the intervention is cost-effective compared with the alternative at the given willingness-to-pay threshold

Abbreviations: QALYs, Quality-adjusted life years; ICER, incremental-cost effectiveness ratio

Summary of company and ERG base case assumptions

Table 7 Assumptions in company and ERG base case

Assumption	Company base case	ERG base case
Time Horizon (Issue 2)	Lifetime horizon of 40 years	10 years
Changes in BCVA resulting from DEX700 treatment in Years 4 and 5 (Issue 3)	Vision improves (last transition probability matrix carried forward)	Vision maintains (3-month probability of gaining or losing at least 10 letters of BCVA of 3.0%, as per stable vision in TA274)
The natural history of vision in eyes with DMO (Issue 6)	TA274 (2.5% improve and 3.5% worsen)	TA613 (0% improve and 3.5% worsen)

All cost effectiveness results presented in the following slides **do not include confidential commercial discounts for comparators**

Abbreviations: DEX700, Dexamethasone 700 µg intravitreal implant in applicator; BCVA, Best-corrected visual acuity; DMO, diabetic macular oedema

Company base case results*

Similar deterministic and probabilistic results

Table 8 Deterministic incremental revised base case results

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NMB (£30k /QALY)
Anti-VEGFs	41,799	7.942	-	-	-	-
DEX700	34,830	8.056	-6,969	0.114	Dominant	10,386

Table 9 Probabilistic incremental base case results (generated by the ERG)

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NMB (£30k /QALY)
Anti-VEGFs	42,001	7.811	-	-	-	-
DEX700	34,977	7.934	-7,024	0.123	Dominant	10,722

*Revised base case after technical engagement

Abbreviations: QALY, quality-adjusted life year; ICER, incremental-cost effectiveness ratio

Company base case results* (2)

Table 10 Scenario analysis (100% aflibercept comparator)

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NMB (£30k /QALY)
Aflibercept	44,379	7.942	-	-	-	-
DEX700	34,830	8.056	-9,549	0.114	Dominant	12,966

Table 11 Scenario analysis (100% ranibizumab comparator)

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NMB (£30k /QALY)
Ranibizumab	37,411	7.942	-	-	-	-
DEX700	34,830	8.056	-2,581	0.114	Dominant	5,998

Adapted from ERG critique and company model. For completeness company provided these in scenario analyses post technical engagement

Abbreviations: QALYs, Quality-adjusted life years; ICER, incremental-cost effectiveness ratio

Company deterministic scenario analysis

Table 12 Company scenario analyses (deterministic)

No.	Scenario (applied to revised company base case)	Incremental costs (£) versus Anti-VEGFs	Incremental QALYs versus Anti-VEGFs	ICER (£) versus Anti-VEGFs	Incr. NMB (WTP threshold of £30,000 per QALY)
1	Company revised base case	-6,969	0.114	Dominant	10,386
2	Time horizon 10 years (Issue 2)	-6,574	0.062	Dominant	8,418
3	DEX700 net-zero impact on vision in years 4 and 5, and 3-month probability of gaining or losing at least 10 letters of BCVA of 3.5% (Issue 3)	-6,635	0.022	Dominant	7,285
4	DMO natural history as per original base case (3.5% improve and 4.5% worsen per cycle) (Issue 6)	-7,055	0.105	Dominant	10,213

Abbreviations: QALY, quality-adjusted life year; ICER, incremental-cost effectiveness ratio; DEX700, Dexamethasone 700 µg intravitreal implant in applicator; anti-VEGF, anti-vascular endothelial growth factor; BCVA, Best-corrected visual acuity

ERG base case results* (1)

Table 13 Deterministic incremental base case results

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NMB (£30k /QALY)
Anti-VEGFs	31,526	4.850	-	-	-	-
DEX700	25,193	4.844	-6,333	-0.006	1,040,800 (SW)	6,150

Table 14 Probabilistic incremental base case results

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NMB (£30k /QALY)
Anti-VEGFs	31,522	4.824	-	-	-	-
DEX700	25,200	4.821	-6,322	-0.003	2,267,457 (SW)	6,238

*Revised base case after technical engagement

Abbreviations: QALYs, Quality-adjusted life years; ICER, incremental-cost effectiveness ratio

ERG base case results* (2)

Table 15 ERG's preferred base case (100% aflibercept comparator)

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NMB (£30k /QALY)
Aflibercept	34,106	4.850	-	-	-	-
DEX700	25,139	4.844	-8,913	-0.006	1,464,837 (SW)	8,730

Table 16 ERG's preferred base case (100% ranibizumab comparator)

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NMB (£30k /QALY)
Ranibizumab	27,138	4.850	-	-	-	-
DEX700	25,193	4.844	-1,945	-0.006	319,691 (SW)	1,763

*Revised base case after technical engagement

Abbreviations: QALYs, Quality-adjusted life years; ICER, incremental-cost effectiveness ratio

ERG base case results* (3)

Table 17 fully incremental base case results

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
DEX700	25,193	4.844	-	-	-
Ranibizumab	27,138	4.850	1,945	0.006	319,691
Aflibercept	34,106	4.850	6,968	0.000	Dominated by ranibizumab

*Revised base case after technical engagement

Abbreviations: QALYs, Quality-adjusted life years; ICER, incremental-cost effectiveness ratio

ERG deterministic scenario analysis

Table 18 ERG scenario analyses (deterministic)

No.	Scenario (applied to company base case)	Incremental costs (£) versus Anti-VEGFs	Incremental QALYs versus Anti-VEGFs	ICER (£) versus Anti-VEGFs	Incr. NMB (WTP threshold of £30,000 per QALY)
1	Company revised base case	-6,969	0.11	Dominant	10,386
2	Distribution of vision in the DEX700 arm is equal to the anti-VEFGF arm from Year 10 (Issue 2)	-6,669	0.06	Dominant	8,539
3	DEX700 transition probabilities in Years 4 are equal to the last transition probability matrix estimated from MEAD and DEX700 transition probabilities in Year 5 maintain vision (Issue 3)	-6,669	0.06	Dominant	8,581
4	Natural history of vision based on TA613[3] (0% improvement, 3.5% worsening) (Issue 6)	-6,440	0.08	Dominant	8,876

Abbreviations: QALY, quality-adjusted life year; ICER, incremental-cost effectiveness ratio; DEX700, Dexamethasone 700 µg intravitreal implant in applicator; anti-VEGF, anti-vascular endothelial growth factor; BCVA, Best-corrected visual acuity; CQ, clarification questions

Key issues

Generalisability, time horizon, BCVA, natural history of vision

Table 19 Key issues

Issue	Resolved?	ICER/ NMB impact
1. Uncertainty around the generalisability of the results from the MEAD trials	No	Unknown
2. Time horizon considered for the economic analysis	No	Small
3. Changes in BCVA resulting from DEX700 treatment in Years 4 and 5 (sham arm as proxy for anti-VEGF)	No	Moderate
4. Changes in BCVA resulting from anti-VEGF treatment in Years 1 to 5	Yes	Uncertain
5. Subsequent treatment following discontinuation of DEX700	Yes	Small
6. The natural history of vision in eyes with DMO	No	Small

Abbreviations: BCVA, Best-corrected visual acuity; anti-VEGF, vascular endothelial growth factor; DMO, diabetic macular oedema; DEX700, Dexamethasone 700 µg intravitreal implant in applicator; ICER, incremental-cost effectiveness ratio

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Thank you.

Back-up slides

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Decision problem

Table 20 Intervention and outcomes from the scope

	Final scope	Company	ERG comments
Intervention	Dexamethasone intravitreal implant	As per final scope	ITC comparing DEX700 in the MEAD trials with DEX700 in the real-world of little relevance to the decision problem
Outcomes	• Best corrected visual acuity • Central foveal subfield thickness • Central retinal thickness • Contrast sensitivity • Mortality • Need for cataract surgery • Adverse effects of treatment • Health-related QoL, including effects of changes in visual acuity		Not all outcomes reported in the clinical effectiveness sections of the company submission, however outcomes covered represent the key clinical outcomes of relevance to clinical practice

Abbreviations: DEX700, Dexamethasone 700 µg intravitreal implant in applicator; ITC, indirect treatment comparison; qoL, quality of life

Pooled MEAD trial baseline characteristics

Table 21 Baseline characteristics for intervention and comparator

Characteristic	Intervention (n=[redacted])	Comparator (n=[redacted])
Mean age, years (SD)	[redacted]	[redacted]
Male, n (%)	[redacted]	[redacted]
Prior laser, n (%)	Yes: [redacted] No: [redacted]	Yes: [redacted] No: [redacted]
Prior anti-VEGF, n (%)	Yes: [redacted] No: [redacted]	Yes: [redacted] No: [redacted]
BCVA < 50 letters, n (%)	Yes: [redacted] No: [redacted]	Yes: [redacted] No: [redacted]
Cataract, n (%)	Yes: [redacted] No: [redacted]	Yes: [redacted] No: [redacted]

Are these baseline characteristics generalisable to NHS clinical practice?

ERG Comments

- Clinical experts reported that prior use of laser was [redacted] in current UK clinical practice
- Total proportion of patients with prior anti-VEGF therapy is [redacted] (Clinical experts estimate 20 to 40%)
- [redacted] compared to a UK RWE audit and than what would be expected in UK clinical practice according to clinical experts

Abbreviations: anti-VEGF, anti-vascular endothelial growth factor; BCVA, Best-corrected visual acuity; RWE, real world evidence

Results from MEAD trials (2)
Best corrected visual acuity (ETDRS method)

Table 22 Proportion of patients with BCVA improvement of ≥ 15 letters from baseline to 39 months

	DEX700 (n=[redacted])	SHAM (n=[redacted])	p-value
Proportion of patients with BCVA improvement of ≥ 15 letters, n (%)	[redacted]	[redacted]	[redacted]

Figure 6 Proportion of patients with BCVA improvement of ≥ 15 letters from baseline to 39 months

Abbreviations: BCVA, Best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study

Results from MEAD trials (3)

Table 23 ≥ 10 letter improvement/worsening in BCVA from baseline (LOCF analysis)

		DEX700 (n=[redacted])	SHAM (n=[redacted])	p-value	Difference, %	95% CI
a)	≥ 10 letter improvement in BCVA from baseline, n (%)					
	Month 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Month 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Month 36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Month 39	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
b)	≥ 10 letter worsening in BCVA from baseline, n (%)					
	Month 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Month 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Month 36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Month 39	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Results for ≥ 10 letter improvement in BCVA from baseline were used in the economic model

Abbreviations: BCVA, best-corrected visual acuity; LOCF, Last observation carried forward; CI, confidence interval

Indirect and mixed treatment comparisons

Company conducted ITCs to explore:

1. How the efficacy of DEX700 investigated in the MEAD trials compares with continued anti-VEGF treatment in the real-world (UK RWE audit)
2. How the efficacy of sham investigated in the MEAD trials compares with continued anti-VEGF treatment in the real-world (UK RWE audit)
3. How the efficacy of DEX700 investigated in the phakic subgroup of the MEAD trials compares with DEX700 in the real-world data from Pareja-Ríos et al. 2018

Approach

- Unanchored MAIC methods and unanchored STC methods used as comparator evidence sources (Pareja-Ríos et al. 2018 and the UK RWE audit) were non-comparative real-world retrospective studies

ERG comments

- ITC comparing DEX700 in the MEAD trials with DEX700 in the real-world to be of little relevance to the decision problem, and results are subject to high levels of uncertainty
- Concerned that data from a UK RWE audit investigating suboptimal anti-VEGF treatment used to provide evidence for the insufficiently responsive to non-corticosteroid population are non-comparative and unsuitable for use in an ITC with evidence from the MEAD trials due to baseline differences between the studies resulting in low ESSs in MAICs

Abbreviations: MAIC, matching-adjusted indirect comparison; STC, simulated treatment comparison; ESS, Effective sample size

Key issue 2: Time horizon (2)

Time horizon considered for the economic analysis

ERG comments

- Company's long term modelling assumptions too simplistic to accurately capture all relevant downstream benefits and costs following discontinuation from treatment
- No treatment waning assumptions modelled, meaning DEX700 maintains a benefit in visual acuity above anti-VEGFs beyond the 5-year treatment period and throughout the remaining time horizon
- Clinical experts would expect visual acuity across all treatments to converge during the off-treatment period

Table 24 Comparison with previous appraisals

Appraisal	Time Horizon
Ranibizumab (TA274)	10 years
DEX700 (TA349)	15 years
Fluocinolone acetonide (TA271/301)	15 years
Fluocinolone acetonide (TA613)	Lifetime (30 years)
Aflibercept (TA346)	Lifetime (35 years)
Age-related macular degeneration guideline (NG82)	Lifetime

Abbreviations: anti-VEGF, anti-vascular endothelial growth factor; DEX700, Dexamethasone 700 µg intravitreal implant in applicator; TA, Technology appraisal; NG, NICE guidance

Key issue 2: Time horizon (3)

Time horizon considered for the economic analysis

Figure 7 Mean BCVA in treated eye(s) over the modelled time horizon (produced by the ERG using the economic model) (original base case)

Company response

- Company asserts it could be argued that treatment effect waning is applied from 5 years, as although the absolute change in BCVA outcomes does not become equalised at this point in time, the rates of improvement and worsening vision are set to be equal
- Outcomes do converge over time in original base case analysis (Figure 7). Although the mean change in BCVA is never equal between treatment arms, the absolute difference between treatment arms declines over time

Abbreviations: DEX700, Dexamethasone 700 µg intravitreal implant in applicator; BCVA, Best-corrected visual acuity; BSE, best-seeing eye; WSE, worst-seeing eye

Key issue 4: Changes in BCVA resulting from anti-VEGF

Changes in BCVA resulting from anti-VEGF treatment in Years 1 to 5

Background

- Company used the sham arm of the MEAD trials as a proxy for continued anti-VEGF use
- ERG does not agree with the company's argument that the sham arm of the MEAD trials likely overestimates the efficacy of continued anti-VEGF

Company

- The sham arm of MEAD is a more appropriate yet conservative proxy for the efficacy of continued anti-VEGFs in insufficient responders as this allows us to model the individual variations in vision losses and gains, while on average resulting in a small gain in vision

ERG comments

- Accepts the company's base case assumption. However, given the large assumptions needed to model continued anti-VEGF treatment, the ERG considers that committee may want to account for this uncertainty by using the lower threshold for cost-effectiveness (that is, an ICER below £20,000 per QALY gained)
- Considers the MEAD sham arm is potentially a reasonable proxy for continued anti-VEGF use and that it is not possible to predict the likely direction of any potential bias in the comparison of DEX700 versus sham (largely due to the use of LOCF in the company analyses of MEAD)

Abbreviations: anti-VEGF, vascular endothelial growth factor; DEX700, Dexamethasone 700 µg intravitreal implant in applicator; ICER, incremental-cost effectiveness ratio

Key issue 5: Treatment following discontinuation

Subsequent treatment following discontinuation of DEX700

Company

- Clinical experts confirmed that some patients would likely receive anti-VEGF again following discontinuation from DEX700 in the absence of other options (approximately 80%)
- Company's revised base case assumes 80% of patients who discontinue treatment with DEX700 will receive subsequent anti-VEGFs for 1 year (an additional one-off cost of £4,009.85 for people in DEX700 arm)

ERG comments

- ERG accepts the company's revised assumption and notes that patients do not discontinue DEX700 in the model when they become pseudophakic

Abbreviations: anti-VEGF, vascular endothelial growth factor; DEX700, Dexamethasone 700 µg intravitreal implant in applicator

ERG's preferred base case, cumulative results (composite comparator)

Table 25 Cumulative results

No.	Results per person	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NMB (£30k /QALY)
0	Company base case						
	Anti-VEGFs	41,799	7.94	-	-	-	-
	DEX700	34,830	8.06	-6,969	0.11	Dominant	10,386
1	DEX700 maintains vision in Years 4 and 5						
	Anti-VEGFs	41,799	7.94	-	-	-	-
	DEX700	35,153	7.96	-6,646	0.02	Dominant	7,311
2	Natural history of vision as per TA613						
	Anti-VEGFs	48,485	7.61	-	-	-	-
	DEX700	42,868	7.59	-5,617	-0.02	272,481 (SW)	4,999
3	10-year time horizon						
	Anti-VEGFs	31,526	4.85	-	-	-	-
	DEX700	25,193	4.84	-6,333	-0.01	1,040,800 (SW)	6,150

Results do not include confidential commercial discounts for comparators

Abbreviations: QALY, quality-adjusted life year; ICER, incremental-cost effectiveness ratio; DEX700, Dexamethasone 700 µg intravitreal implant in applicator; anti-VEGF, anti-vascular endothelial growth factor

Additional cost effectiveness issues

Minimal impact on the cost effectiveness result

Table 26 Additional cost effectiveness issues

Issue	Resolved?	ICER/NMB impact
Cataract extraction rates applied to patients on and off anti-VEGF treatment	Yes	Small
Additional mortality due to DM and severe vision loss	Yes	Small
Disutilities due to AEs • Company included utility decrements due to AEs to align with the ERG's base case in response to TE • ERG noted concern that the raised IOP rate was [redacted] for anti-VEGF treatment than DEX700 treatment • ERG report showed that using a lower a rate of raised IOP in the anti-VEGF arm had a minimal impact on the results, therefore the ERG does not consider it likely to make a substantial difference to the ICER	Unknown	Small
The number of DEX700 injections assumed in Years 4 and 5	Yes	Small

Abbreviations: anti-VEGF, vascular endothelial growth factor; DM, diabetes mellitus; DEX700, Dexamethasone 700 µg intravitreal implant in applicator; ICER, incremental-cost effectiveness ratio;AEs, adverse events; Intraocular pressure, IOP