External Assessment Group Report

Title: Fluocinolone acetonide intravitreal implant for treating chronic diabetic macular oedema in phakic eyes after an inadequate response to previous treatment (Review of TA613) [ID6307]

Produced by	*Warwick Evidence*
Authors	*Mr Mubarak Patel, Research Fellow, Warwick Medical School* *Dr Ewen Cummins, Health Economist, McMDC* *Professor Norman Waugh, Professor of Public Health Medicine, Warwick Medical School* *Anna Brown, Information Specialist, Warwick Medical School* *Dr Jill Colquitt, Clinical Effectiveness Reviewer, Effective Evidence* *Dr Emma Loveman, Clinical Effectiveness Reviewer, Effective Evidence* *Professor Amy Grove, Professor of HTA and Implementation Science, Warwick Medical School*
Correspondence to	*Amy Grove* *Warwick Evidence* *Division of Health Sciences* *Warwick Medical School* *University of Warwick* *Coventry, CV4 7AL* *A.L.Grove@warwickac.uk*
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Dr Dan Todkill, Associate Clinical Professor in Public Health, University of Warwick.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Dr Colquitt, Dr Loveman and Professor Waugh led the critique of the clinical effectiveness evidence. Mr Patel critiqued the company ITC. Dr Cummins critiqued the cost-effectiveness evidence. Anna Brown critiqued and updated the company SLR searches. Professor Amy Grove led the project.

Please note that: Sections highlighted in [redacted] are "[redacted]. Sections highlighted in [redacted].

Acronyms and Glossary

AE	Adverse Effects
AIC	Academic in Confidence
AMD	Age-related Macular Degeneration
AREDS	Age-Related Eye Disease Study Research
AUC	area-under-the-curve
BCVA	Best-corrected visual acuity
BP	Blood Pressure
CIC	Commercial in Confidence
CRT	Central retinal Thickness
CS	Company Submission
DEX	Dexamethasone
DIAMONDS	Diabetic macular oedema and diode subthreshold micropulse laser (DIAMONDS): a pragmatic multicentre allocation concealed double masked randomised trial
DME	diabetic macular edema
DMO	Diabetic Macular Oedema
DR	Diabetic Retinopathy
EAG	External Assessment Group
ESS	Effective Sample Size
ETDRS	Early Treatment Diabetic Retinopathy Study
FAc	fluocinolone acetonide
FAME	Fluocinolone Acetonide for Diabetic Macular Edema
ICE-UK	Iluvien Clinical Evidence UK
ILUVIEN	fluocinolone intravitreal implant
IOP	Intra-ocular pressure
ITC	Indirect Treatment Comparisons
logMAR	Logarithm of the Minimum Angle of Resolution
LOCF	Last Observation Carried Forward
MAIC	Matching-Adjusted Indirect Comparisons
MEAD	Macular Edema: Assessment of Implantable Dexamethasone in Diabetes
META-EYE	Meta-analysis for Eye disease
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
NMA	Network Meta-analysis
NPDR	Non-proliferative diabetic retinopathy
OCT	Optical Coherence Tomography
OZDRY	Ozurdex in refractory diabetic macular oedema
PDR	Proliferative diabetic retinopathy

PIGF	Placental growth factor
QALY	Quality-Adjusted Life Year
QoL	Quality of Life
RESTORE	REcovery and survival of STem cell Originated REd cells
RIDE	A study of ranibizumab in subjects with clinically significant macular edema with centre involvement secondary to diabetes mellitus
RISE	A study of ranibizumab in subjects with clinically significant macular edema with centre involvement secondary to diabetes mellitus
RWE	Real world evidence
SD-OCT	Spectral-domain optical coherence tomography
SLR	Systematic Literature Review
VA	Visual Acuity
VEGF	Anti-vascular Endothelial Growth Factor

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Executive summary

Fluocinolone acetonide intravitreal implant 0.19 mg (fluocinolone) is indicated for:

- the treatment of vision impairment associated with chronic diabetic macular oedema (DMO) considered insufficiently responsive to available therapies; and
- prevention of relapse in recurrent non-infectious uveitis affecting the posterior segment of the eye.

This submission focuses on part of the marketing authorisation: for the treatment of vision impairment associated with chronic DMO considered insufficiently responsive to available therapies.

The EAG consider that the topic meets the criteria for a cost-comparison approach.

- Dexamethasone (TA824) and fluocinolone (ID6307) come from the same class of drugs and are positioned at the same place in the treatment pathway, i.e., after insufficient response to anti-VEGF drugs or macular laser.

Critical issues for consideration

Clinical effectiveness evidence

1. There is no trial directly comparing dexamethasone and fluocinolone. There have been no new trials since the previously assessed FAME (fluocinolone ID6307) and MEAD trials were reviewed (dexamethasone TA824).
    a. However, there are now studies from routine care (i.e., real world evidence [RWE] studies) which provide observational evidence of effectiveness and adverse effects.
    b. The EAG consider that the RWE provides convincing evidence that in eyes with DMO that have not responded sufficiently to previous

treatment, (usually anti-VEGF drugs), fluocinolone improves outcomes for patients. Many patients have improvements (e.g., over 10 or 15 letter gains in BCVA), others have stable VA, but some do lose vision.

2. The FAME trial of fluocinolone in DMO was carried out in eyes that had not failed to respond to anti-VEGF drugs. The MEAD trial recruited a similar population. In both cases, this was because the trials started before anti-VEGF drugs became routinely available.
    a. Therefore, the population in the scope does not match the populations in the trials, which are eyes that that have not responded sufficiently to anti-VEGF drugs.
    b. The definition of *insufficient response* needs consideration. Clinical advisors suggest that insufficient response may mean insufficient treatment due to pressures on the NHS capacity to deliver services to patients.

3. The indirect treatment comparison (ITC) analysis which focused on the FAME cohort and phakic-only subgroup, indicates a reduction in ESS of ~15% after adjustments for imbalanced effect modifiers.
    a. Despite concerns about potential bias compared to MEAD, the ITC reveals no statistically significant differences between fluocinolone and dexamethasone across six outcomes, supporting their equivalence in economic assessments for DMO patients.

4. Reduction in ESS in the FAME cohort's phakic-only subgroup, raises concerns about potential bias compared to MEAD-treatment experienced (TE) subgroup. Therefore, the loss of sample size when considering only the phakic-only subgroup of FAME, should be considered when making comparisons with the MEAD-TE subgroup.
    a. Differences in baseline characteristic highlight the need for exploratory analyses to assess the impact of these variables on treatment effects.

b. Heterogeneity in retreatment rules poses another challenge and the analysis sets focuses on phakic lenses available in FAME, but not in MEAD, necessitating careful consideration of available subgroup data in both studies.

Cost-effectiveness evidence

5. It is not clear from the submission whether the MEAD and FAME completion rates are sufficiently similar so that their dosing frequencies are comparable.
    a. There is little data about the number of fluocinolone and dexamethasone doses beyond 3 years.
    b. Is it best to limit the time horizon to 3 years? If not, what principle should be applied when estimating dosing for years 4, 5 and 6?

6. The RWE studies suggest large proportions of patients revert to anti-VEGF during the first 3-years of treatment.
    a. Clarity is needed as to whether these proportions are the same, and at the same time, for fluocinolone and dexamethasone, and if so what proportions switch to anti-VEGF each year.
    b. If these proportions, or their timings, are different between fluocinolone and dexamethasone, it is not clear to the EAG whether this issue can still be handled within a cost comparison analysis.

7. The EAG suggest that is it likely that sequencing and use of dexamethasone first to assess the likelihood of response, with fluocinolone only being used among dexamethasone responders, result in lower total costs.
    a. This was not modelled or included in the company submission.

8. The company do not provide evidence to determine what proportion of monitoring visits also double as administration visits when an administration is indicated.

9. It is not clear which estimates of monitoring frequencies for OP visits, OCT examinations and fluorescein angiograms are more reasonable. The EAG present an alternative estimate to the one contained in the company submission.

Summary

- The EAG consider a cost-comparison approach is appropriate. The CS provides an adequate description of the condition and treatment pathway.
- The EAG conclude that the CS decision problem adheres to the NICE final scope.
- The company conducted a satisfactory systematic literature review. The two key trials included in the CS as evidence of clinical effectiveness were low risk of bias. RWE provides convincing evidence fluocinolone improves outcomes for patients with DMO that have not responded sufficiently to previous treatment.
- The company MAIC demonstrates the equivalence of fluocinolone and dexamethasone. Despite concerns about potential bias compared to MEAD, the ITC reveals no statistically significant differences between fluocinolone and dexamethasone across six outcomes, supporting their equivalence in economic assessments for DMO patients.
- The company presents a simple cost minimisation model of fluocinolone compared to dexamethasone.
- The company model has the option of probabilistic modelling. This estimates a net cost saving of [redacted], which is little different from the [redacted] deterministic estimate.
- The company presents a range of sensitivity and scenario analyses. The main sensitivities explored are the proportion of dexamethasone administrations as outpatient, this changing the estimated cost saving to between [redacted] and [redacted], and the number of dexamethasone

administrations, this changing the estimated cost saving to between [redacted] and [redacted].

- The EAG makes the four key changes to the company base case, reporting results per eye due to the uncertainty around concurrent bilateral treatment. Changes include introduction of a three-year time horizon; 49% of patients move to anti-VEGF in both arms, (with a third occurring at 6 months, 18 months, and 30 months), adverse event costs (however, these net out to zero) and finally, adding monitoring frequencies and assuming administrations can occur during monitoring visits where indicated. Cumulative EAG costs from these changes are [redacted] for fluocinolone and £4,142 for dexamethasone ([redacted] Net).

1 Background

Fluocinolone acetonide intravitreal implant 0.19 mg (from now on referred to as fluocinolone) is indicated for:

- the treatment of vision impairment associated with chronic diabetic macular oedema (DMO) considered insufficiently responsive to available therapies; and
- prevention of relapse in recurrent non-infectious uveitis affecting the posterior segment of the eye.[1]

This submission focuses on part of the marketing authorisation (MA): *for the treatment of vision impairment associated with chronic DMO considered insufficiently responsive to available therapies.* The MA was granted 4th May 2012.

1.1 *Description of cost-comparison approach*

The rationale for this review is set out in the NICE proposal document for review of TA613 dated 2023. The main reason given for reviewing the TA613 guidance using a cost-comparison approach is the emergence of new evidence.[2]

1.1.1 Related Technology Appraisals

The mainstays of treatment have been laser photocoagulation and anti-vascular endothelial growth factor (VEGF) drugs. NICE guidance has recommended ranibizumab (TA274), aflibercept (TA346), faricimab (TA799) and brolucizumab (TA820) for use in patients with DMO and a central retinal thickness (CRT) of 400 microns or more. Laser remains the first-line treatment in eyes with thinner retinas.[3-6]

In 2015, TA349 recommended the corticosteroid dexamethasone (the implant OZURDEX® Allergan) for treatment of DMO only in pseudophakic patients who had had no response to non-steroid treatments, or in whom such treatments were unsuitable. In 2022, this guidance was replaced by TA824 which recommended dexamethasone for treating DMO only if it has not

responded well to other treatments "*irrespective of whether they have a phakic or pseudophakic lens*".[7]

The company submission (CS) for the review of TA824 argued that the key changes since the publication of TA349 were;

1. The comparator had changed from watch and wait, to continuing anti-VEFG therapy. This was because ophthalmologists would continue those drugs even if ineffective.
2. The emergence of real-world evidence (RWE).

The EAG note that the CS for the current appraisal (ID6307) also includes RWE (see Section 3.1 for EAG critique).

The company reasonably point out that there is now an inequity in the guidance; dexamethasone is approved for phakic eyes but fluocinolone is currently not. Dexamethasone and fluocinolone come from the same class of drugs and are positioned at the same place in the treatment pathway, i.e., after insufficient response to anti-VEGF drugs or macular laser. Intravitreal corticosteroids have an anti-inflammatory effect and so are also used in conditions such as non-infectious uveitis. **Overall, the EAG consider a cost-comparison approach is appropriate.**

1.2 *EAG description of the condition and treatment options*

The CS provides an adequate description of the condition, treatment pathway and position of fluocinolone in CS Document B pages 16-21.

Briefly, people with diabetes are at risk of visual loss from several conditions; including proliferative retinopathy and DMO. Other conditions, like cataracts, show increased frequency in people with diabetes. The risks of cataract increased intra-ocular pressure (IOP) and glaucoma are important in this appraisal because they can be adverse effects (AE) of intravitreal steroids. However, cataract is easily treated by removal of the natural lens and replacement with an artificial lens. Most patients with raised IOP can be

successfully treated with topical medications (eye drops) – only some will develop glaucoma, and few will require surgery for glaucoma.

DMO is the most common cause of sight loss due to diabetes.[8] Minassian et al reported that 7% of people with diabetes had DMO, of whom 2.8% had slight visual impairment and 2.6% had significant visual impairment. So, in England there may be almost 90,000 people with DMO with significant visual impairment. If about 40% do not respond sufficiently to anti-VEGFs or laser treatment, about 36,000 will require other treatments.[9] In people with diabetes, the causes of visual loss vary with age, with DMO accounting for 28% of visual impairment in the 5th and 6th decades.

DMO is due to accumulation of fluid in the retina caused by increased fluid leakage from blood vessels.[10] The prevalence of DMO increases with increasing duration of diabetes. A global meta-analysis by the Meta-analysis for Eye disease (META-EYE) study group concluded that prevalence of DMO under 10 years duration of diabetes was 3%; at 10-19 years, 13%; and after 20 years, 20%.[11] The risk of DMO is increased by smoking, poor glycaemic control and hypertension. It may be precipitated by pioglitazone which can cause oedema.[12]

There is a strong link between poor glycaemic control and prevalence of DMO (see Table 1). In the META-EYE study, prevalence amongst people with normal blood pressure was 5.5% compared to 10.6% in those with hypertension (BP >140/90 or already on anti-hypertensive medications). Hence good control of blood glucose and blood pressure should reduce the number of people developing DMO, and improving control may lead to regression of DMO. (Rapid improvements in control of blood glucose may make DMO worse and gradual improvement is better).[13]

Table 1. Diabetic control and DMO

HbA1c	Prevalence of DMO
7.0% or less	3.6%
7.1 to.0%	6.3%
8.1 to 9.0%	7.7%
Over 9.0%	12.5%

1.2.1 Defining a response and insufficient response

A treatment response can be functional (vision) or anatomic (reduction in retinal thickness on Optical Coherence Tomography [OCT]). However, changes in OCT thickness may not be accompanied by change in vision.

The anti-VEGF drugs have been a major advance in DMO. They act by removing fluid from the retina, but vision may or may not improve. (only about half of the patients get a gain of 10 or more letters, as shown in the RESTORE trial[14] and a small proportion lose more than 10 letters.) Some patients respond very well, some show little response, and some respond partially.

Vision may take time to deteriorate even if oedema is present, so a lack of deterioration may not necessarily indicate a good response if the fluid has not cleared. Absence of DMO can be defined as the lack of intraretinal/subretinal fluid at the macula on Spectral-domain optical coherence tomography (SD-OCT). If there is still fluid in the retina, it will depend on whether there is considerable fluid (e.g. >/=400 microns in central retinal thickness) or mild fluid (< 400 microns). In the former scenario, if anti-VEGF treatment has been optimal and there is an insufficient response then steroids would be considered. If oedema is mild, macular laser would be an option.

It is not known if leaving a little fluid in the macula after a person has been treated extensively will lead to sight loss long term. So, in some patients,

observation without immediate treatment may be an acceptable comparator. The CS notes that a sizeable minority of eyes do not respond to anti-VEGF treatment, citing the EARLY study which found that up to 40% of patients had a <5 letter-change at 3-months following anti-VEGF treatment.[15]

The EAG note that a definition of "insufficiently responsive" is not provided in the NICE scope for this appraisal. (EAG definitions for this appraisal are outlined in Section 3: Critique of the decision problem in the company's submission). We have identified variations in the criteria included in literature and CS.

- The CS uses a 15-letter gain as the primary outcome in their comparison of dexamethasone and fluocinolone. This was the primary outcome in the MEAD[16] and FAME[17] trials.
- Text in TA349 suggests that it would be inappropriate to define response as a gain of five or more letters. This is because DMO is a progressive condition and therefore preservation of vision without improvement may be a valuable outcome.
- Kern et al from Moorfields reported 4-year outcomes in a cohort of 2614 eyes with DMO treated with anti-VEGF drugs. Half achieved BCVA of > 70 letters after starting treatment, but half of those had fallen below 70 letters by about 15 months.[18] People with good vision at start of treatment may gain fewer letters.
- A Cochrane review regards a gain of fewer than five letters or less than 0.1 logMAR units as lack of response.
    - Most trials have used the proportion of patients gaining 10 or more, or 15 or more letters as the primary outcome, including trials of anti-VEGF drugs such as RISE and RIDE and the FAME[17] trial.[19, 20] However gains of this magnitude will not be seen in eyes with good vision to start with so results will depend on case mix.
- The UK audit report by Egan and colleagues on results with ranibizumab for DMO reported that 17% of eyes gained 15 or more letters, 60% were

"*stable*", meaning 0-15 letters gained, but 23% lost letters. The mean letter gain was only 5 letters.[21]

- The EAG suggest that the reduced effectiveness in routine care may simply reflect that the resources available in the NHS may not match those in the trials, for example for monthly injections/reviews. Clinical advisors suggest that patients may be seen only every 6-8 weeks because of pressure in the NHS.

A clear definition of treatment failure is also lacking. The EAG note that if treatment is performed appropriately with anti-VEGF drugs, few people will have no response at all. For example, Vila Gonzale et al (2020) found that only 6% of participants had no reduction in oedema, 22% had full clearance, and 66.5% has partial clearance.[22]

1.2.2 Timing of assessment of response

The EAG note similar inconsistencies in the timing of assessment of response.

- The draft NICE diabetic retinopathy guideline Para 1.5.10[23] recommends assessing response at 12-months. The EAG note that in previous STA of ranibizumab in DMO (TA274),[3] most responders did so within 3-months. Some slower responders achieved useful benefit by 6-months.
- In a study by Vilà González et al,[22] the average time to complete drying of the retina in full responders was 7- months.
- There is strong evidence from trials that most eyes that have not responded well after 3-months of optimum therapy are unlikely to ever do so.[15, 24]
    - However, evidence favours review at 6-months.[25, 26] The NHS England Commissioning advice on anti-VEGFs in DMO suggests review at 6-months with consideration of switching to steroids if response has been insufficient.[27]

In summary, in people with an insufficient response after loading doses of anti-VEGF, improvement is unlikely and an early switch to steroids appears appropriate. In those with some response, it appears that anti-VEGFs could be continued.

1.2.3 Treatment efficacy outcomes

The primary efficacy outcome for assessment in the CS indirect treatment comparison (ITC) (fluocinolone and dexamethasone 0.7mg) was the proportion of subjects considered visual acuity (VA) responders in their study eye. The CS defined VA response as an increase from baseline of 15 or more in BCVA as measured with the ETDRS letters score (CS Document B.3.9.2.1). A ≥15-point increase in BCVA is commonly acknowledged as clinically significant endpoint in ophthalmology trials and thought to reflect a meaningful alteration in VA. **Therefore, the EAG consider the treatment efficacy outcomes presented in the CS to be appropriate.**

1.2.4 Cataract and increased intra-ocular pressure

Cataract means that the lens of the eye becomes opaque, preventing light from reaching the retina. In people with diabetes the risk of cataract is increased. Cataract was the commonest cause (49%) of visual impairment in people with diabetes.[28] The incidence of cataract amongst all people with diabetes was about 50% higher than in the general population (12.4 (95% CI 12-12.7) compared to 7.9 (95% CI 7.6-8.2) per 1000 person years.[29] However, there is an association between DMO and cataract and in people with DMO the incidence of cataract is much higher, about 7.4 times the general population risk.

The EAG note general inconsistencies in the threshold for cataract, some clinicians use 1+ nuclear sclerosis on the AREDS cataract grading system, others may prefer nuclear sclerosis 2+. There are also different types of cataract: nuclear sclerotic, posterior-subcapsular (which has the most effect on visions) and cortical.[30] Nuclear sclerotic is the most common form, strongly

age-related. The form most typically caused by steroids is the posterior-subcapsular, which may develop more quickly than other forms. The nuclear sclerotic form causes myopia which can be helped by spectacles, so may be less likely to require extraction.

In the CS FAME[17] trial, 86% of phakic eyes in the fluocinolone arm developed cataract, compared to 52% in the sham arm (41% in the fellow eyes not in the study). The EAG note that the extra cataracts caused by fluocinolone were seen in 34% of eyes (86 – 52). Those in the fluocinolone arm had cataracts diagnosed and extracted on average 100 days earlier than those in the sham arm, with extraction at a mean of 18 months, and almost all extractions were performed by 24-months.

- Most patients who were phakic at baseline developed cataract, but under half could be attributed to fluocinolone. When considering the use of fluocinolone for chronic DMO in phakic eyes after all other treatments have failed, the following possible outcomes need to be considered;
    - If fluocinolone is not used, there is a high likelihood of central visual loss due to DMO.
    - If fluocinolone is used, an extra 34% will develop cataract and suffer from visual impairment as the cataract develops. But will have it removed, restoring vision.

The EAG recognise that to preserve central vision, many phakic patients will have to have a period of deteriorating vision due to cataract, followed by its extraction. This will be associated with some temporary disutility and the cost of extraction (as described in Section 4.6). It should be noted that some patients with DMO may also have peripheral visual loss due to proliferative retinopathy, but in most patients, this will be treated with pan-retinal laser photocoagulation to preserve vision.

One AE of steroids in the eye is an increase in pressure in the eye (IOP) caused because the normal drainage of aqueous fluid is impaired. Glaucoma

is characterised by increased pressure inside the eye, usually defined as IOP of 21 mm Hg or more with subsequent visual field defects and optic nerve damage. The increased pressure can cause progressive damage to the optic nerve, leading to impaired vision and blindness if not treated. Because of the way in which the nerve fibres are damaged, peripheral vision is lost first, with central vision being affected later. There may be no symptoms in the early stages. NICE Clinical guideline on glaucoma recommends that those at risk of glaucoma due to raised IOP are monitored at 6-monthly intervals, adjusted for their risk of developing glaucoma.[31] However, patients with DMO receiving intravitreal corticosteroid therapy, should be monitored at the frequency stated in the appropriate product SmPC. These patients would therefore be followed up regularly, in accordance with the relevant SmPCs so not all these visits would be additional. Raised IOP post injection of steroids has been found not to be a big concern,[32] but a few patients will require surgery to reduce the pressure.

In summary, the EAG consider that the CS provides an adequate description of the condition, treatment pathway (see CS Figure 1 page 20) and positioning of fluocinolone (CS Document B pages 16-21).

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

The decision problem addressed in this submission is summarised in Table 2.

The EAG make the following assumptions:

- **Chronic** is defined as present for more than 6-months since first detected without clearance during that time. Noting that FAME patients have been treated with anti-VEGFs or laser so all can be regarded as chronic.
- An **inadequate response** means a gain of fewer than 5 letters, or any loss of letters, in people with visual loss at baseline and a <20% reduction in CRT (Downey et al., 2021) In those without visual loss, gains will be smaller, and maintenance will be the outcome."
- **Previous therapy** means laser and anti-VEGF drugs.

The EAG conclude that the CS decision problem adheres to the NICE final scope.

Table 2. The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	*EAG comment*
Population	People with chronic diabetic macular oedema that is insufficiently responsive to available therapies who have phakic lenses.	As per scope		*As per scope*
Intervention	Fluocinolone acetonide intravitreal implant	Fluocinolone acetonide intravitreal implant	Not applicable	*As per scope*
Comparator(s)	Dexamethasone intravitreal implant	Dexamethasone intravitreal implant	Not applicable	*As per scope*
Outcomes	The outcome measures to be considered include: • best corrected visual acuity (the affected eye) • best corrected visual acuity (both eyes) • central foveal subfield thickness • central retinal thickness • contrast sensitivity • mortality • need for cataract surgery. • adverse effects of treatment (including cataract formation and glaucoma) • health-related quality of life, including the effects of changes in visual acuity.	The company will present data relating to all the outcome measures listed that are relevant to the cost-comparison evaluation versus dexamethasone intravitreal implant, with the exception of contrast sensitivity, which is not measured in routine clinical practice in the UK.	Contrast sensitivity is not measured in routine clinical practice in the UK. For the purposes of the cost-comparison versus dexamethasone intravitreal implant, the company will focus primarily on the following outcomes: Efficacy outcomes ▪ Mean BCVA change ▪ ≥ 10/15 letter BCVA improvement ▪ ≥ 10/15 letter BCVA worsening. ▪ Central subfield thickness ▪ Frequency and number of treatment administrations/ implants Safety outcomes: ▪ Ocular events	*As per scope*
Special considerations including issues			As a result of current NICE guidance, an inequality of access persists within the UK DMO patient population.	*The EAG agree that DMO patients with a phakic eye do not have access to fluocinolone.*

related to equity or equality			DMO patients with pseudophakic eyes who are insufficiently responsive to, or are not suitable for, non-corticosteroid treatment currently have access to two NICE-recommended options: dexamethasone intravitreal implant (TA824) and fluocinolone acetonide (FAc) intravitreal implant (TA613). A DMO patient with a phakic eye, however, does not have access to the FAc implant. Consequently, patient access to FAc is presently determined by lens status, whereas patient access to the dexamethasone implant is not. This creates an inequity. There is no evidence to suggest that lens status has any impact on clinical or patient outcomes; FAc implant is equally effective in pseudophakic and phakic eyes. Moreover, this inequity does not align with patient preferences for access to longer-acting treatment options requiring fewer/less frequent injections that can reduce patient stress and treatment burden, nor does it provide value for money to the NHS in the clinical management of DMO.[33]	

3 Summary of the EAG's critique of clinical effectiveness evidence

The CS provides indirect evidence for fluocinolone in comparison to dexamethasone in DMO patients with a phakic lens who have insufficient response to, or who are unsuitable for treatment with, non-corticosteroid treatment. The EAG agree that no direct evidence comparing the efficacy and safety of the technology to the comparator is available. Evidence was identified via a systematic literature review (SLR) which was conducted to a reasonable standard. See CS Document B pages 25-31 for an overview of methods and Appendix D for a full description.

The SLR searches detailed in Appendix D.1.1 used an appropriate selection of databases and trials registries, and extensive reference list checking was also undertaken (Document B.3.1.1, Company response to clarification questions C2. The search strategies included more interventions/comparators than needed for the NICE decision problem. Although a few useful subject headings (such as "intravitreal injections/") and field codes (drug name (.tn) in Embase) were not used. The EAG considers that no relevant trials would have been missed, due to the range of sources searched.

The EAG notes that Table 3 of CS Appendix D provides a list of SLR excluded studies and reasons. However, full citation details (including author details) are not provided. The EAG has checked the list of excluded studies and considers that some may have been useful in the appraisal. A summary is provided in EAG Appendix.

CS Document B Table 4 provides a summary of the 10 trials identified in the company SLR.

- The EAG note four papers in CS Table 4 were on the Retisert™ fluocinolone implant which has a much higher dose of fluocinolone (0.59mg) and is implanted by a surgical procedure not an injection.
    - CS Document B Table 4 states that the follow-up period for the Retisert™ trial was 26 weeks, however it was 3-years. AE such

as cataract and raised IOP were higher with the larger dose, but the benefits did not appear significantly greater.

- The EAG suggest that Pearson 2003 (CS Table 4), may be a dose-ranging pilot for another exclusion, NCT 00502541 (also Pearson et al, includes one full paper and two earlier abstracts).
- No studies of the other fluocinolone implant, (Yutiq,[34]) which has a similar dose to the ILUVIEN® implant were identified by the company for DMO. It is used in uveitis and is also inserted by needle.

Of the 10 trials identified in the company SLR, eight were excluded. The rationale for the exclusion of these studies is presented in CS Appendix D. The EAG agrees with their exclusion.

The remaining two trials (FAME[17] and MEAD[16]) were included in the company ITC (See Section 3.3). The trials are well described in CS Document B pages 31-35 and B.3.3 (B.3.3.1 FAME and B.3.3.5 MEAD).

3.1 *EAG overview of the FAME and MEAD trials*

The evidence for the clinical effectiveness of fluocinolone comes partly from the FAME[17] trial and partly from recent RWE studies.

The FAME[17] trial was reported in detail in the 2019 ERG report, including responses from the company (Alimera) to clarification questions. The trial was accepted as being of good quality but was conducted at a time when anti-VEGF drugs were not routinely used. Hence, FAME did not recruit patients as specified in the NICE scope, i.e., those who had failed on anti-VEGFs treatment. Data on that group, therefore, comes from RWE studies (see Section 3.2).

The FAME[17], and MEAD[16] (dexamethasone evidence) key trials, have been reviewed in previous NICE appraisals TA301/613 and TA824, respectively. To minimise the length of the report for this appraisal, the EAG will focus

primarily on issues identified in previous appraisal and new evidence submitted. The previous EAG report is available should any of the Committee members wish to see greater detail (section B.2.3 of the EAG report of ID1421).

The CS provides a summary of the trials in CS Table 5. CS quality assessment is provided in CS Table 16. The key issues identified by the EAGs in the previous appraisals (TA301/613 and TA824) are presented in Sections 3.1.1 and 3.1.2.

3.1.1 FAME[17]

FAME was conducted as two identical trials across North America, Europe (including 3 UK centres) and India.[17] Both FAME studies used in this submission are three arm studies comparing the safety and efficacy of fluocinolone 0.2 µg/day and fluocinolone 0.5 µg/day implants to a sham intervention in the ratio 2:2:1 in a total of 956 patients with persistent DMO despite having received at least one prior macular laser treatment. Both studies are phase III, randomised, double-masked, sham-controlled RCTs. The CS presents data from the FAME[17] trials in CS sections B.3.3.1 to B.3.3.4. Data were pooled for analysis, although individual results are provided in CS Appendix K. Two doses of fluocinolone were used in FAME[17], 0.2 µg and 0.5µg. The licensed dose is 0.2 µg therefore, the 0.50 µg dose is not discussed further in this report.

3.1.1.1 FAME[17]: Statistical analysis of outcomes

The statistical analysis methods used in the FAME[17] (and MEAD[16]) studies are presented in Table 15 of CS section B.3.4. Sample size calculations were provided and were based on the primary outcome, the proportion of patients who had a ≥15 letter increase in Best-corrected visual acuity (BCVA) at month 24 compared to baseline. The EAG replicated the sample size calculations using the “pwr” package R version 4.1.0 and achieved the same sample size requirements.

The primary efficacy data set was the intention-to-treat set which included all randomised patients who received any study drug. Missing data was imputed using the last observation carried forward (LOCF) method. LOCF is a straightforward method of imputation which assumes data stability over time. This could lead to biased estimates and loss of variability if this assumption of stability does not hold, nor does it address missing data mechanisms, i.e. the reasons for missing data which may be important if certain factors affect missingness. Other methods of imputation may be more appropriate, such as multiple imputation or pattern-mixture models, but LOCF can provide a good basis when the other alternative is to exclude people with missing data, thus reducing the power of the analysis.

Note, the company used the following outcomes results from the clinical effectiveness efficacy results of FAME[17] in the ITC (see Section 3.2);

- Treatment efficacy outcomes; mean change from baseline to EOT in:
    - Proportion of patients achieving ≥15-letter BCVA improvement
    - BCVA letter score
    - CRT
- Safety outcomes; the proportion of patients reporting:
    - Serious ocular AEs
    - IOP-related AEs
    - Cataract-related AEs.

3.1.1.1.1 Key issues relevant to the current appraisal noted in TA613[2]

- **Risk of Bias:** FAME[17] was judged to have a low risk of bias by the EAG for TA613. The control group received a sham procedure so to preserve masking. Two investigators were used. One investigator performed the treatments, and the other masked investigator performed all assessments and determined retreatment eligibility.

- The EAG noted the possibility of the fluocinolone being detected as a floater and unmask patients but thought it unlikely to be a problem because floaters are common in the age group recruited and in those with diabetic retinopathy.

- **Duration of DMO:** TA613 and the current appraisal are concerned with chronic DMO. The results of the FAME[17] trial varied by duration of DMO, with a statistically significant difference only in the chronic group with a longer duration of DMO. The FDA noted that the analysis by duration was not pre-specified in the protocol or the statistical analysis plan. However, the company did inform the FDA that though not mentioned in these documents, the duration of DMO analysis had been pre-planned. The duration was initially described as being at 3-years, but in practice the median durations were 1.7 years for the <3-year group and 5.2 years for the > 3 years group (see pre-planned subgroup using the median duration of diagnosis in Cunha-Vaz et al., 2014).[35]
- **Previous therapy:** the patient population defined in the NICE scope for TA613, and the current appraisal are those who have had an inadequate response to previous therapy (See Table 2). Available therapies approved by NICE include laser photocoagulation for central retinal thickness less than 400 microns, and anti-VEGF drugs. However, the FAME[17] trial was conducted prior to the widespread use of anti-VEGF treatment.
  - Patients in FAME[17] had been treated with laser only, therefore do not match the whole population in the NICE scope and cannot provide evidence on effectiveness in DMO that has not responded to anti-VEGF treatment.
  - In addition, patients may have had only one laser treatment, so it is not fully clear whether patients recruited to FAME[17] were truly unresponsive to laser. However, mean baseline retinal thickness was 461.8 microns, making it less likely for laser to be effective.
- **Lens status:** the NICE scope specifies phakic eyes (See Table 2). Around two-thirds of the patients in FAME[17] had phakic lenses. A post

hoc subgroup analysis was reported in Yang et al 2015[36] to compare outcomes between pseudophakic eyes at baseline and those who had a phakic lens at baseline and were subsequently treated for cataract during the study period.
    - There is no evidence provided for the patients who were phakic at baseline and at follow-up, but this was a very small subgroup in FAME[17] (chronic DMO and phakic-phakic n=17).
- The EAG stated that diagnosis of baseline cataract appeared to have been highly sensitive, based on photographic detection of any degree of opacity. Cataract serious enough to impair visualisation of the retina led to exclusion from the FAME[17] trial.

3.1.2 MEAD[16]

The MEAD[16] studies (MEAD-010 and MEAD-011) were two large, multicentre, sham-controlled, phase 3 RCTs comparing the efficacy and safety of dexamethasone 0.7 mg and 0.35 mg to a sham control in patients with DMO. MEAD-010and MEAD-011 were identical trials and pooled for analysis.[16] Participants were randomised 1:1:1 for a total of 1,048 patients and followed up for 36 or 39 months. The CS presents data from the MEAD[16] trials in CS section B.3.3.5 to B.3.3.8. Whilst two doses of dexamethasone were used in the trial, only the licensed dose of 0.7 mg (DEX700) is discussed in this report.

3.1.2.1 MEAD:[16] Statistical analysis of outcomes

The aim of the MEAD[16] trials was to assess for superiority of the interventions over sham. The planned sample size was 510 patients split equally into three groups which was estimated to provide 80% power to detect a 10% difference between dexamethasone 0.7 mg and the sham group in the outcome of the proportion of patients with a 15-letter improvement in BCVA assume a 5% for sham with a two-sided alpha of 2.5%. The primary efficacy data set was the intention-to-treat population of all randomised patients, and the LOCF method was used to impute missing values (see Table 15 of CS section B.3.4).

3.1.2.1.1 *Key issues relevant to the current appraisal noted in TA824*[7]

- **Risk of bias:** The EAG for TA824 judged the MEAD[16] trials to generally have a low risk of bias based on the full population. The company stated that there was a high risk of informative censoring as participants were lost to follow-up due to reasons related to the study. The ERG noted that the primary reasons for missing data were due to patients discontinuing the study treatment (due to a lack or loss of efficacy or AE) or due to censoring of patients receiving rescue therapy.
- **The natural history of DMO:** The EAG suggest that vision deteriorates over time and therefore, the LOCF approach may be optimistic for both the DEX700 (see TA824 FAD) and sham arms as vision in patients with missing data cannot worsen.
    - Results for both the sham and DEX700 arms were likely to be biased and the EAG considered it difficult to predict the likely direction of the resulting bias.
    - Patients in the DEX700 arm could potentially have a higher BCVA at the point of discontinuation compared with the sham arm, and this benefit would be retained in the LOCF analyses. Additionally, the ERG considered it possible that vision in DEX700 patients could deteriorate more after treatment discontinuation relative to any worsening of vision in sham patients after they discontinued.
- **Statistical power:** The phakic subgroup of the MEAD[16] trials comprised a retrospective post hoc analysis and therefore was not powered to detect a statistically significant difference between treatment groups.
- **Generalisability to UK:** Anti-VEGFs were not widely used at the time the MEAD trials were designed, therefore the generalisability of the results of the MEAD trials to eyes insufficiently responsive to anti-VEGF treatment cannot be assessed.

- The proportion of phakic DMO patients that had pre-existing cataracts at baseline was not aligned with UK clinical practice (proportion redacted), although it was unclear what proportion of cataracts in MEAD were clinically significant.
- The proportion of phakic patients with a baseline BCVA of ≤50 ETDRS letters was also thought to be different from UK clinical practice.
- The company in TA824 considered the baseline characteristics in the MEAD[16] trials to be poorer than those observed in clinical practice and that the outcomes of the MEAD trials could be classified as being conservative.[7] However, the EAG did not consider it possible to predict the direction of any potential resulting bias related to baseline differences in the MEAD trials compared with UK clinical practice.

3.1.3 FAME and MEAD baseline characteristics: phakic eyes subgroup

The CS presents participant characteristics and results from the overall populations of FAME and MEAD in Section B.3.3. From here the EAG does not consider these data in detail. For the present appraisal the phakic subgroups of the trials are only of relevance (See Table 2).

The CS present data from a post-hoc subgroup of participants in FAME with phakic eyes and treated in line with the current marketing authorisation for fluocinolone in document B Section B.3.7.1. However, these results were not used in the ITC of fluocinolone with dexamethasone (see 3.3.1). In MEAD, there are no publicly available data for the phakic subgroup except for those who also had an AE report of cataract. The CS includes data from a subgroup of treatment-experienced (TE) participants from MEAD for the ITC with what the CS names “the ITC cohort” from FAME. This included a subset of participants from FAME who met the more restrictive inclusion criteria of

MEAD (at screening participants had BCVA between ≥ 34 and ≤68 letters at screening; CRT ≥ 300 μm and HbA1c ≤ 10.0%).

The EAG report the participants characteristics and results of the ITC from these populations and those from FAME with phakic eyes provided by the company at clarification stage.

FAME phakic subgroup baseline characteristics were provided in CQ A1 and these are summarised in Table 3 for the 0.19 mg and sham groups. The baseline characteristics appear to be balanced between groups. The baseline BCVA was around 54 letters and CRT was between 441 and 461 μm. The duration of DMO was around 3.5 years and all participants had prior laser therapy. The company clarification response states that participants with phakic lens eyes are younger, more often male, and have a shorter duration of diabetes and DMO than pseudophakic counterparts (not reported here).

The MEAD baseline characteristics in the TE subgroup are reported in Section 3.3.1.

Table 3. Summary table of baseline characteristics in FAME (A+B pooled), phakic subgroup

	FAME (phakic FAS)	
	FAc 0.19 mg	**Sham**
N	235	121
Demographics		
Mean age (SD), yrs	60.2 (9.2)	59.7 (8.9)
Male, n (%)	145 (61.7)	74 (61.2)
Caucasian, n (%)	160 (68.1)	86 (71.1)
Diabetes characteristics		
Diabetes Type, n (%)		
Type 1	17 (7.2)	10 (8.3)
Type 2	214 (91.1)	109 (90.1)
Not recorded	4 (1.7)	2 (1.7)
Mean (SD) duration of diabetes, yrs	16.1 (8.2)	16.0 (7.5)
Mean Hba1c % (SD)	7.9 (1.7)	8.0 (1.9)
DMO characteristics		
Mean (SD) duration of DMO, yrs	3.4 (2.86)	3.6 (2.73)

	FAME (phakic FAS)	
	FAc 0.19 mg	**Sham**
Mean BCVA letter score	53.6 (12.2)	55.4 (11.3)
Mean CRT, µm (SD)	461 (159)	441 (142)
Prior DMO treatment, n (%)		
Laser	235 (100)	121 (100)
Intravitreal corticosteroid	29 (12.3)	14 (11.6)
Intravitreal anti-VEGF	NR	NR

Adapted from clarification response A1

BCVA, best-corrected visual acuity; CRT: Central retinal thickness; DMO, diabetic macular oedema; FAc, Fluocinolone Acetonide; NR, not reported; SD, standard deviation.

3.1.1 Efficacy results of FAME[17] compared to MEAD[16]

The company provided the efficacy endpoints of FAME[17] and MEAD[16] in responses to CQ A8. This included the results for the full analysis set (FAS) and the phakic-eyes subgroup of FAME[17], compared to the FAS and treatment experienced sets of MEAD.[16]

The primary efficacy endpoint presented were the proportion of patients who experiences an increase from baseline of ≥15 letters in BCVA in their study eye. The secondary endpoints were the mean change from baseline in BCVA letter score and the mean change from baseline in foveal thickness as assessed by OCT. Comparing the FAS of both studies, the active treatment was statistically superior to placebo across the three outcomes provided (see Table 4 and Table 5).

- **In the phakic eyes only subgroup of FAME, there were no statistically significant differences between fluocinolone and sham. There was a lack of data concerning the phakic-only subgroup of MEAD. However, there was a statically significant difference between dexamethasone and sham across all the outcomes presented in the treatment-experienced subgroup of MEAD."**

Table 4. Key outcomes in FAME (A+B pooled) phakic subgroup, fluocinolone 0.2 µg versus Sham at 36 months

	FAc 0.19 mg		Sham		
	N	Result	N	Result	P-value
Primary efficacy endpoint					
Proportion with an increase of ≥15 letters in BCVA in their study eye	236	28.4%	121	19.8%	0.114
Secondary efficacy endpoints					
Mean change from baseline in BCVA letter score (SD)	236	+5.0 (18.8)	121	+2.2 (14.4)	0.111
Mean change from baseline in foveal thickness as assessed by OCT µm (SD)	236	-166.8 (203.2)	121	-128.4 (216.8)	0.109

Adapted from clarification response A8

BCVA, best corrected visual acuity; FAc, Fluocinolone Acetonide; OCT, optical coherence tomography, SD, standard deviation.

Table 5. Table of key outcomes in MEAD (pooled) TE subgroup, dexamethasone 0.7 mg versus Sham at 36 months

	DEX 0.7mg		Sham		
	N	Result	N	Result	P-value
Primary efficacy endpoint					
Proportion with an increase of ≥15 letters in BCVA in their study eye	247	21.5%	261	11.1%	0.002
Secondary efficacy endpoints					
Mean change from baseline in BCVA letter score (SD)	247	+3.2 (8.7)	261	+1.5 (7.5)	0.024
Mean change from baseline in foveal thickness as assessed by OCT µm (SD)	247	−126 (131)	261	−39 (121)	<0.001

Adapted from clarification response Table A8.2
BCVA, best corrected visual acuity; FAc, Fluocinolone Acetonide; DEX dexamethasone, OCT, optical coherence tomography, SD, standard deviation.

3.1.2 Adverse events

Adverse events (AE) are reported in CS Section B.3.10 for fluocinolone (from the integrated analysis of FAME) and dexamethasone (from the pooled safety analysis from MEAD) for:

- The proportion of patients reporting serious ocular AEs;
- The proportion of patients reporting IOP-related AEs (any AE related to increased IOP or glaucoma); and
- The proportion of patients reporting cataract-related AEs (assessed only in patients with a phakic lens at study baseline).

The proportion of patients reporting serious ocular AEs were reported for the whole populations only (CS Table 32 for fluocinolone and CS Table 33 for dexamethasone), these were not presented for the phakic population. The EAG requested these data for the phakic subgroups and the ITC subgroup of FAME in clarification A3. The company provided data for serious ocular AEs in their response, presenting a more detailed breakdown of the events than originally reported in CS Table 32. The EAG has reproduced the key data from the clarification response in Table 6.

Similarly, the proportion of participants reporting IOP-related AEs were reported for the whole populations only (CS Table 31 for fluocinolone and CS Table 33 for dexamethasone), but these were not presented for the phakic population.

In the phakic eyes; cataract was reported in 81.7% of fluocinolone 0.19 mg group compared with 50.4% of the sham group. Cataract surgery was performed in 80% and 27.3% of participants in the two groups respectively.

For dexamethasone, in the TE subgroup, in the phakic eyes; cataract was reported in 70.3% of the dexamethasone 0.7 mg group compared with 20.1% of the sham group.

Table 6. Serious ocular AEs for FAME (A+B pooled) phakic subgroups

N (%)	FAc 0.2 µg/day N=235	Sham N=121
Cataract Operation	188 (80.0)	33 (27.3)
Glaucoma	6 (2.6)	0
Intraocular pressure increased	9 (3.8)	0
Trabeculectomy	7 (3.0)	0
Trabeculoplasty	1 (0.4)	0
Vitrectomy	13 (5.5)	10 (8.3)
Vitreous Haemorrhage	8 (3.4)	4 (3.1)
ITC Cohort – Phakic only		
	N=138	**N=75**
Cataract Operation	107 (77.5)	19 (25.3)
Glaucoma	3 (2.2)	0
Intraocular pressure increased	4 (2.9)	0
Trabeculectomy	3 (2.2)	0
Trabeculoplasty	0	0
Vitrectomy	6 (4.3)	7 (9.3)
Vitreous Haemorrhage	3 (2.2)	2 (2.7)
Adapted from clarification table A3.1		

3.1 *EAG critique of CS real-world evidence*

The re-appraisal of dexamethasone in TA824 was prompted by the emergence of "*real-world evidence*" which informed that appraisal.[7] In this appraisal the company include non-randomised observational evidence of the efficacy and safety of fluocinolone (real-world studies) in Section B.3.6.7 and Section B.4.

Of relevance are the following sources of evidence; fluocinolone (3 studies)[37-40] and dexamethasone (4 studies),[41-44] and an meta-analysis of nine real-world studies by Fallico et al.[45]

Limited details of the studies are reported in the CS, therefore the EAG has assessed the quality of the studies and summarised the key issues and results (see Table 7 and Table 8), together with some additional relevant studies that were identified.[46-48] The EAG performed additional searches for recent RWE, but resources do not permit inclusion of all. The search strategies are reported in appendix 1.

3.1.1 Systematic reviews of RWE

3.1.2 Meta-analysis of nine real-world studies[45]

The CS summarises this review in CS Document B.3.6.7.1.

Searches for RWE were conducted on Pubmed, Embase, and Medline databases from inception to 16 October 2020. Searches included the terms 'fluocinolone acetonide', 'diabetic macular edema', 'diabetic macula oedema', 'macula edema', 'macular oedema', 'diabetic retinopathy' and connected using Boolean operators and/or. Eligibility criteria were studies had to report on the use of fluocinolone 0.2 mg/day intravitreal implant for chronic DMO, outcomes reported at 24 months or longer follow-up, report data on the primary outcome of change in BCVA, and to include a minimum of 10 patients in the primary outcome.

A total of 1,001 records were identified. After title and abstract and full-text screening, 11 articles were included in the meta-analysis. The PRISMA flow chart of the study selection process is presented in Figure 1 of the Fallico paper.[45] The authors compared outcomes from nine RWE studies to outcomes from FAME.[17]

The CS submission did not consider the risk of bias of the meta-analysis. Therefore, the EAG has quality assessed the study using ROBIS (see EAG Appendix). Overall, the Fallico review was considered to have a high risk of bias, mostly due to insufficient details of any eligibility criteria to allow a judgement of the appropriateness of the included studies. Minimal summary information of the included populations was provided, so it is therefore difficult to establish the similarities or differences to the FAME[17] and MEAD[16] trial populations. The review does report that three studies included only pseudophakic eyes and three others reported the number of phakic participants who had undergone cataract surgery. Duration of DMO, baseline BCVA, proportion with prior anti-VEGF or steroids were not reported. Studies on the duration of DMO revealed inconsistencies, with a potential error in one

study.[49] Other studies reported DMO durations ranging from two years to 4.7 years, though Ahmed,[50] Bailey,[37] and Fusi-Rubiano[51] did not provide this information (see Table 7 and Table 8).

3.1.2.1 Primary studies included in Fallico[45] meta-analysis

The EAG compared the characteristics of each of the studies included in this meta-analysis. The characteristics chosen were the ones that were identified by the company as important treatment effect modifiers in the ITC analyses. Seven studies were retrospective case series (5 UK[37, 50-53] and 2 Germany[49, 54]) and two were prospective (UK, Germany and Portugal[39]), and USA.[55]

Duration of DMO was reported as 7.14 months in Rehak but it is likely that this is an error.[49] In the other five studies that reported duration of DMO it ranged from 2 years to 4.7 years[39, 52-55] (not reported in Ahmed, Bailey, Fusi-Rubiano).[37, 50, 51]

Prior treatments were inconsistently reported across the RWE studies. One study did not report the proportions receiving prior treatments for DMO (Mansour).[55] The proportions receiving prior laser ranged from 26.9% (Ahmed)[50] to 92.5% (Augustin).[54] Anti-VEGFs were previously used in 58.3% (Panos)[52] to 100% of participants in one study (Rehak);[49] studies reported prior intravitreal corticosteroid use, ranging from 32.8% (Bailey)[37] to 76.9% (Ahmed).[50] Triamcinolone and/or dexamethasone were reported to be previously used in six studies. Rates ranged from 23.8% (Young)[53] to 55.2% (Fusi-Rubiano)[51] for triamcinolone and from 19.0% (Young)[53] and 51% (Rehak)[49] for dexamethasone.

Presence of cataract at baseline was reported in only one study (Augustin)[54] but all studies had a high proportion of participants with pseudophakic eyes at baseline, all greater than 75% with the exception of one study which had a proportion pseudophakic of 46.9% (Rehak).[49]

Baseline CRT differed widely across the eight included RWE studies that reported this (Chakravathy did not report this).[39] The lowest CRT was 383.1 µm (Mansour)[55] and the highest 600.8 µm (Ahmed).[50]

Baseline BCVA, where reported as letters, also varied across the studies. This ranged from 41.8 letters (Ahmed)[50] to 62.6 letters (Rehak).[49]

Overall there was heterogeneity across the nine RWEs meta-analysed in the Fallico meta-analysis factors considered to be treatment effect modifiers.[45] While these findings offer valuable insights into the real-world landscape of using fluocinolone for DMO management, the observed heterogeneity underscores the importance of cautious interpretation.

3.1.2.2 Statistical methods of the meta-analysis

The primary outcome analysed was change in BCVA from baseline to 24-month follow-up, reported as mean difference (MD). Additional outcomes include change in BCVA at 36 months, central macular thickness (CMT) change, the proportions of eyes receiving supplementary intravitreal therapy, cataract surgery (phakic eyes only), IOP lowering drops, and glaucoma surgery. The results from the RWE were meta-analysed in Stata 16 with a significance level of 5% unless otherwise stated.

Heterogeneity was tested using the Cochrane's Q-statistic and I-squared values. Cochrane's Q-statistic is a measure of the total variability in effect sizes among the studies in a meta-analysis. If the p-value associated with the Q-statistic is statistically significant, it suggests that there is significant heterogeneity. I-squared is a measure of the proportion of total variability in effect sizes that is due to heterogeneity rather than chance. In this publication, any I-squared values over 50% were explored further for potential heterogeneity. Fixed-effects models were used if statistical heterogeneity was not reached. Random-effects models were used with the DerSimonian-Laird method applied if either a p-value for the Q-statistic < 0.1 or I-squared > 50%.

The DerSimonian-Laird method is a statistical technique utilized in meta-analyses to estimate the between-study variance and calculate a more

conservative pooled effect size in random-effects models. This approach is used when it is assumed that the true effect size varies across studies due to heterogeneity. Benefits of the method include its ability to account for heterogeneity, providing a more robust estimate of the pooled effect size. However, it has limitations, such as sensitivity to the number of studies and heterogeneity, and it may overstate the uncertainty of the effect size when the number of studies is small. Publication bias was explored using Funnel plots and using Egger's test.

3.1.2.3 Results of Fallico et al[45]

Table 19 of CS B.3.6.7.1 compares the results of the meta-analysis by Fallico et al[45] and FAME[17] for the outcomes of BCVA at 24 months and 36 months, central macular thickness, and pooled proportions of cataract surgery, intra-ocular pressure lowering drops, glaucoma surgery, and supplementary IVT. Results were consistent with the FAME[17] trial results. These results are also presented below in Table 7 and Table 8.

For all four outcomes that were meta-analysed, the pooled estimate of the mean difference from Fallico et al was not statistically different to that of FAME.[45] Results of the 24-month CMT did differ between FAME and Fallico et al where the mean difference of CMT at 24-months was -168 μm in FAME compared to the published MA result of -127 μm.[45] However this was not a statistically significant difference as the 95% confidence intervals overlapped between the two results. Statistical heterogeneity was a concern in this MA with a published I-squared of 79% and 84% from the EAG. Both values indicate a substantial amount of heterogeneity in the analysis.

This suggests that the variation between the studies is more than what would be expected by chance alone and a few things could have been considered by Fallico et al.[45] If sources of heterogeneity were apparent when comparing the study designs or populations of the included studies, such as specific subgroup differences, subgroup analyses or meta-regression could have been employed to explore these potential sources of heterogeneity.

Another method would be to perform a sensitivity analysis where one or more studies are removed at a time to see whether this significantly impacts the results. Results that reduce the I-squared a meaningful amount should be explored further. The EAG performed this sensitivity analysis and found that removing each study from the meta-analysis results in the I-squared staying in the range 80 to 87%, with the exception of removing the MD from Mansour et al. 2020 which reduced I-squared to 62%. This suggests that this study may have been a major source of heterogeneity, it might be substantially different from the others in terms of methodology, population, or other factors, and its inclusion was driving the high heterogeneity observed in the original analysis. This was a key limitation in the meta-analysis for this outcome.

Table 7. Results of the meta-analysis conducted in Fallico et al.[45] compared to FAME[17] plus results of the EAG's replication of the meta-analysis

Meta-analysis results	Outcome	MD	95% CI		I-squared
Fallico et al.	24-month BCVA gain	4.52	2.56	6.48	0%
EAG overall (fixed)		4.52	2.56	6.48	0%
FAME		4.40	2.64	6.16	
Fallico et al.	36-month BCVA gain	7.89	4.70	11.07	0%
EAG overall (fixed)		7.89	4.70	11.07	0%
FAME		8.10	6.34	9.86	
Fallico et al.	24-month CMT	-127.20	-175.36	-79.03	79%
EAG overall (random)		-127.20	-176.96	-77.44	84%
FAME		-167.80	-193.28	-142.33	
Fallico et al.	36-month CMT	-169.76	-205.71	-133.81	32%
EAG overall (fixed)		-169.76	-205.71	-133.81	32%
FAME		-180.80	-205.88	-155.72	

The difference between the pooled proportion of patients in Fallico et al[45] who underwent cataract surgery, took IOP lowering drops, or who received supplementary intravitreal therapy was different to the proportion in FAME.[17] Although the 95% confidence intervals for FAME were not presented, it is possible that the proportions for cataract surgery and intravitreal therapy significantly differ between Fallico et al[45] and FAME.[17]

The EAG conclude that the proportions who underwent glaucoma surgery were comparable.

Table 8. Results of the comparison of outcomes in Fallico et al[45] to FAME[17] presented as pooled proportions

Pooled proportions results (%)	Fallico et al[45]	FAME FAME[17]
Cataract surgery	39 (18, 62)	80
IOP lowering drops	27 (19, 36)	38.4
Glaucoma surgery	3 (1, 5)	4.8
Receiving supplementary intravitreal therapy	39 (31, 48)	15.2

3.1.1 Kodjikian[56] systematic review of RWE

The company submission did not include the systematic review by Kodjikian, also published in 2021.[56] The EAG provide a summary below with comparison made to the Fallico review.[45]

The Fallico review includes nine studies, whereas Kodjikian includes 21. Lists provided in EAG Appendix. However, the Kodjikian review includes seven studies with fewer than 20 eyes on the steroid in question: Coelho 2019, Elaraoud 2016, Figueira 2017, La Mantia 2018, Massin 2016, McCluskey 2019 and Schechet 2019.[57-63] The EAG would exclude studies with fewer than 20 eyes, and even that number may be too low.

The Fallico review criteria excluded any studies with fewer than 10, but in practice it did not include any of the seven studies with fewer than 20, because they only included studies with at least 24-month follow-up.[45] In Kodjikian the mean follow-up is 20 months but range was from 8-36 months.[56] Fallico also excluded studies that included only vitrectomised eyes.[45]

Fallico included two studies not in the Kodjikian review, Mansour 2020 and Ahmed 2020,[50, 55] because they were published after the Kodjikian search data of March 2020 but were found by the Fallico search in October 2020.

The study by Rosenblatt 2020[64] was not included by either review, despite being published online in 2019. It may have been too early for Kodjikian and the follow-up too short for Fallico. No lists of excluded studies are provided.

Assessing the quality of the Kodjiikian review using the NIH criteria, the EAG considered the Kodjiikian review to be of low quality (see EAG Appendix) because a number of quality factors could not be determined from the publication, including the comprehensiveness of the search strategy and the

review processes, and because there was no risk of bias assessment of the included studies undertaken.

3.1.1 Primary studies of RWE

The EAG carried out a rapid search for RWE studies but did not have time to carry out a full review of every such study. (The search strategy is in EAG appendix). We provide summaries and quality assessment of the most relevant RWE studies identified in Sections 3.1.2 and 3.1.3. Studies with under 20 eyes or with under 12 months follow-up, and studies that included only vitrectomised eyes were excluded. Studies in Section 3.1.4 include studies examining the sequence of steroid treatment that starts with short-acting dexamethasone and then, depending on efficacy and safety, switches to longer-acting fluocinolone.

3.1.2 Fluocinolone RWE studies

Medisoft audit study: (Bailey et al 2022,[37] Mushtaq 2023[65]) was a retrospective audit study of fluocinolone in 227 patients with chronic DMO from 14 sites in the UK. The study had unclear reporting of some quality criteria (Table 10). Only 11.3% of the eyes had phakic lenses, compared with around 64% and 73% in FAME[17] and MEAD[16], respectively. Results were reported separately for pseudophakic eyes but not phakic eyes. Duration of DMO was similar to FAME[17] but slightly longer than MEAD[16]. Baseline BCVA was slightly worse than in MEAD[16], such that the final value in Bailey was similar to the baseline in MEAD[16].

A high proportion (79.7%) had received prior anti-VEGF treatment. The proportion with corticosteroid treatment was higher than in MEAD[16], but fewer had received laser treatment. BRVA increased from 52.6 letters to 57.1 letters at 48 months, with improvements seen from month three. Results were similar between pseudophakic eyes and the overall population. Only 66 patients had CRT measured, this showed a statistically significant improvement from 460.3

μm to 340.5 μm. Mean IOP was stable throughout the study. IOP events are summarised in Table 9. Additional treatment was received by 55.9% of patients over 36 months, with anti-VEGF treatment in 48.8%. A recent abstract[65] of results at a mean follow-up of 64 months reported mean BRVA was 59.2 letters at 3 years and 60.5 letters at 6 years. Additional treatments were not reported. Over 6-years, mean BCVA increased by approximately eight letters, though this was achieved with almost half receiving supplementary anti-treatment.

IRISS registry study: is the largest and longest RWE study (Khoramnia 2023, Chakravarthy 2019)[38, 39] which was an observational phase 4 post-regulatory approval study sponsored by Alimera Sciences. The study had retrospective and prospective data collection and was conducted in 47 European centres (31 UK centres). Eyes were treated from 2013 to 2017. The reporting of some quality criteria was unclear (Table 10).

All indications were included (556 patients, 695 eyes); 16.3% had phakic lenses and 96.7% had DMO. Eyes with DMO and data on duration of DMO were classified as short-term (duration ≤3.6 years, 319 eyes) or long-term (>3.6 years, n=322). Chronic DMO was defined by the median duration of DMO, which was similar to that in FAME.[17] Baseline BCVA was 52.9 letters and 51.6 letters in the short- and long-term subgroups, respectively.

Almost all (95%) had had prior treatment, mainly anti-VEGFs (78.8%), with 38.4% having had corticosteroids (not specified in the supplementary table) and 59.4% laser treatment. People with a shorter duration (under 3-years) of DMO experienced greater VA gains than those with a longer duration. By 48 months BCVA in the short-term subgroup was 57.9 letters, whilst those in the long-term had an initial gain that decreased to 50.9 letters. IOP-lowering medication was used in 35.1% of DMO eyes, with 13.5% having an IOP increase of 10 mmHg or more.

In the phakic group, cataract extraction was performed at the time of the fluocinolone implant in 29.2%, and after implant in 64.6% at a mean 13.6-months. Most people had just one fluocinolone implant, 6.6% had two implants and one person had three implants. Additional intravitreal or laser treatment was administered in 43.7% of all patents. With 24% having anti-VEGFs, 24% having laser and 10.6% having additional steroids (implying other than fluocinolone in about 4%). Of the 31 UK centres, six or seven had been involved in the Medisoft study by Bailey et al which appears to be an overlapping time period (first analysis 2016 data, with mean follow-up just over a year). It is not clear if some of the Medisoft group patients were also included in IRISS. Findings from this study suggest that earlier treatment of DMO appears more effective.

Holden et al 2017: reported outcomes from 208 UK participants in a retrospective case series undertaken in 13 UK centres.[46] The study was designed and funded by Alimera Sciences; who also commented on the manuscript. The study was very detailed with useful subgroup reporting according to baseline VA and number of prior treatments. Fluocinolone treatment occured between April 2013 and April 2015. Follow-up was 12 months from fluocinolone implant. The study had unclear reporting of some quality criteria (Table 10). Only 11% of the implanted eyes had phakic lenses, which is much lower than in FAME[17] and MEAD[16] (64% and 73% respectively).

Despite this limitation, there were a number of similarities at baseline between Holden's population and those in FAME[17] and MEAD[16], including duration of DMO, baseline BCVA and CRT. Anti-VEGFs were previously used in 82% which was much higher than in FAME and MEAD as would be expected from the time periods. Prior laser at 63% was similar to the rate in MEAD, but lower than the rate in FAME. At 12 months BCVA was 51.8 and IOP increased from 15.0 (13.0-18.0) to 18.0 (15.0–21.0) mmHg. IOP-lowering therapy was used in 15% of patients not previously requiring this. Cataract surgery was performed

0 to 3 months in 73% of eyes with phakic lenses, with most being performed at the time of implant. One additional cataract removal was performed between 3 and 12 months. Additional treatments between 6-12 months included anti-VEGF in 28% (Table 9). BCVA improved by 5 letters or more in 44% at 12 months after fluocinolone treatment; 30% had gains of 10 or more letters; and 18% of 15 or more letter. However, 245 lost 5 or more letters and 14% lost 10 or more. All but one of the centres were also in the IRISS study.

Mushtaq 2021: reported a retrospective audit of three large centres in the West Midlands, UK, funded by Alimera Sciences.[66] A total of 96 patients (96 eyes) with at least three years follow-up were included. The study had unclear reporting of some quality criteria (Table 10) and does not report lens status. Mean duration of DMO (3.7 years) was similar to FAME,[17] whereas baseline BCVA (mean 49.0 letters) was lower, and CRT 529.3 µm was greater than both FAME and MEAD. The majority (91.7%) of patients had prior anti-VEGF treatment. Mean BCVA was 54.5 letters at 1 year and 53.0 letters at 3 years; mean CRT decreased to 331.1 µm at 3 years. CRT reduced by 20% or more in 75% but only about half of these eyes had BRVA improved by 5 or more letters. Increased IOP ≥ 30 mmHg or ≥ 25 mmHg was experienced by 12.5% and 24% of patients, respectively, and 17.7% required a change to or started IOP lowering therapy. Selective laser trabeculectomy was received by 2 eyes, cyclodiode laser treatment by 1 eye, and 1 eye had trabeculectomy due to neovascular glaucoma. Post implant, 44.8% had anti-VEGF treatment. Therefore, 78% maintained or improved (53%) BRVA by 3 years but 12% lost 10 or more letters by then. Those losing letters had longer duration of DMO and a greater number of previous treatments.

Dobler 2023: reported outcomes for 31 eyes of 25 patients (from an original cohort of 60 eyes – 21 patients died despite a baseline age of only 67 years) treated with fluocinolone at a single UK centre and followed for 5-years.[40] The study had unclear reporting of some quality criteria (Table 10). None of the patients had phakic lenses. Mean duration of DMO (5.9 years) was longer

than in FAME[17] and MEAD[16], and baseline mean BCVA (48) was worse than in the trials. Baseline HbA1c was not reported. A majority (97%) of patients had received previous anti-VEGF treatment, 58% had had corticosteroids (mainly triamcinolone) and 68% had had laser treatment. BCVA improved to 52.3 letters (p<0.001 versus baseline) 1 year after fluocinolone treatment but fell to 48.3 letters at 5 years.

At 5-years, 13 had improved, eight experienced no change, and 10 deteriorated. The mean baseline CTR was 477 and reduced to 310.2 μm after 5 years (p<0.001). IOP-lowering medication use increased to 70% at 5 years from 16% at baseline (p<0.001), with additional treatment for IOP required in four eyes (Table 9). Rescue intravitreal therapy was received by 58% of eyes over 5 years (Table 9). Rescue therapy means repeat treatment at a mean of 29 months in 18/31. No details of the criteria for repeat are provided. Five had a second fluocinolone implant but 16/31 got anti-VEGFs, despite previously being non-responders. Only three received macular laser despite CRT rendering most eligible.

Alfaqawi et al 2017 and 2018: conducted a small retrospective study (n=23, 28 eyes) in a single UK centre with 12 months follow-up.[47, 67] The study had unclear reporting of some quality criteria (Table 10) but received no commercial funding. All patients had pseudophakic lenses, four eyes had cataract surgery at the time of fluocinolone implant. Compared with FAME[17] and MEAD[16], the mean duration of DMO (6 years) was longer, BRVA (47 letters) was worse, and CRT (494 μm) was greater. Unlike FAME and MEAD, most people had received anti-VEGFs, 89.3% had prior laser therapy, and three patients had received dexamethasone implant. At 12 months, a statistically significant improvement in both VA and CTR was observed (55 letters and 262 μm, respectively). IOP of 10 mmHg or more and initiation of IOP-lowering drops occurred in 11% of eyes. Three-year outcomes for 22 eyes were reported in a conference abstract,[67] with mean BCVA 52 letters and 49 letters at 1 and 3 years, respectively. Mean CTR was 346 at μm at 36

months. Over half of patients received additional treatments, either anti-VEGF injection, dexamethasone implant, or laser, mostly in year 3 (Table 9).

- This study came from the Birmingham and Midlands Eye Centre and patients were treated from April 2014 to April 2015. The three-centre Midlands study by Mushtaq et al above included 37 patients from this centre, treated in 2015 and 2015. It is therefore possible that the eyes in Alfaqawi are a subset of those in Mushtaq 2021.

Augustin et al 2020: report data on results with fluocinolone in 81 eyes of 63 patients (bilateral treatment in 29%) in 16 sites in Germany.[54] The eyes had chronic DMO (mean duration 3.8 years) that had had a poor response to first-line treatment. The proportion phakic was 24.7%. Poor responses include persistent or recurrent oedema or no improvement in VA. They had been heavily treated with anti-VEGF drugs (98%), laser (93%) or triamcinolone (42%), therefore match the NICE scope for this appraisal (see Section 2). Before fluocinolone treatment, 22% were being treated for raised IOP and this rose to 27% afterwards. BCVA improved by 5.5 letters by month nine after fluocinolone and this was maintained to month 30. CRT fell from 502 microns to 318 at month 30. Surgery for raised IOP was required in 4%. Nine eyes had repeat fluocinolone, three in the first 30 months and four afterwards. The study had unclear reporting of some quality criteria.

Ruiz-Moreno et al 2023: report on 31 eyes treated with fluocinolone after being insufficiently responsive to previous treatments (anti-VEGF in 84%, laser in 16%, dexamethasone in 19 - 61%), 32.2% had phakic eyes.[68] In this Spanish study, median follow-up was 3 years. The study had unclear reporting of some quality criteria. BCVA improved by six letters (not significant because of small numbers) and CRT from 474 microns before fluocinolone to 334 afterwards. Additional treatment was required in 19 or the 3 eyes.

Panos et al 2020 is a study London which reported that South Asian and Black people did less well after fluocinolone than a White group.[52]. The Asian and Black groups were combined as a 'Black, Asian and Minority Ethnic group' (BAME) in the study. CRT fell by 40 microns in the BAME group, and by 169 in the White group. LogMAR improvement was slightly better in the White group. However, participant numbers included in the were very small – six White, six Black, 12 Asian and follow-up to 36 months was achieved in only nine eyes. Results for the overall group are shown in Table 11. The study had unclear reporting of some quality criteria and is too small to be of value.

Putri et al 2018 and Parker et al 2019: are two other single centre UK retrospective studies which were reported as conference abstracts.[69, 70] Limited details are available on their methods, baseline characteristics or results (Table 9).

- At three years follow-up of 37 eyes, Parker 2019 reported an improvement in VA from 53 letters to 58 letters and in CMT from 550 µm to 357 µm.[69] IOP was controlled by local therapy in eight eyes and one eye had surgery for raised IOP. Seventy percent of patients had additional anti-VEGF treatment, and 5% had laser treatment.
- Putri 2018 reported outcomes for 26 eyes followed for at least 36 months.[70] BRVA increase by 8.2 letters from a baseline of 40.1 letters, and CRT reduced by 175 µm from a baseline of 568 µm. Half of patients had IOP ≥ 21.0 mmHg, 34.6% had new or change in IOP-lowering drops, and one eye had trabeculectomy. Additional anti-VEGF treatment was used in 38.5% of eyes and laser in 11.5%.

3.1.2.1 Additional treatments:

In the 14 UK Centre Medisoft RWE study of the effects of fluocinolone in routine NHS care,[37] 56% had had additional treatment with anti-VEGF drugs or laser by three years. Of these, 49% had anti-VEGF treatment and 10.5% had laser. The paper does not give reasons for additional treatment or how successful it was. The additional therapies were roughly evenly spread over

the three years. It is unclear why anti-VEGF treatment was used as additional treatment in eyes which had not responded before fluocinolone was tried. On consultation with EAG clinical experts, reasons may include;

- The average gain in BCVA after fluocinolone was quite small – approximately five letters. Only 25% of eyes gained 10 or more letters, and just over half gained <5 letters.
- The anti-VEGF drugs have some effect in over 90% of eyes, even though the effect is small in 30-40%. Therefore, the ophthalmologists may have thought additional anti-VEGF treatment was worth attempting. The EAG note an evidence gap here; in eyes poorly responsive to anti-VEGFs it is unclear if response improves after fluocinolone.
- Medisoft does not report what the anti-VEGFs were given for – some may have been for PDR.

The mean number of fluocinolone injections in this study was 1.14 per eye, with the mean interval to second implant being 38 months.[37] The repeat rate appears low; however, reasons are not provided. It is possible that second implants were used in only good responders – the 17% with 15 or more letter gain. Therefore, cost may have been a consideration.

The proportions of patients having supplementary treatment after steroid injections varies amongst RWE studies from 20% (five of 25 eyes)[71]), to 21%,[72] to 33%,[73] 38% (IRISS),[38] and 48% (PALADIN).[43] The EAG note a possible selection effect in some studies where fluocinolone was only started in eyes responsive to dexamethasone.

3.1.3 Dexamethasone RWE studies

Faes et al 2023 was a retrospective case series funded by Abbvie and the NIHR, undertaken in one tertiary centre in the UK.[48] The study included 240 participants who received a dexamethasone implant. However, patients were only followed up for 6-months, so this study is not reported in detail here. The study had unclear reporting of some quality criteria (Table 10). BCVA

improved by 5 or more letters in about half but the effect was not sustained after one injection.

Lam et al 2015: This retrospective case series reports results for a small sample (n=24) of people with DMO implanted with dexamethasone, as well as results for those having the implant for other conditions.[44] The study was undertaken in 10 centres in Canada, and was funded by Allergen Inc. (A subsidiary of Abbvie).

The proportion with phakic lenses in people with DMO was 32.4% which is lower than in FAME[17] or MEAD,[16] but results were presented for BCVA outcomes for those with phakic lenses and those with pseudophakic lenses. Other baseline characteristics can be seen in Table 9, the mean duration of DMO was not reported but 94.1% had a diagnosis for at least 12 months and 55.9% had prior laser treatment. The baseline CRT was 450.4 µm which was similar to FAME and MEAD. The BCVA was reported in logMAR only. At follow-up, the duration of which was not defined, the mean change in BCVA in the phakic eyes was -0.6 logMAR (SD 0.6). The mean change in CRT was -190.9 µm (SD 23.5). Increased IOP occurred in 25%. Cataract surgery was performed in 27.3% of phakic eyes. Repeat dexamethasone implants was used in 44.1% and 41.2% had one of any number of additional treatments or procedures.

Malclès et al, 2017: (Lyon, France) report the RELDEX study, a series of 128 eyes in 89 patients, about 25% previously untreated and 44.5% phakic.[74] Previous treatments included anti-VEGFs (70%), laser (16%) and steroids (16%). Mean follow-up was only 16 months but 31 had 30 months or more. BCVA improved from 51 at baseline to 61 at 36 months.

Complete drying was seen in 36%, improvements of 10 letters or more in 52% and gains of 15 letters or more in 25%, at month 36 (number uncertain but at most the 31 at 30 months). However, about-12% lost 10 or 15 letters.

Additional treatments were few – no laser and only five had anti-VEGFs for unsatisfactory efficacy. Mean time to repeat dexamethasone was 7.3 months. Inpatients followed for 3 years; the mean number of dexamethasone injections was 3.6. The number of clinic visits declined over time – 5 in first year, 3.4 in second year and 3 in third year. Baseline HbA1c was 7.7%. Malcles et al identified seven other studies of dexamethasone (with more than 30 eyes) in routine care but none had more than 6 months follow-up.[74] The study had unclear reporting of some quality criteria.

Singer et al 2018; report results of dexamethasone in 180 eyes from 18 centres in the USA, 29.4% were phakic eyes.[75] Follow-up was for 12 months. The study had unclear reporting of some quality criteria. Most (94%) eyes had had previous treatment with anti-VEGF or laser or both. Over the follow-up period, 435 of eyes had one dexamethasone injection, 25% had two and 20% had three. The mean interval between injections was 5-months. Additional treatment was given to 45% of eyes, mainly anti-VEGF drugs but also some steroids, either triamcinolone or fluocinolone. Therefore, 55% required no additional treatment. BCVA improved from a mean 54 letters at baseline with gains of 10 or more letters in 58% and 15 or more in 36%.

Rosenblatt et al, 2020: study from the European DME Registry Study[64] reported the results of dexamethasone from 340 eyes of 287 patients in 25 centres in eight European countries, with one UK centre, (Moorfield Hospital). The study presents results in two ways, by individual injections, and by patients having series of injections. There were 150 patients in the series report. All had two or more injections, with 444 injections in total, with 3-6 months between injections. 26% had had three injections and 7% had had four, and 5% had more than four. The average number of injections per eye was 2.4 in the first year, followed by 0.2 in the second year and 0.03 in the third (though there were few eyes with 3-year follow-up). Follow-up was for a mean of 20 months. Almost all eyes had had previous treatment, with anti-VEGF drugs (94%) or laser (84%, or intravitreal steroids (18%, not specified); 60%of eyes were phakic.

Gains of 10 or more letters were seen in 36% and of 15 or more letters in 20.5%, but 8% lost more than 15 letters and 12% lost more than 10. Additional rescue treatment was observed in 19%, of which 66% received laser and 25% anti-VEGFs. (rescue reasons were not defined but based on "*physicians' discretion*"). Two-thirds of the 19% only had one additional treatment, and 31% two. The mean baseline CRT was 519 microns in the series group, and fell by 151 microns, so many would be under the 400 microns laser threshold. Rosenblatt et al report that the maximum effect was seen three months after dexamethasone insertion and suggest that treatment might be given more often than 6-monthly. The study had unclear reporting of some quality criteria.

- Whilst longer follow-up would be useful; this study suggests that a smaller proportion of eyes have additional treatments after dexamethasone than after fluocinolone. (Note, this comparison of drug case series in different circumstances and, it appears, different attitudes to laser therapy.)

Lau et al, 2021: report data from Sunderland, UK via two conference abstracts.[76] In this study a series of 89 eyes were followed for 24 months. No details of previous treatments are given. In the first 12 months, approximately half the eyes received only one dexamethasone injection, with about a third receiving two and 12% (11 or 89) receiving three. Baseline BCV was 55 letters, improving by 10 letters at 24 months in the group receiving three doses but changing little in the eyes receiving only one or two injections, though because of small numbers these differences were not statistically significant.

Sepetis et al 2018: reported results of dexamethasone in 30 eyes of 25 patients from Portsmouth UK.[77] Anti-VEGF drugs had previously been tried in only 13 eyes, therefore this study is less useful for the patient group in this appraisal. By 18 months, the average number of dexamethasone doses was 3.6.

Table 9. Summary table of RWE studies

Study details	Key baselines, mean (SD) or %	Key outcomes	Additional treatments
Fluocinolone studies			
Bailey 2022[37] Medisoft audit study Retrospective 14 UK centres N=227, 256 eyes Follow-up: mean 4.3 years Statistical and writing support by Alimera	Phakic: 11.3% Duration of DMO: 4.4 (2.9) years HbA1c: NR CRT (n=66): 460.3 µm BRVA: 52.6 letters Prior treatment Laser: 31.6m% Corticosteroid: 32.0% Anti-VEGF: 79.7%	Month 48 BRVA: 57.1 letters CRT: 340.5 µm IOP increase of ≥10 mmHg: 28.9% IOP-lowering medication: 29.7% Laser trabeculoplasty: 0.8% IOP-lowering surgery: 2.7% Cataract: NR	Mean 1.14 FAc implants per eye, (0 with >2 implants) Over 36 months: Any laser or intravitreal: 55.9% Laser: 10.6% Corticosteroid: 9.4% Anti-VEGF: 48.8%
Mushtaq 2023[65a] Medisoft audit study Retrospective case series 14 UK centres N=256, 30 eyes Follow-up: ≥36 months, mean 62.4 months Funding: Alimera Sciences	Phakic: NR Duration of DMO: NR HbA1c: NR CRT: NR BRVA: 56.8 (15.6) letters Prior treatment: NR	BRVA, letters 3 years: 59.2 (SD 17.1) 6 years: 60.54 (SD 15.6) IOP lowering drops: 36.1% (vs 21.5% pre-implant) IOP > 30 mmHg: 25.5%	NR
Khoramnia 2023[38] IRISS registry study 47 centres (31 UK) All indications: N=556, 695 eyes DMO N=672 eyes Follow-up: mean 3.2 years Funding: Alimera sciences	All eyes (n=695) Phakic: 16.3% Duration of DMO (n=641): 3.6 years HbA1c: NR CRT: NR BCVA: 52.2 (19.1) letters [short term DMO: 52.9 (19.3); long term DMO 51.6 (18.80)]	BCVA, letters Short term chronic DMO ≤3.6 years (n=319): 1 year: 56.8 (17.3) 48 months: 57.9 (16.5) Long term chronic DMO >3.6 years (n=322): 1 year: 54.6 (18.6) 48 months: 50.9 (19.9)	All eyes (n=695) Mean 1.07 FAc implants per eye; 6.6% had 2 implants, and 0.1% had 3 implants. Any intravitreal or laser: 43.7% Laser: 23.7% Corticosteroid: 10.6% Anti-VEGF: 4.3%

	Prior treatment Laser: 59.4% Corticosteroid: 38.4% Anti-VEGF: 78.8%	DMO eyes (n=672) IOP increase of ≥10 mmHg: 15.3% IOP-lowering medication: 35.1% Trabeculoplasty: 1.2% Trabeculectomy: 1.9% Other surgical procedure: 2.4% Total population, phakic eyes (n=113) Cataract extraction at FAc implant: 29.2% Cataract extraction after FAc implant (mean 13.6 months): 64.6%	
Holden 2017[46] Retrospective case series 13 UK centres N=208, 233 eyes Follow-up: 12 months Funding: Alimera Sciences	Phakic: 11% Duration of DMO: median 2.7 (IQR 0.7-2.7) years HbA1c: NR CRT: 482 µm BCVA: mean 52.0 letters Prior treatment Laser: 63% Corticosteroid: 43% Anti-VEGF: 82%	BCVA, ETDRS letters: 51.8 IOP: Increase from 15.0 (13.0-18.0) to 18.0 (15.0–21.0) mmHg Eyes newly prescribed IOP-lowering therapy post-implant: 15% Cataract surgery at 0-3 months: 73% (54% at time of implant) of phakic lenses Cataract surgery at 3-6 months: 3.8% Cataract surgery at 6-12 months: 0	Additional treatments (at 6-12 months) Anti-VEGF: 28% Steroid injection: 5% Laser: 5% Cataract surgery: 0%
Mushtaq 2021[66] Retrospective case series 3 UK centres N=96, 96 eyes Follow-up 36 months Funding: Alimera Sciences	Phakic: NR Duration of DMO: 3.7 (1.7) years HbA1c: NR CRT:529.3 (157.2) µm BRVA: 49.0 (16.5) letters Prior treatment Laser: 86.5% Corticosteroid: 37.5% Anti-VEGF: 91.7%	BRVA 1 year: mean 54.5 letters 3 years: mean 53.0 letters CRT 1 years: mean 356.2 µm 3 years: mean 331.1 µm IOP ≥ 30 mmHg: 12.5% IOP ≥ 25 mmHg: 24.0% Required changed to or started IOP-lowering therapy: 17.7% Selective laser trabeculectomy: 2 eyes Cyclodiode laser treatment: 1 eye	Anti-VEGF: 44.8%

		Trabeculectomy due to neovascular glaucoma: 1 eye	
Dobler 2023[40] Retrospective case series 1 UK centre N=25, 31 eyes Follow-up: 5 years Funding not reported	Phakic: 0% Duration of DMO: 5.9 (3.5) years HbA1c: NR CRT: 477.1 µm (159.5) BCVA: 48.1 (16.2) letters Prior treatment Laser: 68% Corticosteroid: 58% Anti-VEGF: 97%	BCVA, letters 1 year: 52.3 (SD 17) 5 years: 48.3 (SD 23) CRT 1 year: 323.7 µm (SD 117) 5 years: 310.2 µm (SD 116) At 5 years IOP lowering drops: 70% of eyes Selective laser trabeculoplasty (SLT) only: 2 eyes Cyclodiode laser: 1 eye SLT and incisional glaucoma surgery: 1 eye	Rescue intravitreal therapy therapy over 5 years: 58% of eyes Anti-VEGF: 16 eyes Dexamethasone: 2 eyes FAc (one): 5 eyes PRP laser: 2 eyes Macular laser: 3 eyes
Alfaqawi 2017[47] Retrospective case series 1 UK centre N=23, 28 eyes Follow-up 12 months Funding: none	Phakic: 0 Duration of DMO: 6 (SD 2) years HbA1c: NR CRT: 494 µm VA: 47 (18) letters Prior treatment Laser: 89.3% Corticosteroid: 57.1% Anti-VEGF: 92.9% Dexamethasone: 10.7%	VA: mean 55 (SD 17) letters CRT: mean 262 (SD 121) µm IOP ≥ 10 mmHg and initiation of IOP-lowering drops: 11%	Anti-VEGF: 2 eyes
Alfaqawi 2018[67a] Retrospective case series 1 UK centre N=18, 22 eyes Follow-up 36 months Funding: NR	Phakic: 0 Duration of DMO: NR HbA1c: NR CRT: NR VA: 47 (15) letters Prior treatment: NR	BCVA 1 year: mean 52 (SD 17) letters 3 years: mean 49 (SD 18) letters CRT 3 years: mean 346 (SD 130) µm Raised IOP: 14% (controlled by IOP-lowering drops and selective laser trabeculoplasty)	Additional treatment: 55% Anti-VEGF: 9 eyes DEX: 2 eyes Laser: 2 eyes (Mostly in year 3)

Chronopoulos 2022[71] Retrospective case series 1 German centre N=25, 27 eyes Follow-up: 24 months Funding: None	Phakic: 4% Duration of DMO: 4.5 (2) years HbA1c: NR CRT: 497 (176) µm BRVA: 49 letters Prior treatment Laser: 59.3% Triamcinolone: 33.3% DEX: 74.1% Anti-VEGF: 85.2% Pars plana vitrectomy: 37%	BRVA I year (26 eyes): 60 letters 2 years (16 eyes): 65 letters CRT 1 year (25 eyes): 340 µm (SD 181) 2 years (16 eyes: 278 µm (SD 50) Cataract surgery: 1 patient IOP ≥21.0 mmHg: 12%	Anti-VEGF: 5 eyes
Singer et al 2018[55, 75, 78, 79] The Paladin study Prospective phase 4 study 41 US centres N=202, 159 eyes 94 eyes with 36 months follow-up Follow-up: 36 months Funding: Alimera Sciences	N=94 with follow-up Phakic: 11.7% Duration of DMO: NR HbA1c: NR CRT: 386.1 (134.5) µm BCVA: 62.3 (15.78) letters Prior treatment: NR	36 months, n=94 BCVA (n=89): 66.03 letters CRT (n=92): 327.09 µm IOP increase >10 mmHg: 27.7% IOP increase >25 mmHg: 29.8% IOP increase >30 mmHg: 12.8% Trabeculoplasty:1.1% Incisional IOP-lowering surgery 5.3% Any IOP-lowering medication: 22.3%	25.53% rescue free at 36 months
Augustin 2020[54] Retrospective case series 16 German centres N=63, 81 eyes Follow-up: 30.8 (SD 11.3) months Funding: none	Phakic: 24.7% Duration of DMO: 3.8 (SD 2.9) years HbA1c: NR CRT µm: 502 BRVA: 49 letters Prior treatment: Laser: 92.5% Ranibizumab 91.1% Bevacizumab 44.3%	At 36 months BRVA: 52.4 BRVA change from baseline: 3.4 (figure shows 2.7) CRT: 318 µm CRT change from baseline: -158 µm New cataract: 21.3% IOP Increase of ⩾10 mm Hg: 22.2%	Supplemental therapies (undefined): 39.7%

	Aflibercept 6.3% Triamcinolone 41.8% Dexamethasone 24.1%		
Panos 2020[52] Retrospective case series 1 UK centre N=24, 246 eyes Follow-up: ≥ 24 months Funding: none	Phakic: NR Duration of DMO: 23.6 (range: 10–37) months HbA1c: NR CRT: 471 (SD 99) µm BRVA: 0.62 (SD0.27) LogMAR Prior treatment: Focal/grid macula laser: 75% Ranibizumab: 58.3% Triamcinolone: 29.2%	At 24 months BRVA: 0.61(SD 0.31) LogMAR BRVA increase ≥ 5 letters: 37.5% CRT: 381 (SD 94) µm CRT reduction ≥50 µm: 71.4% Cataract surgery: NR IOP >26 mmHg: 16.7%	Triamcinolone: 8.3% DEX: 4.2% Ranibizumab: 33.3% Aflibercept: 16.7%
Eaton 2019[80] Retrospective case series 4 USA centres N=130, 160 eyes Follow-up: 407.8 (7–756) days Funding: Alimera Sciences.	Phakic: 22.5% Duration of DMO: 4.4 (range 0–32) years HbA1c: 7.07 CRT: 370.4 µm BRVA: 60[b] letters Prior treatment, % eyes: Anti-VEGF: 76.9% Steroid: 56.3% Laser: 50.0%	At 24 months BCVA: 58[b] letters (n=9) CRT: 276.6 µm (n=6) At 15 months CRT: 310.1 µm (n=65) Cataract surgery: NR IOP-lowering surgery: 1.3% IOP elevation to ≥ 21 mmHg: 30.6% eyes IOP elevation to ≥ 25 mmHg:15.0% eyes IOP elevation to ≥ 30 mmHg: 5.0% eyes	Anti-VEGF: 74.6% Steroids: 14.9% Laser: 10.4%
Ruiz-Moreno 2023[68] Prospective phase 4 study Multicentre (number NR) in Spain N=31, 31 eyes Follow-up: median 35.9 months	Phakic: 32.3% Duration of DMO: 14.6 (10.2) years HbA1c: 6.8 (0.9) % CRT: 474.0 (135.1) µm BCVA: 56.1 (12.3) letters Prior treatment Laser: 61.3% Corticosteroid: 64.5% Anti-VEGF: 83.9%	Month 24 BCVA: 62.4 (17.0) letters CST: 334 (135.6) µm Cataract in study eye: 16.1% IOP increase ≥10 mmHg: 16.1%	Additional treatment 61.3% Anti-VEGF: 78.9% Corticoid: 57.9%

Parker 2019[69a] Retrospective case series 1 UK centre (Medisoft audit data) N=31, 37 eyes Follow-up: minimum 36 months in 23 eyes Funding: NR	Phakic:0 Duration of DMO: 6.5 years HbA1c: NR CMT: 550 (167) µm VA: 53 (20) letters Prior treatment: NR	3 years VA: 58 (14) letters CMT: 357 (162) µm IOP controlled by local therapy: 8 eyes Surgery for raised IOP: 1 Vitreous haemorrage:1 Subconjunctival haemorrhages: 2	Anti-VEGF: 70% Laser: 5%
Putri 2018[70a] Retrospective case series 1 UK centre N=26, 26 eyes Follow-up: ≥ 36 months Funding: NR	Phakic: NR Duration of DMO: 20.4 (11.8) years HbA1c: NR CRT: 568 (164) µm BRVA: 40.1 (21.4) letters Prior treatment: NR	3 years BRVA: increase of 8.2 (20.2) letters CRT: reduction of 175 (209) µm IOP ≥21.0 mmHg: 50% New or change in IOP-lowering drops: 34.6% Trabeculectomy: 3.8%	Anti-VEGF: 38.5% Laser: 11.5%
Dexamethasone studies			
Faes 2023[48] Retrospective case series 1 UK centre N=240 Follow-up: 6 months Funding: Abbvie and NIHR	Phakic: 29.2% Duration of DMO: NR HbA1c: NR CRT: 420 µm (SD 142) BCVA: 56.0 (16.3) letters Prior treatment Laser: NR% Corticosteroid: NR% Anti-VEGF: 100%	BCVA: 57.1 letters (SD 16.2) BCVA change: 1.18 letters (SD 11.1) CRT µm: 412 (SD 146) CRT change: -24.2 µm (SD 152) IOP ≥25 mmHg: 19 (7.9%) IOP ≥35 mmHg: 1 (0.4%) IOP ≥10 mmHg increase from baseline 0 (0%) IOP-lowering medication: 7.9% Cataract surgery: 21.4% of phakic eyes	Retreatment anticipated and administered in those who failed to sustain a positive response (n=119) before VA benefit was lost: 55/119 (46%) [23% of whole population]: Anti-VEGF: 5.4% Dexamethasone: 13.3%
Lam 2015[44] (CHROME) Retrospective case series 10 Canadian centres	Phakic: 32.4% Duration of DMO: mean NR, 94.1% ≥12 months HbA1c: NR CRT: 450.4 µm (SE 26.0)	Peak mean change in BCVA logMAR, phakic eyes: -0.6 (SD 0.6) Peak mean change in BCVA logMAR, pseudophakic eyes: 1.4 (SD 0.5)	Repeat DEX implant: 44.1% Systemic steroids: 0 Any other treatment/procedure: 41.2%

All indications: N=101, 120 eyes DMO: n=24, 34 eyes Follow-up: not reported (minimum 3 months) Funding: Allergan Inc	BCVA logMAR: 0.60 (SE 0.07) Prior treatment Laser: 55.9% Corticosteroid: 0% Anti-VEGF (bevacizumab): 47.1%	Peak mean change in CRT: -190.9 µm (SD 23.5) Increased IOP: 25% Cataract surgery: 27.3% of phakic eyes	
Malcles et al 2017[74] (Reldex Study) Retrospective case series 2 French centres DMO: n=89,128 eyes Follow-up: mean 16 (1-40) months Funding: NR	Phakic: 44.5% Duration of DMO: 24.7 (2–108) months HbA1c: 7.7 CRT µm: 450 (SD 175.3) BCVA: 50.5 (SD 20.8) letters Prior treatment Laser: 16.4% Corticosteroid: 15.6% Anti-VEGF: 70.3%	BCVA At 2 years: 56.0 (95% CI, 51.4–60.6) letters At 3 years: 60.6 (95% CI, 52.0–69.2) letters Phakic mean change NR (state no significant difference to pseudophakic) CRT At 2 years: 377 µm At 3 years: 280 µm Cataract surgery: 47% of phakic eyes IOP ≥25 mmHg at any visit: 10.2% IOP ≥10 mmHg from baseline: 19%	Mean DEX implants: 3.6 (95% CI, 3–4) Focal laser: 0 Anti-VEGF: n=7
Singer 2018 (REINFORCE study) Prospective Case series 18 USA centres N=177, 180 eyes Follow-up: NR Funding: Allergan plc	Phakic: 29.4% Duration of DMO: >2 years 43.3% HbA1c: mean NR CRT µm: 424.6 (SD138.2) BCVA: 54.4 letters Prior treatment Laser: 35.6%	Mean change BCVA, area under the curve: +3.6 letters (SD 9.0) BCVA improved by 10 letters: 57.6% BCVA improved by 15 letters: 36.0% CRT mean (SD) maximum change during the study: −137.7 (119.6) µm (95% CI, −158.15, −117.29) IOP increased: 6.2%	Mean DEX implants: 2.0 (SD 1.1) Additional intravitreal injections: 45.0%
Rosenblatt et al 2020[64] (European DME Registry Study) Retrospective case series 25 centres in 8 European countries and Israel	Overall group Phakic: 60.3% Duration of DMO: mean 24.3 (SD 28.8) months HbA1c: 7.69 (SD 1.18) CRT µm: 498 (SD 139)	BCVA improvement 15 letters: 22.7% BCVA improvement 10 letters: 37.8% BCVA reduction 15 letters: 7.6% BCVA reduction 10: 12.5% Mean change in BCVA: 6.8 (SD 11.1) letters	762 injections in 340 eyes mean DEX injections per eye: 2.24 (SD 1.11) mean DEX injection per patient (range, 2 -8)

DMO: n=287, 340 eyes Follow-up: mean 1.7 (SD 0.8) years Funding: NR Analysis also undertaken by injection series (2 or more DEX injections) but not extracted here n=150, 171 eyes Follow-up: mean 20 months	BCVA: 61.9 (SD 13.5) letters Prior treatment Laser: 83.7% Corticosteroid: 17.6% Anti-VEGF: 94.1% **Injection series analysis set** Phakic: 63.7% Duration of DMO: 27.0 months HbA1c: 7.67 CRT µm: 519.2 BCVA: 57.46 letters Prior treatment Laser: 83.1% Corticosteroid: 15.3% Anti-VEGF: 81.4%	Mean change in CMT: -174 (SD 171) µm Increase IOP >10 mmHg: 6.8% Increase IOP >35 mmHg: 0.9% **Injection series analysis set** BCVA improvement 15 letters: 20.5% BCVA improvement 10 letters: 35.7% BCVA reduction 15 letters: 7% BCVA reduction 10: 12.3%	Rescue therapy within 6 months of follow-up: 8.0% of 762 injections Laser: 67.2% Steroid: 1.6% Anti-VEGF: 26.2% Other: 5.0% **Analysis by series:** 444 injections in 171 eyes Mean DEX injections per eye Injections: 2.60 (SD 1.0) Rescue therapy: 18.7% Laser: 65.9% Steroid: 2.3% Anti-VEGF: 25.0% Other: 6.8%
Lau 2021[76a] Retrospective case series 1 UK centre DMO: n=74, 89 eyes Follow-up: NR Funding: NR	Phakic: NR Duration of DMO: NR HbA1c: NR CRT µm: NR BCVA (letters): 1 implant: 55.2 2 implants:54.1 3 implants: 54.8 Prior treatment Laser: NR Corticosteroid: NR Anti-VEGF: NR	BCVA change at 24 months 1 implant: 1.23 2 implants: -1.2 3 implants: 9.88 CRT change at 24 months 1 implant: 78.91 2 implants: 102.53 3 implants: 189.00 IOP change (mmHg) at 24 months 1 implant: -0.766 2 implants: 2.47 3 implants: 2.13	NR
Sepetis 2018[77a] Retrospective case series 1 UK centre DMO: n=25	Phakic: 0 Duration of DMO: 30 months HbA1c: NR	VA at 18 months: 65.6 (SD 11.85) letters CRT at 18 months: 321.5 (SD 71) µm Received ‘drops’ to lower IOP: n=7	Mean implants at 18 months: 3.6 Ranibizumab: 3 eyes

Follow-up: NR Funding: NR	CRT µm: 436.8 (range 330-748) VA: 63.8 letters (range 35-76) Prior treatment Laser: NR Corticosteroid: 3 eyes Anti-VEGF: 10 eyes		

Table 10. JBI checklist for case series: Fluocinolone studies

Checklist questions	Bailey 2022[37]	Dobler 2023[40]	Khoramnia 2023[38]	Holden 2017[46]	Alfaqawi 2017[47]	Faes 2023[48]	Lam 2015[44]
1. Were there clear criteria for inclusion in the case series?	Unclear	Yes	Yes	Yes	Yes	Yes	Yes
2. Was the condition measured in a standard, reliable way for all participants included in the case series?	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
3. Were valid methods used for identification of the condition for all participants included in the case series?	Unclear	Unclear	Unclear	Unclear	Yes	Unclear	Unclear
4. Did the case series have consecutive inclusion of participants?	Unclear	Unclear	Unclear	Unclear	Yes	Unclear	Unclear
5. Did the case series have complete inclusion of participants?	Unclear	No – 31 of 60 eyes included	Unclear	Unclear	Unclear	Unclear	Unclear
6. Was there clear reporting of the demographics of the participants in the study?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
7. Was there clear reporting of clinical information of the participants?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
8. Were the outcomes or follow-up results of cases clearly reported?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
9. Was there clear reporting of the presenting site(s)/ clinic(s) demographic information?	No	No	No	No	No	Yes	No
10. Was the statistical analysis appropriate?	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Table continued on next page

Checklist questions	Augustin 2020[54]	Panos 2020[52]	Eaton 2019[80]	Ruiz-Moreno 2023[68]
1. Were there clear criteria for inclusion in the case series?	Yes	Yes	Unclear	Yes
2. Was the condition measured in a standard, reliable way for all participants included in the case series?	Unclear	Unclear	Unclear	Yes
3. Were valid methods used for identification of the condition for all participants included in the case series?	Unclear	Unclear	Unclear	Yes
4. Did the case series have consecutive inclusion of participants?	Unclear	Unclear	Unclear	Unclear
5. Did the case series have complete inclusion of participants?	Unclear	Unclear	Unclear	Unclear
6. Was there clear reporting of the demographics of the participants in the study?	Yes	Yes	Yes	Yes
7. Was there clear reporting of clinical information of the participants?	Yes	Yes	Yes	Yes
8. Were the outcomes or follow-up results of cases clearly reported?	Yes	Yes	No	Yes
9. Was there clear reporting of the presenting site(s)/ clinic(s) demographic information?	No	No	No	No
10. Was the statistical analysis appropriate?	Yes	Yes	Unclear	Yes

Table 11. Quality assessment – JBI checklist for case series: Dexamethasone studies

Checklist questions	Faes 2023[48]	Lam 2015[44]	Malclès 2017[74]	Rosenblatt[64]
1. Were there clear criteria for inclusion in the case series?	Yes	Yes	Yes	Yes
2. Was the condition measured in a standard, reliable way for all participants included in the case series?	Unclear	Unclear	Unclear	Unclear
3. Were valid methods used for identification of the condition for all participants included in the case series?	Unclear	Unclear	Unclear	Unclear
4. Did the case series have consecutive inclusion of participants?	Unclear	Unclear	Yes	Yes
5. Did the case series have complete inclusion of participants?	Unclear	Unclear	Unclear	Unclear
6. Was there clear reporting of the demographics of the participants in the study?	Yes	Yes	Yes	Yes
7. Was there clear reporting of clinical information of the participants?	Yes	Yes	Yes	Yes
8. Were the outcomes or follow-up results of cases clearly reported?	Yes	Yes	Yes	Yes
9. Was there clear reporting of the presenting site(s)/ clinic(s) demographic information?	Yes	No	No	No
10. Was the statistical analysis appropriate?	Yes	Yes	Yes	Unclear

3.1.4 RWE: Steroid sequencing - Fluocinolone after trial of short-acting steroids

Two studies from the USA provide data on results of fluocinolone in eyes in which a short-acting steroid had been tried. The EAG note that this in line with practice in the USA.

- **The PALADIN study: case series of fluocinolone implant safety with a particular focus in IOP.**

PALADIN followed the indications for fluocinolone in the USA, where it is used only after a prior test treatment with a short-acting steroid to assess efficacy and effect on IOP, with the long-acting steroid being used if short-acting steroids are well-tolerated with no concerns about IOP. In PALADIN, the preceding steroid was mainly dexamethasone, with some triamcinolone.

The aim of the study was to assess the effect of fluocinolone on IOP and to see how often the short-term challenge failed to predict IOP problems with fluocinolone. The 2-year results are reported by Mansour et al (115 eyes)[55] and the 3-year results (94 eyes) mainly by Singer et al[43] with additional data by Roth et al and Sheth et al.[78, 79] Only 10% of eyes were phakic.

Singer et al report that by 3 years, CRT had declined by 61 microns from baseline and BCVA had risen by 3.6 letters – so maintaining the previous effect of dexamethasone.[43] The mean IOP remained stable throughout the 3-years with surgical intervention for raised IOP in under 2%. IOP-lowering eye drops were required at some time in the 36 months by 38% of eyes. In 22% of eyes, raised IOP was not predicted by the short-term steroid challenge, meaning that continued monitoring is required. No details are provided regarding previous treatment with anti-VEGF drugs, however Mansour and colleagues[55] state that corticosteroids are second-line treatments after an insufficient response to anti-VEGF drugs. (Therefore, PALADIN aligns to the NICE scope population for this appraisal).

- **The USER Study: US Retrospective chart Review in patients receiving fluocinolone.**

The USER study was carried out in four centres.[80] Patients had DMO for a mean of 4-years before receiving fluocinolone and had been treated with anti-VEGF drugs (77%), laser (50%) or short-acting steroids (56%) which aligns to the NICE scope population for this appraisal (chronic DMO insufficiently response to first-line treatments, see Section 2). Eaton and colleagues suggest that eyes treated according to the US indication for fluocinolone (after a "challenge" with short-acting steroids with fluocinolone used if no problems with raised IOP) will have significantly fewer problems with IOP than seen in the FAME trial. Data were collected for 36 months before, and 24 months after fluocinolone administration. The study reported that VA was maintained, and CRT fell from baseline 370 microns to 323 at 18 months. The proportion of eyes with CRT < 300 rose from 18% before fluocinolone to 69% at 18 months. (Eaton et al provide data to 24 months but numbers by then were very low so it is safer to use data to only 18 months.) The use of anti-VEGF and other treatments fell markedly after fluocinolone was used, from every 3-months to only every 14 months.

3.1.4.1 Treatment switching RWE

- A consensus article by eight UK ophthalmologists,[81] suggested another approach to steroid treatment, starting with an injection of dexamethasone then switching to fluocinolone if CRT has reduced by 20% or more. Downey and colleagues consider both efficacy and the burden of treatment. Their suggestion of trying dexamethasone first means that if eyes do not respond, it would not be repeated, thereby reducing the risk of AE. It might also identify patients likely to have problems with raised IOP. If there was a spike in IOP after the first dexamethasone implant, it would not be repeated and the effect would wear off after a few months, whereas once fluocinolone is implanted the effect would last for 3 years. In patients whose eyes did not

respond to steroids, the cost of six months of dexamethasone would be incurred compared to three years of fluocinolone. The EAG note that The Downey consensus group was funded by Alimera.

- The system of starting with dexamethasone then switching to fluocinolone has been reported in several studies from Europe. Chronopoulus and colleagues from Germany reported a series of 27 consecutive eyes with DMO poorly responsive to anti-VEGF treatment.[71] Most had been treated with dexamethasone (some with triamcinolone) and had an initial good response (not defined) but had relapsed after 3-4 months. Fluocinolone was introduced to provide longer term effects. BRVA improved from 49 letters at baseline to 60 at 12 months and 65 at 24 months.
- Rousseau and colleagues from France investigated the timing of a switch from dexamethasone to fluocinolone in patients who's DMO had been adequately controlled by repeated dexamethasone injections.[72] Authors noted that the action of dexamethasone was faster, being achieved at 3-months than that of fluocinolone (11 months). However, their 55 eyes required repeated dexamethasone injections. Therefore, fluocinolone was a way of reducing the burden of treatment. Rousseau and colleagues wanted to administer fluocinolone before the effect of dexamethasone was wearing off, so they implanted fluocinolone one month after the last dexamethasone injection. As expected, there were no changes in CMT (stable around 300 microns) of BCVA (an increase from 62.3 to 64.6 is reported as statistically significant but is not clinically so). There was no change in mean IOP.
- Baillif and colleagues reported on 113 eyes switched from dexamethasone to fluocinolone in 30 centres (one centre, Nantes, France also included patients in the Rousseau study but from an earlier time).[73] All had been treated with dexamethasone and responded but BCVA improved slightly after the switch to fluocinolone (54 to 60). At month 12, most 65% of eyes were stable but 35% had gained 10 or

more letters. CMT and IOP were also stable. Patients were started on fluocinolone at an average of 11 weeks after the last dexamethasone injection but 75% were started within 8 weeks. Additional treatments (anti-VEGF drugs or repeated dexamethasone) were required in 33%, more commonly in those receiving fluocinolone a longer time after dexamethasone.

- Vaz-Pereira and colleagues report a case series with switching from short-term dexamethasone to longer-term fluocinolone in 44 eyes in 36 patients who had not responded sufficiently on anti-VEGF treatment and had progressed to dexamethasone.[82] Patients received an average of 1.9 dexamethasone injections (range 1 to 4). The interval between last dexamethasone and fluocinolone insertion is not reported. BCVA improved from baseline 42 letter to 57; CRT fell by 120 microns and IOP was stable.

In summary, there is a reasonable evidence base to support the proposal by Downey and colleagues[81] that after insufficient response to anti-VEGF drugs, steroid treatment should begin with dexamethasone. If that is successful and safe, then a switch to fluocinolone will reduce the burden of treatment.

3.1.5 Summary of RWE

There have been no new RCTs of fluocinolone in DMO. The RWE studies presented in this report are partially represented in the CS. The EAG carried out a rapid search to assess the volume of new evidence and identified a second systematic review by Kodjikian and colleagues[56] which included some studies excluded in the Fallico review.[45] However, the EAG conclude that neither review is up-to date.

Overall, the EAG view is that the RWE provides convincing evidence that in eyes with DMO that have not responded sufficiently to previous treatment, (usually anti-VEGF drugs), fluocinolone improves outcomes for patients. Many patients have improvements (e.g., over 10 or 15 letter

gains in BCVA), others have stable VA, but some do lose vision. Therefore, improved treatment of DMO is required, or better diabetes care to prevent it. The EAG notes the evidence for fluocinolone to be used after a trial of a short-acting steroid. In UK practice this would be dexamethasone as triamcinolone would be used off-licence. This approach seems to have advantages in that fluocinolone is used only in eyes that have responded to a short-acting steroid without serious elevation of IOP.

3.1.5.1 Combination treatment of DMO – a role for laser?

In their submission, the company compared fluocinolone only with dexamethasone. This is in line with the rules for cost-comparison submissions, in which the drug being appraised need only be compared with one already approved drug.

However, the EAG note that there could be other comparators. NICE recommended anti-VEGF drugs rather than laser when CRT was > 400 microns, because laser is less effective in thicker retinas.[3] In the MEAD trial[16] the CRT at baseline in the 0.7mg group was 463 microns. The thickness fell by 111.6 during the trial. In the FAME trial[17], baseline CRT was 461. It fell rapidly (a detectable change by the end of first week) to 318 at months 6, 293 at month 24 and 280 at month 36. In sham eyes the corresponding figures were 396, 340 and 309.

The falls in CRT suggest that laser becomes an option after steroid treatment. For example, if the first injection of dexamethasone reduces CRT below 400, patients could then have laser treatment. If CRT rises again, the dexamethasone could be repeated. Therefore, patients might alternate between dexamethasone and laser, or have other combinations, during the three-year period, reducing the cost. Because fluocinolone lasts for approximately three years, there would be no savings in the first three years.

3.2 *Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison*

No phase III RCTs were identified that investigated the efficacy and safety of fluocinolone 0.19 mg for DMO. Therefore, a meta-analysis was not performed. The following section details the ITC methods employed by the company to compare fluocinolone 0.19 mg from the FAME[17] trials to dexamethasone 0.7 mg in the MEAD[16] trials.

3.2.1 Key participant characteristics at baseline in the populations used in the company's ITC from FAME[17] and MEAD[16]

CS section B.3.9.3.1 reports a comparison of baseline characteristics between the cohort of the FAME[17] trial used in the ITC (see Section 3.2.4) and the treatment experienced subgroup of MEAD[16], and presents key demographic and baseline characteristics in CS Table 28. Note that the treatment experienced subgroup of MEAD[16] were those who had either laser or medical treatment and were analysed in the publication by Augustin et al.[83] The EAG have summarise key baseline characteristics from the FAME[17] and MEAD[16] populations in Table 11.

The CS states that in general the characteristics were similar between the trials but there were some differences with greater central retinal thickness in FAME[17], fewer had a phakic lens and more who had received prior laser therapy. As described in Section 3.1, these were three of the five variables the CS identified as potential treatment effect modifiers (duration of DMO, prior DMO treatment [specifically, a history of laser therapy], presence of cataract, baseline CRT, baseline BCVA) and were assessed for imbalance statistically using the overall population rather than by the treatment arms.

While the EAG would not rely on statistical analysis of differences between baseline characteristics it does appear that these three factors were different between the populations in the trials (see Table 11). The impact of these imbalances is unclear. The company undertook analyses matching on these

factors which did not reduce the effective sample size (ESS) substantially (See Section 3.2.1.1.2).

The ERG considers changes in glycaemic control, changes in blood pressure control and severity of cataract at baseline to also be potential effect modifiers. HbA1c at baseline appeared balanced between the trials. Data on the additional treatment effect modifiers were requested at clarification (A10 and A11) however, the company replied that the absence of data on the severity of cataract, changes in glycaemic control, and changes in blood pressure control over the three-year trial period are not available for MEAD and an analysis is not possible. The company also reports that these factors are not anticipated to bias results in the presented ITC. No data for these potential effect modifiers from FAME were available in the CS, the clinical study report, or the clarification response.

The EAG also notes that the proportion of patients having received intravitreal corticosteroid were lower in the FAME[17] trial, and it is possible that prior intravitreal anti-VEGF treatment rates were also different between the two cohorts. However, this cannot be established as data were reported to be not estimable for FAME[17] due to a high proportion of missing data. The observed differences between the proportions receiving prior laser, corticosteroid and anti-VEGF treatments are likely due to the different eligibility criteria of the cohorts being compared, where the MEAD[16] subgroup analysis included those with prior laser, or 'medical treatment' and the FAME[17] trial required all participants to have received prior laser.

The CS (Section B.3.11, Conclusions) reports that the CS clinical experts consulted during the development of the ITC stated that treatment experience is likely to be a treatment effect modifying factor for both fluocinolone and dexamethasone intravitreal implants. However, the CS analysis of potential treatment effect modifiers refers to specifically a history of laser therapy as a

treatment effect modifying factor. The EAG note that other treatments have not been considered as treatment effect modifiers in the CS analyses.

The EAG summarise key baseline characteristics from the FAME and MEAD populations in Table 12.

Table 12. Key participant characteristics at baseline in the populations used in the company's ITC from FAME[17] and MEAD[16]

	FAME[17] (ITC cohort)			MEAD[16] (TE cohort)		
	FAc 0.19 mg	Treated sham	All	DEX 0.7 mg	Treated sham	All
N	221	118	339	247	261	508
Demographics						
Mean age (SD), yrs	63.7 (9.4)	62.0 (9.3)	63.1 (9.4)	62.5 (9.5)	63.0 (8.3)	62.8 (8.9)
Male, n (%)	134 (60.6)	73 (61.9)	207 (61.1)	150 (60.7)	168 (64.4)	318 (62.6)
Caucasian, n (%)	172 (77.8)	89 (75.4)	261 (77.0)	188 (76.1)	192 (73.6)	380 (74.8)
Diabetes characteristics						
Diabetes Type, n (%)						
Type 1	20 (9.0)	6 (5.1)	26 (7.7)	27 (10.9)	23 (8.8)	50 (9.9)
Type 2	197 (89.1)	112 (94.9)	309 (91.2)	220 (89.1)	238 (91.2)	458 (90.2)
Not recorded	4 (1.8)	-	4 (1.2)	-	-	
Mean (SD) duration of diabetes, yrs	16.4 (9.8)	15.2 (8.9)	16.0 (9.5)	16.4 (8.7)	16.2 (9.7)	16.3 (9.2)
Mean Hba1c % (SD)	7.4 (1.2)	7.4 (0.9)	7.4 (1.1)	7.5 (1.1)	7.5 (1.0)	7.5 (1.0)
DMO characteristics						
Mean (SD) duration of DMO yrs	2.5 (2.8)	3.2 (4.4)	2.8 (3.4)	2.3 (2.2)	2.7 (2.4)	2.5 (2.3)

	FAME[17] (ITC cohort)			MEAD[16] (TE cohort)		
	FAc 0.19 mg	Treated sham	All	DEX 0.7 mg	Treated sham	All
Mean BCVA letter score	55.6 (9.3)	55.5 (9.7)	55.5 (9.4)	55.2 (9.6)	56.1 (9.1)	55.7 (9.3)
Mean CRT, µm (SD)	494 (128)	495 (125)	495 (127)	478 (153)	472 (131)	474 (142)
Lens status, n (%)						
Phakic	139 (62.9)	75 (63.6)	214 (63.1)	182 (73.7)	179 (68.6)	361 (71.1)
Pseudophakic	82 (37.1)	43 (36.4)	125 (36.9)	65 (26.3)	82 (31.4)	147 (28.9)
Prior DMO treatment, n (%)						
Laser	221 (100)	118 (100)	339 (100)	231 (93.5)	243 (93.1)	474 (93.3)
Intravitreal corticosteroid	41 (18.6)	20 (16.9)	61 (18.0)	58 (23.5)	61 (23.4)	119 (23.4)
Intravitreal anti-VEGF	NE*	NE*	NE*	25 (10.1)	26 (10.0)	51 (10.0)

Adapted from CS Table 28

*Values were not estimable due to a high proportion of missing data.

Abbreviations: BCVA, best-corrected visual acuity, CRT, central retinal thickness, DEX 0.7 mg, dexamethasone intravitreal implant 0.7 mg, DMO, diabetic macular oedema, FAc 0.19 mg, fluocinolone acetonide intravitreal implant 0.19 mg, NE, not estimable, SD, standard deviation, TE, treatment experienced, VEGF, vascular endothelial growth factor.

3.2.1.1 Phakic eyes subgroup

The EAG requested an analysis of the ITC in people with phakic eyes only in clarification A10 (discussed further in Section 3.2.1.1.1). The baseline characteristics for this additional ITC which was of a phakic population treated with fluocinalone compared with a phakic and pseudophakic population treated with dexamethasone can be seen in Table 13. The company noted that there were differences between the 'all' populations of both trials in the mean age at baseline, the mean duration of diabetes, and the mean CRT. The EAG also notes that the proportions having received laser were higher in the phakic ITC cohort of FAME and the proportion having prior intravitreal

corticosteroid were lower in phakic ITC cohort of the FAME trial. It is not possible to establish if prior intravitreal anti-VEGF treatment rates differed between the two cohorts.

Table 13. Key participant characteristics at baseline from FAME phakic eyes and MEAD phakic and pseudophakic eyes

	FAME (phakic ITC cohort)			MEAD (TE cohort)		
	FAc 0.19 mg	Treated sham	All	DEX 0.7 mg	Treated sham	All
N	139	75	214	247	261	508
Demographics						
Mean age (SD), yrs	60.7 (9.1)	60.2 (8.5)	60.6 (8.9)	62.5 (9.5)	63.0 (8.3)	62.8 (8.9)
Male, n (%)	92 (66.2)	48 (64.0)	140 (65.4)	150 (60.7)	168 (64.4)	318 (62.6)
Caucasian, n (%)	101 (72.7)	56 (74.7)	157 (73.4)	188 (76.1)	192 (73.6)	380 (74.8)
Diabetes characteristics						
Diabetes Type, n (%)						
Type 1	12 (8.6)	5 (6.7)	17 (7.9)	27 (10.9)	23 (8.8)	50 (9.9)
Type 2	124 (89.2)	70 (93.3)	194 (90.7)	220 (89.1)	238 (91.2)	458 (90.2)
Not recorded	3 (2.2)	-	3 (1.4)	-	-	
Mean (SD) duration of diabetes, yrs	14.8 (9.4)	13.8 (8.0)	14.4 (8.9)	16.4 (8.7)	16.2 (9.7)	16.3 (9.2)
Mean Hba1c % (SD)	7.5 (1.2)	7.3 (0.9)	7.4 (1.1)	7.5 (1.1)	7.5 (1.0)	7.5 (1.0)
DMO characteristics						
Mean (SD) duration of DMO, yrs	2.4 (2.8)	2.9 (4.6)	2.6 (3.6)	2.3 (2.2)	2.7 (2.4)	2.5 (2.3)
Mean BCVA letter score	55.6 (9.5)	56.2 (9.7)	55.8 (9.6)	55.2 (9.6)	56.1 (9.1)	55.7 (9.3)
Mean CRT, µm (SD)	491 (125)	490 (119)	491 (123)	478 (153)	472 (131)	474 (142)
Lens status, n (%)						
Phakic	100%	100%	100%	182 (73.7)	179 (68.6)	361 (71.1)
Pseudophakic	0	0	0	65 (26.3)	82 (31.4)	147 (28.9)
Prior DMO treatment, n (%)						
Laser	139 (100)	75 (100)	214 (100)	231 (93.5)	243 (93.1)	474 (93.3)
Intravitreal corticosteroid	21 (15.1)	10 (13.3)	31 (14.5)	58 (23.5)	61 (23.4)	119 (23.4)
Intravitreal anti-VEGF	NE[a]	NE[a]	NE[a]	25 (10.1)	26 (10.0)	51 (10.0)

From Clarification Table A10.1. [a]Values were not estimable due to a high proportion of missing data.

3.2.2 ITC method: Naïve comparison

The first ITC method used in the CS was an adaptation of the Bucher method.[84] The Bucher method involves calculating the weighted average of effect sizes from the identified studies, considering sample size and variance. It provides a pooled estimate while giving greater weight to studies with larger sample sizes and smaller variances. The naïve comparison used by the company follows a similar path whereby the indirect estimate of fluocinolone vs dexamethasone equals the direct estimate of fluocinolone vs sham minus the direct estimate of dexamethasone vs sham and the variance of the indirect estimate is the sum of the direct estimates of fluocinolone vs sham and dexamethasone versus sham.

Bucher's method relies on the assumption that the two studies in the comparison are similar and that true underlying effect size between studies do not differ. The company acknowledges that due to the heterogeneity likely present between the studies, the results of naïve analysis are liable to bias. **The EAG agrees with this conclusion that the naïve analysis are subject to bias.**

3.2.1 ITC method: Adjusted comparison

This method used the same approach as the naïve analysis but using the cohort of FAME[17] that followed the more limiting inclusion criteria of MEAD:[16] (1) BCVA between 34 and 68 letters, inclusive; (2) CRT ≥ 300 μm; and (3) HbA1c ≤ 10.0%. A censoring algorithm was applied which discontinues patients when they started to receive additional treatment for DMO. Estimates of fluocinolone versus sham were recalculated on this ITC cohort and then the indirect estimate between fluocinolone and dexamethasone were calculated.

3.2.1 ITC method: Matching-adjusted indirect comparison

The matching-adjusted indirect comparison (MAIC) was conducted to account for imbalances in treatment effect modifiers (TEMs) between FAME[17] and MEAD.[16] It involves adjusting for important baseline characteristics by matching patients in different studies, in this case matching FAME to MEAD,

allowing for a more meaningful comparison of treatment outcomes. As individual patient data was available for FAME, participants from FAME were weighted so that important TEMs were comparable to the aggregate data from MEAD. **The EAG agree that this approach was the most suitable (see Section 4.12).**

3.2.1.1 Feasibility

The company did not conduct a full feasibility assessment of the ITC methods presented in the submission due to time constraints. The company provided a report of the ITC which provided detail of the methods used as response to CQ A12, however, this did not differ considerably from what was presented in the original CS. **The EAG could not critique the feasibility of the ITC methods further.**

3.2.1.2 Treatment effect modifiers

The TEMs were identified by three UK clinicians with experience in treatment DMO. They were asked to list potential TEMs and the directionality of the impact. The five TEMs identified by the three clinicians were duration of DMO, prior DMO treatment, presence of cataract, baseline CRT and baseline BCVA. These are detailed in Table 7 of CS D.1.2, including the expected effect of the TEM, if there was an imbalance between FAME[17] and MEAD[16] with respect to this TEM, and how they were adjusted for in the MAIC. As data for presence of cataract was not available, the variable lens status (phakic vs pseudo-phakic) was used in its place as a proxy.

The EAG asked the company for clarification on which clinician identified a characteristic as a potential TEM which was provided in Table A13.1 of CQ responses question A13. In this table, clinicians were asked which characteristics they believed would be TEMs but only due to correlations with other factors.

It would have been useful to have assessed the effect of changes in HbA1c and blood pressure over the 3-year period, but the EAG acknowledges that the necessary data were not collected and therefore, is not available. When

the FAME[17] trial was performed, anti-VEGF drugs were not generally available, so patients had not received them. We now have the situation where intravitreal steroids are being considered after anti-VEGF treatment has proved insufficiently effective. However, given the uncertainty surrounding why some eyes respond to anti-VEGFs while others do not, it is not possible to identify any effect modifiers related to that.

It would have been useful to know if any significant proportion of patients in the FAME[17] trial were on rosiglitazone or pioglitazone; and if so whether those drugs (which can precipitate DMO) were stopped. Rosiglitazone is no longer used.

However, any improvements in DMO due to improved glycaemic control or stopping the TZD drugs, would have applied to both arms. As noted earlier, good glycaemic control and effective treatment of blood pressure reduces the risk of DMO so there is scope for prevention. In addition, earlier diagnosis and treatment with laser may reduce the need for anti-VEGF and steroid drugs.

Significant imbalances between the studies with regards to TEMs were identified if the between-group difference had a p-value of less than 0.05.

3.2.1.3 Statistical methods employed to match populations

The weighting and matching procedure used the ‘maic’ package in R version 4.2.2. The base case MAIC-reweighted ITC cohort was matches based only on CRT and lens status, two of the three TEMs where significant imbalances existed between FAME[17] and MEAD.[16] An adjusted-MAIC was performed as a scenario analysis which reweighted the FAME cohort based on all TEMs, whether they were imbalanced or not with respect to MEAD.

Both MAIC cohorts were used to recalculate the key efficacy and safety estimates from FAME and then compared to MEAD in the ITC.

3.2.1 Results of the ITCs

Results of the base case ITC, MAIC when matching on imbalanced effect modifiers only and censoring at the point of additional therapy, between fluocinolone and dexamethasone are presented in Table 14. **For most ITC methods in most of the outcomes, there were no statistically significant differences between fluocinolone and dexamethasone.**

Table 14. Results of the ITC analysis tabulated from the figure of results presented in CS Document B and Appendix J

	Treatment difference				
Outcome	**Estimate**	**LCI**	**UCI**	**P-value**	**Treatment favoured numerically**
Proportion of patients achieving ≥15-letter BCVA improvement from baseline to EOT	2.4	-8.6	13.4	0.667	FAc
Mean change from baseline in BCVA letter score from baseline to EOT	1.6	-3.3	6.5	0.522	FAc
Mean change in CRT from baseline to EOT	-10.9	-70.9	48.9	0.722	DEX
Proportion of patients experiencing serious ocular AEs	-1.4	-6.6	3.8	0.599	FAc
Proportion of patients experiencing IOP-related AEs	-8.0	-18.5	2.5	0.136	FAc
Proportion of patients experiencing cataract-related AEs (in phakic eyes)	-10.5	-26.6	5.6	0.201	FAc

FAc fluocinolone DEX dexamethasone

The EAG note that population analysed in this ITC were treatment-experienced patients including eyes with both phakic and pseudo-phakic lenses. This differs from the modelled population in the economic section of the submission which were people with chronic DMO that is insufficiently responsive to available therapies who have phakic lenses (See Section 5.1.1).

The company provided an explanation for presenting this analysis in response to CQ A10; where they state that since there is limited published evidence for

dexamethasone in a phakic lens only population, the approach presented in the submission was taken.

The EAG requested that the company perform an ITC on the modelled population as part of the clarification stage, and also requested updates to the TEM that potentially affect treatment-experienced patients including eyes with both phakic and pseudo-phakic lenses. These were provided by the company in response to CQ A10 and discussed in Section 3.3.1.1 below.

3.2.1.1.1 Results in patients with phakic eyes only

3.2.1.1.2 Effective sample size (ESS)

Table A10.2 provides the ESS of the FAME ITC cohort – phakic only. The pre-weighting sample size of the fluocinolone group was 139. After adjusting on imbalanced TEMs, the ESS is 119 (86% of pre-weighting), and after adjusting based on all TEMs, the ESS reduced to 111 (80% of pre-weighting). The EAG agrees with the company that the reduction of ESS is not substantial and is acceptable. However, the reweighted characteristics of the FAME[17] cohort still differed to MEAD,[16] so these results will be biased, as the company alluded to in the clarification responses.

However, Table A10.3 from the CQ responses also presents the ESS for each ITC comparison. For several outcomes, such as change in BCVA and CRT there are large reduction in the sample size of the analysis. This is mainly attributable to missing data for patients at month 36 following the application of post-subsequent treatment censoring consistent with MEAD. Large decreases in ESS means the power of the analysis is likely to be compromised, resulting in large confidence intervals due to lower precision, challenging the interpretability of the results.

3.2.1.1.3 Direct estimates of fluocinolone versus sham after MAIC and sham-comparability

Table A10.3 from the CQ responses presents the results of direct estimates of fluocinolone vs sham from the FAS cohort, and then FAS-phakic results alongside the results of the MAIC which adjusted for imbalanced TEMs, the relevant inputs for this ITC are presented below in Table 15.

Comparing MEAD-TE to FAME-phakic for the primary outcome (proportion achieving a change in BCVA of at least 15 letters), there is a statistically significant difference in the placebo estimates as the 95% CIs do not overlap, no such difference exists when comparing MEAD-TE to FAME-phakic MAIC which is expected as the MAIC-adjusted group should conform to the MEAD-TE group. For the mean change in BCVA outcome, there are no statistically significant differences between the sham groups. For the mean change in CRT outcome. There are statistically significant differences between the sham groups of MEAD-TE and the two FAME groups, with the sham groups of the FAME subgroups reducing significantly more than the sham in MEAD.

For the comparison of the three safety outcomes, there were significant differences between the sham groups fluocinolone-phakic and MEAD-TE.

Table 15. Direct estimates of fluocinolone vs sham in FAME phakic and dexamethasone versus sham from MEAD-TE

		Intervention			Sham control		
Trial	**Outcome**	**Treatment**	**N**	**Result**	**Treatment**	**N**	**Result**
MEAD - TE	Proportion of patients 15-point letter scores at month 36	DEX 0.7 mg	247	21.5%	Sham	261	11.1%
FAS - PHAKIC		FAc 0.19 mg	236	28.4%	Sham	121	19.8%
ITC cohort - Phakic MAIC*		FAc 0.19 mg	119	25.0%	Sham	64	10.6%
MEAD - TE	Mean change from baseline in BCVA at month 36	DEX 0.7 mg	247	3.2 (8.7)	Sham	261	1.5 (7.5)
FAS - PHAKIC		FAc 0.19 mg	236	5.0 (18.8)	Sham	121	2.2 (14.4)
ITC cohort - Phakic MAIC*		FAc 0.19 mg	52	7.4 (10.4)	Sham	11	2.5 (7.7)
MEAD - TE		DEX 0.7 mg	247	-126 (131)	Sham	261	-39 (121)

FAS - PHAKIC	Mean change from baseline in CRT at month 36	FAc 0.19 mg	236	-167 (203)	Sham	121	-128 (217)
ITC cohort - Phakic MAIC*		FAc 0.19 mg	50	-168 (143)	Sham	10	-78 (136)
MEAD - TE	Proportion of patients experiencing serious ocular AEs	DEX 0.7 mg	247	6.9%	Sham	261	0.8%
FAS - PHAKIC		FAc 0.19 mg	236	10.6%	Sham	121	5.8%
ITC cohort - Phakic MAIC*		FAc 0.19 mg	119	6.9%	Sham	64	0.9%
MEAD - TE	Proportion of patients experiencing IOP-related AEs	DEX 0.7 mg	247	38.1%	Sham	261	4.6%
FAS - PHAKIC		FAc 0.19 mg	236	35.2%	Sham	121	11.6%
ITC cohort - Phakic MAIC*		FAc 0.19 mg	119	30.8%	Sham	64	4.7%
MEAD - TE	Proportion of patients experiencing cataract-related AEs (in phakic eyes)	DEX 0.7 mg	182	70.3%	Sham	179	20.1%
FAS - PHAKIC		FAc 0.19 mg	236	81.4%	Sham	121	50.4%
ITC cohort - Phakic MAIC*		FAc 0.19 mg	119	62.7%	Sham	64	24.3%
FAc fluocinolone DEX dexamethasone FAS full analysis set							

* Adjusted for imbalanced EMs with censoring

As the sham-responses between MEAD-TE and FAS-phakic MAIC were comparable, with no significant differences between them for all six outcomes analyses. This highlights that the matching process successfully balanced the baseline characteristics, including the placebo response, between the sham arms of the two-trial subgroup, which allows for a more accurate interpretation of fluocinolone versus dexamethasone.

3.2.1.1.4 Results

The main results of the new ITC which compared the efficacy and safety of fluocinolone versus dexamethasone in the phakic-eyes only subgroup of FAME to the treatment-experienced subgroup of MEAD are presented in Table 16. For brevity, these only include the results for the main ITC, the MAIC when matching on imbalanced TEMs only and with censoring at the point of additional therapy.

Table 16. Results of the phakic-eyes only ITC tabulated from response to CQ A10 (MAIC adjusted for imbalanced TEMs only and with censoring)

	Treatment difference				
Outcome	Estimate	LCI	UCI	P-value	Treatment favoured numerically
Proportion of patients achieving ≥15-letter BCVA improvement from baseline to EOT	4.0	-9.09	17.09	0.549	FAc
Mean change from baseline in BCVA letter score from baseline to EOT	3.3	-2.51	9.11	0.266	FAc
Mean change in CRT from baseline to EOT	12.0	-98.50	122.5	0.831	FAc
Proportion of patients experiencing serious ocular AEs	-0.1	-5.98	5.78	0.973	FAc
Proportion of patients experiencing IOP-related AEs	-11.8	-28.37	4.78	0.201	FAc
Proportion of patients experiencing cataract-related AEs (in phakic eyes)	-7.5	-19.84	4.84	0.234	FAc

There were no significant differences between the results of this ITC and the original ITC which the company presented in CS document B. The only difference between the two ITCs was that the ITC result of the mean change in CRT from baseline to EOT favoured fluocinolone instead of dexamethasone (as can be seen in Table 14) but this result is not significant.

The EAG note that there were no statistically significant differences in the ITC results between fluocinolone and dexamethasone across all six outcomes.

3.2.2 Conclusions of the EAG critique of the ITC

3.2.2.1 Summary of the original MAIC

In the six outcomes analysed, the MAIC demonstrated the equivalence of fluocinolone and dexamethasone. In assessing the fluocinolone and dexamethasone groups from the FAME[17] and MEAD[16] trials through the MAIC, notable challenges emerged. Despite efforts to align baseline characteristics, differences in retreatment rules and unavailable data, especially regarding phakic eyes in MEAD[16], posed potential comparability

issues. **The ITC results, while generally showing no statistically significant differences between fluocinolone and dexamethasone, warrant cautious interpretation due to these study design disparities.** Acknowledging limitations in data availability and trial nuances is essential for a nuanced understanding of the comparative efficacy between the two treatments.

3.2.2.2 Summary of the new MAIC

The ESS in analysis for the FAME[17] ITC cohort, particularly in the phakic-only subgroup, indicates some reduction in ESS (approximately 15%) after adjustments for imbalanced TEMs. While the EAG deems the reduction acceptable, concerns arise about biased results due to reweighted cohort differences compared to MEAD.[16] Large decreases in ESS, notably in outcomes like change in CRT, may compromise analysis power, leading to imprecise results. Despite comparable sham-responses between MEAD-TE and FAS-phakic MAIC, the new ITC results show no statistically significant differences between fluocinolone and dexamethasone across six outcomes, aligning with the original ITC findings presented in CS document B. The sole difference, favouring fluocinolone in mean change in CRT, lacks statistical significance.

The following analyses from the ITC in the clinical effectiveness section of the CS was used in the company's economic analyses:

- "*No significant differences were observed between the two therapies across any of the examined efficacy and safety endpoints. In the absence of a head-to-head comparison, the findings of this report can be used to inform pharmacoeconomic assessments of the most cost-effective treatment for patients with DMO who are unsuitable for, or insufficiently responsive to non-corticosteroid treatment.*"
- As evidence that fluocinolone 0.2 mg/day is equivalent to dexamethasone is supported by the ITC, the company did not consider

any difference in effect between fluocinolone and dexamethasone in the cost-comparison.

Note, the EAG requested the data required to replicate the ITC analyses during the clarification stage, but the data required to assess the ITC in detail did not arrive in time to complete the assessment ahead of submission.

3.3 *Summary of the clinical effectiveness evidence*

In summary, the company produced a satisfactory SLR. There are no trials directly comparing dexamethasone and fluocinolone. The final two key trials; (FAME[17], and MEAD[16]) included in the CS were rated as low risk of bias.

These trials have been reviewed in previous NICE appraisals TA 301/613 and TA824, respectively. The FAME trial of fluocinolone in DMO was carried out in eyes that had not failed to respond to anti-VEGF drugs. The MEAD trial recruited a similar population. In both cases, this was because they were started before anti-VEGF drugs became available.

a. The population included in the scope for this appraisal does not match the populations in the trials, which are eyes that that have not responded sufficiently to anti-VEGF drugs.

There have been no new trials since FAME and MEAD were published.

b. However, there are now studies from routine care (i.e., RWE studies) which provide observational evidence of effectiveness and adverse effects.
c. The EAG consider that the RWE provides convincing evidence that in eyes with DMO that have not responded sufficiently to previous treatment, (usually anti-VEGF drugs), fluocinolone improves outcomes for patients. Many patients have improvements (e.g., over 10 or 15 letter gains in BCVA), others have stable VA, but some do lose vision.

The CS presented an ITC using MAIC which demonstrated the equivalence of fluocinolone and dexamethasone. The ITC focused on the FAME cohort and phakic-only subgroup. The analysis indicates a reduction in ESS of approximately 15% after adjustments for imbalanced effect modifiers. Despite concerns about potential bias compared to MEAD, the ITC reveals no statistically significant differences between fluocinolone and dexamethasone across six outcomes, supporting their equivalence in economic assessments for DMO patients.

4 Summary of the EAG's critique of cost comparison evidence submitted

4.1 *The company model structure*

The company presents a simple cost minimisation model of fluocinolone compared to dexamethasone. It has a quarterly cycle, a 6-year time horizon and discounts costs at an annual 3.5%.

The model has the option of incorporating deaths, general population mortality having a DMO multiplier applied to it. This is not within the company base case. It has minimal effect upon results, and the EAG does not consider it any further.

4.2 *Number of administrations*

Dosing for fluocinolone is based upon individual patient data from FAME ITC phakic population (N=139) (see Section 3.1.3). The values for the FAME FAS population (N=376) are presented by way of comparison. It is assumed that there are no fluocinolone administrations in years 4, 5 and 6. Dosing for dexamethasone is based upon the distribution of patients receiving a total of 1, 2, 3, 4, 5, 6 and 7 administrations during MEAD as reported in Boyer et al,[16] coupled with an assumption that doses are 6 months apart with the 7th dose being at month 36. Based upon the TA824 base case, it is assumed that there will be 1 additional dexamethasone administration in both year 4 and year 5, but none in year 6. The TA824 estimates for years 4 and 5 were based upon two company clinical experts' opinion in 2022. This results in the following annual administrations, Table 17.

Table 17. Company base case: Dosing

	FLUO		
Year	ITC phakic	FAS	DEXA
1	[redacted]	[redacted]	1.87
2	[redacted]	[redacted]	1.32
3	[redacted]	[redacted]	0.83
4	[redacted]	[redacted]	1.09
5	[redacted]	[redacted]	1.00
6	[redacted]	[redacted]	0.00
Total	[redacted]	[redacted]	6.11

The company also supplies three RWE scenarios based upon the mean number of implants reported in three studies: 1.16 from the MediSoft study,[37, 65] of 256 eyes, 1.16 from the Birmingham study of 31 eyes and 1.07 from the NHS Majority study of 695 eyes. The additional 0.16, 0.16 and 0.07 administrations are assumed to occur towards or at the end of the first three years, so benefitting from discounting. (see full review of RWE in Section 3.1).

4.3 *Monitoring visits*

Monitoring visit frequency is the average of the responses of three company experts. Estimates were provided for the number of consultant outpatient visits, the number of OCT examinations and the number of fluorescein angiograms. Within this one expert suggested there would be no fluorescein angiograms, the other two suggesting there would be.

This results in the following monitoring visit frequencies by arm and by year, see Table 18.

Table 18. Company base case: Monitoring visits

	OP		OCT		FA	
Year	FLUO	DEXA	FLUO	DEXA	FLUO	DEXA
1	3.7	4.7	2.8	3.4	0.7	0.7
2	3.2	4.7	4.2	3.7	..	..
3	3.2	4.7	3.2	3.7	..	..
4	3.7	4.7	3.2	3.7	0.3	0.3
5	3.2	4.7	3.2	3.7	..	..
6	3.2	4.7	3.2	3.7	..	..

Dexamethasone is estimated to require around 40% more consultant OP visits and 10% more OCT examinations.

4.4 *Adverse events*

Rates of endophthalmitis, vitreous haemorrhage and retinal detachment are taken from TA824. Rates of raised IOP, cataract extraction and vitrectomy are taken from TA613. The annual rates of cataract are increased by 60% due to patients being phakic. At clarification the company suggests this should be an

annual rate of 41%, which the EAG thinks is likely to be based upon the rate among FAME phakic patients.

It is assumed that fluocinolone has double the rate of vitrectomy of dexamethasone, based upon company expert opinion.

This results in the following rates of adverse events, see Table 19.

Table 19. Company base case: AE

	TA824			TA613			
	Endophthalmitis	Vitreous Haemorrhage	Retinal Detachment	Raised IOP	Cataract Extraction	Vitrectomy	Vitrectomy
Year	Both DEXA and FLUO					DEXA	FLUO
1	0.4%	0.4%	0.2%	25.8%	12.3%	1.0%	2.0%
2	0.4%	0.4%	0.2%	13.2%	49.5%	1.0%	2.0%
3+	0.4%	0.4%	0.2%	9.2%	17.4%	2.2%	4.4%

Note that the rates of raised IOP, cataract extraction and vitrectomy are annual rates, but that the modelling assumes that the rates of endophthalmitis, vitreous haemorrhage and retinal detachment are per administration so are 3-4 times greater with dexamethasone than with fluocinolone.

4.5 *Administration costs*

Fluocinolone and dexamethasone are assumed to be administered 95% as outpatient and 5% as day case. 2021/22 NHS reference cost BZ87A for minor vitreous procedure of £156.16 for OP and £1,364.27 for day case result in a mean cost per administration of £225.12.

4.6 *Monitoring visit costs*

Monitoring visits are costed using 2019/20 NHS reference costs: £101 for an ophthalmology consultant led face to face OP visit, £52 for direct access

diagnostic imaging ultrasound scan of less than 20 minutes for OCT and BZ87A minor vitreous procedure OP visit for fluorescein angiogram.

It is assumed that all monitoring visits are dedicated monitoring visits, with administrations requiring a separate dedicated administration visit.

This results in the following annual monitoring costs by year, fluocinolone being expected to provide reasonable cost savings each year due to reduced monitoring requirements. See Table 20.

Table 20. Company base case: Monitoring visit costs by year

Year	FLUO	DEXA
1	£614	£753
2	£541	£678
3	£489	£678
4	£586	£724
5	£489	£678
6	£489	£678

4.7 *Adverse event costs*

These are an average of a variety of NHS reference costs. Other than raise IOP and cataract extraction, all are an average of NHS inpatient costs. The EAG thinks that the unit costs are broadly reasonable within the current context and does not review them further as they have little effect upon results. The EAG only presents the average costs per event in Table 21.

Table 21. *Company base case: Adverse event costs per event*

	Cost
Endophthalmitis	£1,119
Vitreous haemorrhage	£1,068
Retinal detachment	£1,210
Raised IOP	£1,024
Cataract extraction	£1,269
Vitrectomy	£1,068

4.8 *The company base case results: Deterministic*

For each eye treated, the company base case estimates the following costs by arm. The costs per patient have the 13% uplift applied for bilateral phakic DMO involvement. See Table 22.

Table 22. Company base case: Results

	FLUO	DEXA	Net
Drug cost	[redacted]	£4,987	[redacted]
Administration	[redacted]	£1,290	[redacted]
Monitoring	[redacted]	£3,946	[redacted]
Endophthalmitis	[redacted]	£26	[redacted]
Vitreous haemorrhage	[redacted]	£24	[redacted]
Retinal detachment	[redacted]	£14	[redacted]
Raised IOP	[redacted]	£739	[redacted]
Cataract	[redacted]	£1,572	[redacted]
Vitrectomy	[redacted]	£108	[redacted]
Per eye	[redacted]	£12,706	[redacted]
Per person	[redacted]	£14,302	[redacted]

4.9 *The company base case results: Probabilistic*

The company model has the option of probabilistic modelling. This estimates a net cost saving of [redacted], which is little different from the [redacted] deterministic estimate.

Within the cost minimisation the PSA simply assumes that the mean of each parameter has a standard error that is 10% of the mean value. Consequently, the probabilistic modelling provides no additional information. This is not a particularly unusual approach for varying unit costs and other parameters with no obvious estimate for a standard error. Of some concern is that this approach is also used for the assumed number of doses. It might be possible to more formally address this, but given the model structure and time horizon the EAG thinks it is unlikely that there are any significant non-linearities.

The EAG recollection is that under the previous NICE methods guide cost minimisation was not required to submit probabilistic modelling. The January 2022 NICE HTA Manual does not particularly make this distinction, though it does note in section 4.7.16 that for cost-comparison analyses "*the level of*

complexity of the sensitivity analysis should be appropriate for the model being considered in terms of the pathway complexity and available data". The EAG does not consider the probabilistic modelling any further.

4.10 *The company sensitivity and scenario analyses*

The company presents a range of sensitivity and scenario analyses.

The sensitivity analyses that vary inputs by ±20% are presented in CS Table 56 on page 143. The main sensitivities explored are the proportion of dexamethasone administrations as outpatient, this changing the estimated cost saving to between [redacted] and [redacted], and the number of dexamethasone administrations, this changing the estimated cost saving to between [redacted] and [redacted].

A number of scenarios around RWE dosing for fluocinolone are presented. These suggest a lower mean than the [redacted] of the company FAME base case ranging from 1.07 to 1.16. These increase the cost savings from [redacted] to [redacted] and [redacted] respectively. But these analyses do not take into account the RWE additional treatments with anti-VEGF, laser and corticosteroids as reviewed in Section 3.1.4 which the EAG believes may largely invalidate them.

A 3-year time horizon to match the trials' durations causes the cost savings to reverse from [redacted] to a net cost of [redacted].

Halving the assumed post year 3 dexamethasone administrations causes the cost savings to fall from [redacted] to [redacted], while assuming no difference in routine clinical management causes them to fall from [redacted] to [redacted].

4.11 *Company model EAG cross check rebuild*

The EAG has rebuilt the company model. The only error within it is that the base case estimates that each treated eye will have 1.36 cataract extractions. This should be capped at a maximum of 1.00. But the rate of cataract extractions is common to both arms and their costs cancel to a net zero cost, so the EAG has not corrected this.

4.12 *EAG commentary on the submission*

4.12.1 Economic studies

The economic studies in this section were funded by the company (Alimera Sciences).

Holden and colleagues paper is a detailed and thorough cost comparison of NHS costs in the 12 months before and 12 months after fluocinolone insertion.[85] Excluding the cost of the fluocinolone insert, mean costs per patient were £2,691 in the year before and £1,239 in the year after. The main saving was in anti-VEGF drugs, which it seems likely were costed at list prices. The second biggest difference was a reduction in cataract extraction, though that savings is only about a tenth of the saving on the anti-VEGFs. Whether that should be counted is debatable. The fluocinolone cost used was £5,500. Annual reduction in other costs was £1,436 which would accumulate to £4,356 in the 3-year life of the fluocinolone insert. No comparison with dexamethasone is made.

Pochopien and colleagues includes a Markov model comparing fluocinolone and dexamethasone for the pseudophakic in which the key assumption is a greater effect on BCVA with fluocinolone than with dexamethasone: a letter gains of 10.9 and 7.2 at 36 months.[86] These figures are said to come from an network meta-analysis (NMA) which is available as a supplementary file. That NMA also compares fluocinolone with a range of anti-VEGFs. In the NMA the difference in BCVA score seems to be 0.98 letter for chronic pseudophakic eyes, favouring fluocinolone, not the 3.64 used in the economic analysis. The NMA is light on detail, and the difference in figures between the NMA and the economics is not explained. No forest plot with differences for phakic eyes is presented. Utilities are based on the Czoski-Murray AMD artificial contact lens study, which has been criticised in past STAs (see Section 1). Compared to dexamethasone, the authors estimate an extra 0.126 QALYs at an additional cost of £1,777, though again this appears to be at list prices.

Cutino et al provide another Markov model, based on the FDA indication for fluocinolone in eyes previously treated with other steroids but with no

significant rise in IOP.[87] The model uses a 15-year horizon. Data for the first 3-years come from FAME. Data for the next 12 years is based on "*the average proportion of patients with an increase, decrease or no change in BCVA*". The source of these inputs is not given. No repeat fluocinolone is mentioned.

4.13 *Years 1, 2 and 3 dosing calculations*

The calculation of the proportion receiving a fluocinolone administration or a dexamethasone administration does not consider censoring. Censoring due to trial drop out should be handled as discontinuation of treatment. But censoring due to end of trial, or closure of trial site, or patient moving away or any other reasons that would not result in cessation of treatment in real world practice should be treated as censoring rather than as discontinuation of treatment.

The company provided completion rates at clarification for the FAME trials, see Table 23. (The company also provided the same data for the phakic subgroup of FAME, this showing similar proportions remaining, though by month 36 slightly fewer in the placebo arm: 64.5%).

Table 23. Completion rates for MEAD and FAME

	MEAD		FAME	
Month	DEXA	PLAC	FLUO	PLAC
6	94.0%	78.6%	95.2%	94.1%
12	83.2%	63.1%	87.8%	85.4%
24	72.4%	49.7%	76.9%	72.4%
36	64.1%	43.4%	72.9%	68.1%

The rates of completion in the placebo arm of MEAD are somewhat less than those in the placebo arm of FAME. This may be due to study protocol differences. For instance, MEAD required patients to withdraw from the trial if a non-study treatment was to be used, whereas FAME "discouraged" the use of non-study medicines. The rates of completion in the dexamethasone arm of MEAD are that bit less than those in the placebo arm of FAME.

At end of 36 months the reasons for discontinuation are presented below in Table 24.

Table 24. Reasons for discontinuation from MEAD and FAME

	MEAD		FAME	
	DEXA	PLAC	FLUO	PLAC
Ocular AE	8.0%	7.7%	n.a.	n.a.
Non-Ocular AE	4.8%	3.4%	n.a.	n.a.
AEs	12.8%	11.1%	1.1%	2.7%
Efficacy	6.6%	24.0%	0.0%	1.6%
LTFU	3.1%	5.1%	9.8%	13.0%
Personal reasons	4.0%	7.4%		
Protocol violations	0.9%	0.3%	0.5%	1.1%
Death			7.2%	5.9%
Other	8.5%	8.6%	8.5%	7.6%
Discontinued	35.9%	56.6%	27.1%	31.9%
Completed	64.1%	43.4%	72.9%	68.1%

For the MEAD trial “other” reasons for discontinuation included site closure, consent withdrawal, poor compliance, sponsor request, patient relocation and participation in another trial. The FAME trial does not report the reasons for “other” but this was extremely low at 0.3% and 0.0% for fluocinolone and placebo respectively. The EAG has added 8.2% and 7.6% consent withdrawal to this for consistency with the MEAD reporting. It is unclear whether deaths within MEAD were counted as non-ocular AEs or “other”.

The dosing for both fluocinolone and dexamethasone may have been underestimated. But there is no obvious means forward other than to note the higher completion rates for fluocinolone and in particular for placebo in FAME compared to dexamethasone and placebo in MEAD, without particularly knowing the reasons why. The company may be able to correct fluocinolone dosing for these aspects but is unlikely to be able to address this for dexamethasone.

4.14 *Dosing in years 4+*

TA613 assessed fluocinolone for the same indication as the current assessment. The company niched fluocinolone to those who already had symptomatic cataract. The company base case modelled number of fluocinolone implants after year 3 is redacted. The EAG report noted that “*the 36% proportion of patients who are retreated is based upon the proportion of*

the chronic phakic in FAME who achieved a gain of at least 15 letters at 36 months". ERG expert opinion suggests that in practice the retreatment criterion might be looser at say a 10 letters gain, but that retreatment would be more guided by whether the eye had dried than the letters gained. It can also be noted that among the subgroup with cataract extraction by 36 months, the proportion gaining at least 15 letters at month 36 in the fluocinolone arm was 42%".

With regards the number of eyes drying, the conference abstract for the UK observational study of Parker et al[69] noted that among 60 pseudophakic DMO eyes all of which had previously been treated with either anti-VEGF or dexamethasone and which had a minimum follow up of 6 months after fluocinolone implant 47% of eyes had dried.

The TA613 FAD concluded "*The company estimated that about 36% of people with phakic eyes in the FAME treatment arm would have been retreated because they achieved an improvement in BCVA of 15 or more letters. In people with phakic eyes who had their cataract removed during the trial, this number was higher (42.3%). The committee concluded that about 42% of people with phakic eyes and symptomatic cataracts will be retreated and accepted the assumption in the ERG's base-case model*".

Since the company modelling adopts the TA824 dosing assumptions for dexamethasone in year 4 and 5 the EAG thinks it most reasonable to adopt the TA613 dosing assumptions for fluocinolone. But this does lead to a disconnect in that the TA824 dosing is largely by assumption while the assumed year 4+ dosing for fluocinolone is response related. The EAG addresses this within a sensitivity analysis: SA01G.

4.15 *RWE dosing for fluocinolone*

The larger fluocinolone RWE studies typically report lower dosing than occurred during FAME. This may be because FAME discouraged the use of rescue medication which may have encouraged additional use of fluocinolone, and the mean of 1.39 implants. As explored later, the RWE studies saw

extensive use of rescue medication, with up to 50% of patients receiving additional anti-VEGF after fluocinolone.

The European IRISS study with a mean follow-up of 38 months among 695 eyes reported a mean of 1.07 implants, the UK Medisoft with a mean follow up of 52 months among 256 eyes reported a mean of 1.14 implants while the German RETRO-ideal study with a mean follow up of only 31 months among 81 eyes reported a mean of 1.09 implants.

This suggests that when exploring the IRISS based 24% of patients receiving subsequent anti-VEGF the number of fluocinolone administrations which results should be viewed alongside the IRISS 1.07 mean. The situation is more complicated when exploring the UK Medisoft 49% of patients receiving subsequent anti-VEGF due to the longer mean follow up of 50 months, but again the Medisoft mean 1.14 fluocinolone administrations should be borne in mind.

4.16 *RWE dosing for dexamethasone*

There is a dearth studies that report RWE dosing for dexamethasone. Rosenblatt et al[64] in the RWE European ARTES study with a mean follow up of 20 months among 171 eyes in their injection analysis series provide the distribution of the numbers of dexamethasone doses with a mean of 2.60, while across all 340 eyes studied the mean was 2.25. (See Table 25).

Table 25. *Dexamethasone dosing: MEAD vs ARTES*

		Rosenblatt ARTES	
Doses	MEAD	Injection series	All patients
1	13%	0	25%
2	16%	62%	43%
3	11%	26%	21%
4	12%	7%	8%
5	14%	2%	2%
6	25%	1%	1%
7	9%	1%	1%
8		1%	0%

But the above is unsatisfactory due to the Rosenblatt mean follow up of 20 months having a ±10 month associated with it, which appears to be the standard deviation though it seems quite large for this. This means that

among the 2.60 mean number of treatments among the injection series group a reasonable number would have occurred after 20 months, but also that some patient's follow up will have been less than 20 months.

Rosenblatt et al also report the mean number of injections by year, noting some follow up data stretching into year 3. This can again be compared with the company estimates from the MEAD trial, but is against unsatisfactory due to it being unclear quite how Rosenblatt et al have treated censoring and duration of follow up within this. (see Table 26).

Table 26. ***Dexamethasone dosing by year: company MEAD vs ARTES***

		Rosenblatt ARTES	
	Company MEAD	Injection series	All patients
Year 1	1.87	2.39	1.83
Year 2	1.32	0.18	0.31
Year 3	0.83	0.03	0.11
Total	4.02	2.60	2.25

However, just as the fluocinolone RWE suggests slightly lower real-world dosing than during FAME, Rosenblatt et al may suggest lower dexamethasone dosing than during MEAD. Again, while speculation this may be due to rescue therapies among those not responding well to dexamethasone. When exploring patients switching to anti-VEGF the resulting mean dosing for dexamethasone can be compared with the above.

4.16.1 Switching to anti-VEGF and other treatments

The company model structure does not consider retreatment with anti-VEGF. This is the key weakness of the model. Fluocinolone lasting for three years is an advantage in terms of administration costs. But it is a disadvantage for those with an insufficient response to fluocinolone who require rescue treatment with an anti-VEGF. For these patients the three-year cost of fluocinolone is a sunk cost. This does not apply to dexamethasone. Those with an insufficient response to dexamethasone who require rescue treatment with an anti-VEGF can have their dexamethasone treatment stopped. This echoes the UK consensus article of Downey et al[81] (Funded by Alimera) which suggests starting with dexamethasone and only progressing to

fluocinolone if there is a sufficient response to dexamethasone, as reviewed in the clinical effectiveness Section 3.1.4 on combination treatment for DMO.

During FAME anti-VEGFs were not well established and use of other medications during FAME was discouraged, with only 3.3% receiving subsequent anti-VEGF. During MEAD use of non-study treatments required withdrawal from the study.

The European IRISS study reported in Khoramnia et al[38] considered 695 DMO eyes (98% were identified as DMO) treated with fluocinolone among 556 patients, among which 79% had received anti-VEGF prior to fluocinolone, 59% laser and 38% corticosteroids. The mean follow was 38 months, this ranging between 0.7 months and 65 months. The average number of fluocinolone administrations was 1.07. The proportions of patients subsequently receiving anti-VEGF was 24% with 5.9 average administrations. 24% also received laser and 11% corticosteroids, with 1.6 and 1.9 average administrations respectively. The proportion of patients getting rescue treatments was 35.6%, 44.1% and 20.3% in years 1, 2 and 3.

The UK Medisoft study reported in Bailey et al[37] considered 256 DMO eyes treated with fluocinolone among 227 patients, among which 80% had received anti-VEGF prior to fluocinolone, 56% laser and 32% corticosteroids. The mean follow was 52 months, with a minimum follow up of 36 months. The average number of fluocinolone administrations was 1.14. The proportions of patients subsequently receiving anti-VEGF was 49% with 7.7 average administrations. Eleven percent also received laser and 9% corticosteroids, with 1.4 and 1.5 average administrations respectively. The proportion of patients getting rescue treatments was 34.0%, 40.6% and 35.2% in years 1, 2 and 3.

The German RETRO-ideal study reported in Augustin et al[54] considered 81 DMO eyes treated with fluocinolone among 63 patients, among which at least 91% had received anti-VEGF prior to fluocinolone, 93% laser and at least 42% corticosteroids. The mean follow was 31 months. The average number of fluocinolone administrations was 1.09. The proportions of patients

subsequently receiving anti-VEGF was 25% with 2.9 average administrations. 17% also received laser and 11% corticosteroids, with 1.3 and 1.0 average administrations respectively.

The other fluocinolone RWE studies are somewhat smaller but also typically report high rates of anti-VEGF subsequent to fluocinolone use. Of the UK studies Fusi-Rubiano[51] with 36 months follow up among 29 eyes reports 62% subsequent anti-VEGF, Young[53] with 27 months average follow up among 21 eyes reports 24%, Dobler[40] with 60 months follow up among 31 eyes reports 52%. The abstracts of Mushtaq[65] with a follow up of up to 36 months among 96 eyes reports 42%, Alfaqawi[67] with a follow up of 36 months among 22 eyes reports 55% and Putri[70] with a follow up of at least 36 months among 26 eyes reports 38%.

There is a paucity of similar data within the dexamethasone studies. As already noted, MEAD required study withdrawal if a non-study treatment was to be used.

Rosenblatt et al[64] report somewhat lower rates of rescue: across 370 eyes with an unreported mean duration of follow up only 4.7% anti-VEGF but 12% laser, and across 171 "*injection series*" eyes with a mean follow up of 20 months 6.4% anti-VEGF and 17% laser.

Lam et al[44] report for 120 eyes with a maximum follow up of 36 months and the numbers of patients receiving individual brands of anti-VEGF treatments. If it is assumed that a patient only ever received one brand of anti-VEGF 11.7% received anti-VEGF. Use of more than one brand for a patient would reduce this percentage.

The Singer et al[75] study in the USA of dexamethasone among 180 eyes and 177 patients with 90% of DMO patients, 93.8% having has another prior treatment, with a maximum follow up of 12 months and an overall maximum of 16 months reported 45% anti-VEGF use, 5% laser and 7% corticosteroids.

Studies are summarised in Table 27 and Table 28.

Table 27. *RWE fluocinolone studies dosing, prior treatment and subsequent treatment*

Author	Khoramnia	Bailey	Augustin	Fusi-Rubiano	Young	Dobler	Mushtaq	Alfaqawi	Putri
Year	2022	2022	2020	2018	2019	2023	2023	2018	2018
Study	IRISS	Medisoft	RETRO	..	Medisoft	..	..	..	..
Location	Europe	UK	Germany	UK	UK	UK	UK	UK	UK
N Eyes	695	256	81	29	21	31	96	22	26
N Patients	556	227	63					18	
Mean FU (mth)	37.8	51.4	30.8	36	27	60	≤ 36	36	≥ 36
Study admins	1.07	1.14	1.09	1.00		1.16			
Prior Tx					90.5%				
Anti-VEGF	78.8%	79.7%	91.1%+				92.0%		80.8%
Laser	59.4%	56.2%	92.5%				86%+		42.3%
Steroids	38.4%	32.0%	41.8%+				37%+		
Subs. Tx.				62.1%		58.0%	44.8%		
Anti-VEGF	24.3%	48.8%	24.7%	62.1%	23.8%	51.6%	41.7%	54.5%	38.5%
N Admins	5.9	7.7	2.9		12.2	6.4	7.1		2.9
Laser	23.7%	10.5%	17.3%	13.8%	9.5%		7.3%	9.1%	11.5%
N Admins	1.6	1.4	1.3						0.9
Steroids	10.6%	9.4%	11.1%	10.3%			8.3%	9.1%	
N Admins	1.9	1.5	1.9						

Table 28. RWE dexamethasone studies dosing, prior treatment and subsequent treatment

Author	Rosenblatt	Rosenblatt	Lam	Singer
Year	2022	2022	2015	2018
Study	ARTES	ARTES	CHROME	REINFORCE
Location	EU	EU	Canada	USA
N Eyes	340	171*	34	180
N Patients	287	150		177
Mean FU (mth)	Unclear	20.4	Unclear	≈12
Study admins	2.24	2.60	1.60	
Prior Tx				93.8%
Anti-VEGF	94.1%	81.4%	55.9%	
Laser	83.7%	83.1%	55.9%	35.6%
Steroids	17.6%	15.3%	44.1%	
Subs. Tx.		18.7%		
Anti-VEGF	4.7%	6.4%	11.7%	45.0%
Admins				
Laser	12.1%	17.0%	5.9%	5.0%
Admins				
Steroids	0.3%	0.6%	20.6%	6.7%
Admins				

* Injection series study subset

The EAG believes that the key weakness of the company model structure is that it does not consider rates of subsequent anti-VEGF treatment. Other subsequent treatments such as laser and corticosteroids might also warrant consideration.

If the proportions receiving subsequent treatments and their timings are assumed to be the same for fluocinolone and dexamethasone there are sunk cost arguments. EAG expert opinion is that those in the dexamethasone arm who revert to anti-VEGF will have their dexamethasone treatment stopped..

If the proportions receiving subsequent treatments and their timings differ between fluocinolone and dexamethasone the company model may require extensive revision. It may also not be possible to address the topic within a

cost comparison, though the availability of data to populate a cost utility model should be considered before concluding this.

The EAG can only address the simpler situation that assumes the same rates of rescue anti-VEGF at the same time points, hence a common cost of rescue anti-VEGF in each arm which nets out to zero. This will assume that among those switching to anti-VEGF there are no subsequent fluocinolone or dexamethasone administrations. The rates of subsequent anti-VEGF will be taken from the UK Medisoft study, 49%, for the EAG revise base case and the European IRISS study, 24%, within a scenario analysis. The timing of anti-VEGF will be informed by the UK Medisoft study and the European IRISS study which both suggest that among those receiving subsequent treatments to fluocinolone around a third do so in each year, the EAG assuming these to be at 6 months, 18 months and 30 months. This is intended to illustrate the sunk cost argument around fluocinolone use.

4.17 *Sequencing of treatments*

The company model compares fluocinolone with dexamethasone. It does not consider whether sequencing of treatments might lead to lower total costs due to the sunk cost arguments around fluocinolone. Using dexamethasone first to assess response with subsequent use of fluocinolone among responders might result in lower total costs.

4.18 *Dexamethasone dosing at 36 months*

There is some ambiguity about whether the company estimated 9% of dexamethasone patients having an administration at 36 months should be treated as falling within year 3 or year 4. This matters for two reasons. Firstly, the EAG revised base case restricts the time horizon to 3 years. Secondly, if it is most reasonable to assume it applies to year 4 it should in effect be ignored as already occurring within the assumed average of 1 dose during year 4. However, the company approach assumes 6 months elapse between each dexamethasone dose which may not have been strictly adhered to during MEAD. The dexamethasone SmPC notes that retreatment may be performed

"*after approximately 6 months*". Since there seems to be some evidence that more frequent dosing may be more therapeutic the EAG revised base case will retain the 9% within the three-year time horizon and as additional dosing when extending the time horizon to 6 years.

4.19 *Adverse events*

The incidence of raised IOP and cataract is assumed to be the same for fluocinolone and dexamethasone. It can be noted in passing that over the 6-year time horizon each eye is assumed to have an average 0.78 raised IOP and 1.36* cataract extractions (*12.3%+49.5%+4.25*17.4%). These are common to both arms so the net costs of these are zero. Since the net costs are zero the EAG has not corrected the model to limit the cataract extractions per eye to one.

The annual incidence of vitrectomy for dexamethasone is taken from TA613, 1.0%, 1.0% and 2.2% for years 1, 2 and thereafter respectively. The annual incidence of vitrectomy for fluocinolone is assumed to be double that of dexamethasone. These annual rates are applied over the 6-year time horizon of the modelling result in a total of 11% for dexamethasone and 23 for fluocinolone, discounted costs of £108 and £216 per eye so net costs per eye of £108, and with the 13% uplift for bilateral involvement £121 per person.

The handling of vitrectomy as ongoing is despite the company base case assuming that those receiving dexamethasone receive an additional single dose in years 4 and 5 and that there are no additional fluocinolone doses in years 4, 5 and 6, though 29% and 9% of fluocinolone patients receive an additional implant in years 2 and 3. It may be questionable to apply the ongoing annual rate of vitrectomy in years 4, 5 and 6. This may also argue for a 3 year time horizon, the lack of information on adverse events after year 3 paralleling the lack of good information about dosing after year 3.

Rates of endophthalmitis, vitreous haemorrhage and retinal detachment of 0.4%, 0.4% and 0.2% respectively were taken from TA824. These were assumed to be per dose rather than per year of treatment. Since the 6.11 average dexamethasone doses is 4.4 times the 1.39 average fluocinolone

doses, the incidence of endophthalmitis, vitreous haemorrhage and retinal detachment for dexamethasone were estimated to be 4.4 times larger than for fluocinolone. For the company base case this results in net savings of £49 per eye, and £55 per patient. During the first three years of the model it is still estimated that dexamethasone result in roughly three times as many events as fluocinolone.

The company MAIC provides results for adverse effects in CS Tables 29 and 30. In Table 30, there appear to be fewer cataract and IOP AEs with fluocinolone. However, in the published FAME and MEAD papers, cataract extraction in drug groups is reported in 80% in FAME and 59% in MEAD. Cataract extraction in sham groups was 27% in FAME and 7.2% in MEAD so the differences between sham and active groups are similar. Surgery for glaucoma is reported in 1.2% in MEAD and 6.1% in FAME. Use of IOP medications occurred in 42% and 9% in MEAD for dexamethasone and placebo compared to 38% and 14% in FAME for fluocinolone and placebo.

In the light of this the EAG thinks there is not good evidence that rates of adverse events differ. In particular there is not good evidence that rates of endophthalmitis, vitreous haemorrhage and retinal detachment are 3-4 times greater with dexamethasone than with fluocinolone. The EAG revised base case will remove adverse events, presenting a scenario that applies the company assumptions.

4.20 *Bilateral involvement: combining monitoring visits*

The company model assumes 13% concurrent bilateral treatment. This has no effect upon whether fluocinolone is estimated to be more costly, less costly or the same cost as dexamethasone. It just inflates all costs by 13%. upon the proportion with bilateral phakic DMO during FAME. The proportion with bilateral treatment could be somewhat higher than this, potentially being the proportion of phakic DMO patients with DMO in their fellow eye, regardless of whether the fellow eye was phakic or not. But it must be noted that the fluocinolone SmPC states "*Administration in both eyes concurrently is not recommended*" with the dexamethasone SmPC having very similar wording.

Concurrent bilateral treatment may enable monitoring visits for both eyes to be combined.

4.21 *Bilateral involvement: timing of concurrent treatment*

While the SmPCs of fluocinolone and dexamethasone state that administering treatment to both eyes concurrently is not recommended, this may not be followed to the letter in the real world, or concurrent dosing may be viewed differently for fluocinolone compared to dexamethasone. Having treated one eye with fluocinolone without any adverse events other than perhaps cataract, treating the other eye after any cataract extraction in the first eye and before the three year point may not be viewed as particularly breaching the SmPC concurrent treatment recommendation.

Given the ongoing nature of dexamethasone treatment concurrent treatment may be more problematic. In other words, the timing of the treatment of the other eye may differ between fluocinolone and dexamethasone. If this occurs, not only would there be cost differences if for no other reason than discounting but there would be quality of life effects. If treating the second eye is cost effective, which is not a given, this might be expected to improve the overall cost effectiveness of fluocinolone. Concurrent treatment compared to sequencing the treatment of bilateral involvement might also facilitate one stop bilateral monitoring visits which could also improve overall cost effectiveness.

4.22 *Monitoring visit frequency*

The three company experts suggest total OP monitoring visits during the first three years for fluocinolone and dexamethasone of 7.0 and 9.0, 12.0 and 15.6 and 11.0 and 18.0: absolute increases of 2.0, 3.6 and 7.0 respectively.

EAG expert opinion suggests accords most closely with the first company expert: for fluocinolone in 4 monthly in year 1 and 6 monthly thereafter compared to 4 monthly throughout for dexamethasone. The third company expert who anticipates two monthly monitoring for dexamethasone is seen as too high and as skewing results.

The EAG base case will apply the estimates of the first company expert, also revising administrations of dexamethasone to coincide with the 4 monthly monitoring.

4.23 *One stop or two stop monitoring and treatment*

The company model assumes that all monitoring visits are dedicated monitoring visits and that all administration visits are dedicated administration visits. EAG expert opinion suggests that monitoring and where indicated an administration are typically “one-stop” within a single patient visit, and that the OCT element takes around 15 minutes of this. The EAG base case will assume that where a monitoring and administration coincide this will incur the company administration cost, plus an allowance for 15 minutes additional consultant time for the OCT.

4.24 *NHS Reference Costs: Cross check*

For both fluocinolone and dexamethasone the company assumes that 95% will be administered at a consultant led outpatient appointment. But 5% are assumed to be day cases, requiring a hospital bed for treatment. The unit costs of these are taken from the 2020/21 NHS reference costs for minor vitreous retinal procedures, £165.16 and £1,364.27 resulting in an average administration cost of £225.12.

The EAG has not been able to source the company 2019/20 RD40Z ultrasound of less than 20 minutes average cost of £52.47 from within the Direct Accessed Diagnostic Services worksheet. The HRG summary worksheet suggests an average across those with and without contrast of £41.70. The corresponding entries within the 2021/22 NHS reference costs suggest an average of £68.99. It can be noted that the 2021/22 NHS reference costs for retinal tomography is £125.83.

For reasons that are not clear the company uses the 2019/20 NHS reference cost of £137.53 for an outpatient minor vitreous retinal procedure for fluorescein angiography. The EAG sources a cost of £129.62 for this. The corresponding 2021/22 reference cost is £169.73.

The EAG does not think that fluorescein angiography should be costed as an outpatient minor vitreous procedure. Digital retinal photography appears to be the currency code that is closest to fluorescein angiography, though this will encompass a lot of retinal photography that does not involve the fluorescein. The 2021/22 NHS reference cost is £178.43.

The company costs an ophthalmology consultant led OP visit at £101.95 from 2019/20 reference costs, though the EAG sources a marginally different £101.80. The corresponding cost within the 2021/22 NHS reference costs is £143.93.

4.25 *EAG unit costs of administration and monitoring*

In the light of the above the EAG will retain the company estimate of £225.12 per administration. But where monitoring and administration coincide in a "one stop" model the 15 minutes of consultant time will be costed based upon the 2022 PSSRU Unit Costs of Health and Social Care £143 per hour for a hospital based medical consultant.

Where monitoring occurs without an administration the EAG will apply the £143.93 2021/22 NHS reference cost for an outpatient appointment. A scenario analysis will be presented that also adds 15 minutes of consultant time to this for OCT.

4.26 *Raised IOP requirement for surgical intervention*

The costing for raised IOP assumes that 50% require surgical intervention. The EAG think this will be at most 10% though may vary by severity of raised IOP. This has minimal effect upon results, but the EAG will present a scenario of only 10% requiring surgery for raised IOP.

5 EAG cost comparison results

The EAG makes the following changes to the company base case, reporting results per eye due to the uncertainty around concurrent bilateral treatment. Results are presented in Table 29.

- **EAG01:** Three-year time horizon
- **EAG02:** 49% move to anti-VEGF in both arms, with a third occurring at 6 months, 18 months, and 30 months.
- **EAG03:** Adverse event costs net out to zero so can be ignored.
- **EAG04:** Apply EAG monitoring frequencies and assume that administrations can occur during monitoring visits where indicated.

Table 29. ***EAG model revisions: Costs per eye treated***

	FLUO	DEXA	Net
Company base case	[redacted]	£12,705	[redacted]
EAG01: Three year time horizon	[redacted]	£8,127	[redacted]
EAG02: 49% revert to anti-VEGF	[redacted]	£9,063	[redacted]
EAG03: AEs net out so can be ignored	[redacted]	£10,223	[redacted]
EAG04: Monitoring frequency	[redacted]	£10,487	[redacted]
EAG05: Unit costs	[redacted]	£14,301	[redacted]
EAG06: One stop monit & admin possible	[redacted]	£11,296	[redacted]
Cumulative EAG01 to EAG06	[redacted]	£4,142	[redacted]

The results for EAG02 which assumes 45% patients in both arms revert to anti-VEGF may appear peculiar, with costs falling on both arms. This occurs because the anti-VEGF element is not costed. Costs are underestimated in both arms, but they are underestimated by the same amount in both arms so do not affect the net cost estimate. The disaggregate costs for the EAG revised base case are presented below in Table 30.

Table 30. ***EAG revised base case: Disaggregate results: Costs per eye treated***

	FLUO	DEXA	Net
Drug cost	[redacted]	£2,776	[redacted]
Administration	[redacted]	£832	[redacted]
Monitoring	[redacted]	£533	[redacted]
Endophthalmitis	[redacted]	£0	[redacted]
Vitreous haemorrhage	[redacted]	£0	[redacted]
Retinal detachment	[redacted]	£0	[redacted]
Raised IOP	[redacted]	£0	[redacted]
Cataract	[redacted]	£0	[redacted]
Vitrectomy	[redacted]	£0	[redacted]
Per eye	[redacted]	£4,142	[redacted]

The administration and monitoring costs may at first appear peculiar. They key point to note that fluocinolone is still anticipated to result in overall cost savings from these combined. Dexamethasone has a lower monitoring cost due to these costs only including monitoring visits at which no administration occurred.

Zero adverse event costs are not realistic. But it reflects the assumption that there is no good evidence for them differing by arm, or at least not to the extent modelled by the company. If this is accepted their contribution to net costs is zero. Scenario analyses explore this assumption.

5.1.1 The EAG performs the following scenario analyses.

- **SA01:** 6-year time horizon and for those remaining on fluocinolone or dexamethasone treatment:

a: 0.00 doses of fluocinolone in year 4 and 1.00 doses of dexamethasone in both of years 4 and 5

b: 0.36 doses of fluocinolone in year 4 and 1.00 doses of dexamethasone in both of years 4 and 5

c: 0.42 doses of fluocinolone in year 4 and 1.00 doses of dexamethasone in both of years 4 and 5

d: 0.00 doses of fluocinolone in year 4 and 0.82 doses of dexamethasone in both of years 4 and 5

e: 0.36 doses of fluocinolone in year 4 and 0.82 doses of dexamethasone in both of years 4 and 5

f: 0.42 doses of fluocinolone in year 4 and 0.82 doses of dexamethasone in both of years 4 and 5

g: 0.51 doses of fluocinolone in year 4 based upon the 49% switching to anti-VEGF and [redacted] doses of dexamethasone in both of years 4 and 5 to maintain the same ratio between treatments as during years 1-3

- **SA02:** 24% of patients move to anti-VEGF, and 0% of patients move to anti-VEGF.
- **SA03:** Only 50% one stop administration and monitoring, and 0% one stop administration and monitoring at monitoring visits where an administration is indicated.
- **SA04:** The ophthalmology OP cost is insufficient for a monitoring visit and requires an additional 15-minutes allowance for OCT.
- **SA05**: Company monitoring frequency estimates.
- **SA06:** Company AE rates.
- **SA07:** SA06 and only 10% raised IOP requiring surgery.

The EAG results of these seven scenario analysis are presented in Table 31.

Table 31. ***EAG scenario analyses: Costs per eye treated***

	FLUO	DEXA	Net
EAG revised base case	[redacted]	£4,142	[redacted]
SA01a: 0.00 yr 4 FLUO, 1.00 yr 4&5 DEXA	[redacted]	£5,897	[redacted]
SA01b: 0.36 yr 4 FLUO, 1.00 yr 4&5 DEXA	[redacted]	£5,897	[redacted]
SA01c: 0.42 yr 4 FLUO, 1.00 yr 4&5 DEXA	[redacted]	£5,897	[redacted]
SA01d: 0.00 yr 4 FLUO, 0.82 yr 4&5 DEXA	[redacted]	£5,715	[redacted]
SA01e: 0.36 yr 4 FLUO, 0.82 yr 4&5 DEXA	[redacted]	£5,715	[redacted]
SA01f: 0.42 yr 4 FLUO, 0.82 yr 4&5 DEXA	[redacted]	£5,715	[redacted]
SA01g: 0.51 yr 4 FLUO, 0.76 yr 4&5 DEXA	[redacted]	£5,649	[redacted]
SA02a: 24% move to anti-VEGF	[redacted]	£4,713	[redacted]
SA02b: 0% move to anti-VEGF	[redacted]	£5,260	[redacted]
SA03a: 50% One stop admin and monit.	[redacted]	£4,312	[redacted]
SA03b: 0% One stop admin and monit.	[redacted]	£4,483	[redacted]
SA04: OP cost + 15 min for monitoring	[redacted]	£4,274	[redacted]
SA05: Company monitoring frequencies	[redacted]	£4,715	[redacted]
SA06: Company AE rates	[redacted]	£5,393	[redacted]
SA07: SA06 + 10% IOP surgical	[redacted]	£5,240	[redacted]

5.2 *Summary of the cost-effectiveness evidence*

- The company presents a simple cost minimisation model of fluocinolone compared to dexamethasone.
- The company model has the option of probabilistic modelling. This estimates a net cost saving of [redacted], which is little different from the [redacted] deterministic estimate.
- The company presents a range of sensitivity and scenario analyses. The main sensitivities explored are the proportion of dexamethasone

administrations as outpatient, this changing the estimated cost saving to between [redacted] and [redacted], and the number of dexamethasone administrations, this changing the estimated cost saving to between [redacted] and [redacted].

- The EAG makes the four key changes to the company base case, reporting results per eye due to the uncertainty around concurrent bilateral treatment. Changes include introduction of a three-year time horizon; 49% of patients move to anti-VEGF in both arms, (with a third occurring at 6 months, 18 months, and 30 months), adverse event costs (however, these net out to zero) and finally adding monitoring frequencies and assuming that administrations can occur during monitoring visits where indicated.
    - Cumulative EAG costs from these changes are [redacted] for fluocinolone and £4,142 for dexamethasone ([redacted] Net).

6 Equalities and innovation

As stated in the CS Document B B.1.14; the patient population (those registered blind) addressed in this submission is a protected group under the Equality Act 2010.

The EAG recognise that in eyes in which dexamethasone has been effective, and CRT is below 400 microns, clarity is needed as to whether laser should be a required treatment. The alternative is clinicians progress straight to fluocinolone. A trial is required randomising such patients to laser or fluocinolone.

7 EAG commentary on the robustness of evidence submitted by the company

The overall robustness of the evidence is provided by the EAG below.

7.1 *Clinical effectiveness evidence summary*

1. There is no trial directly comparing dexamethasone and fluocinolone. There have been no new trials since the previously assessed FAME (fluocinolone ID6307) and MEAD trials were reviewed (dexamethasone TA824).
    a. However, there are now studies from routine care (i.e., RWE studies) which provide observational evidence of effectiveness and adverse effects.
    b. The EAG consider that the RWE provides convincing evidence that in eyes with DMO that have not responded sufficiently to previous treatment, (usually anti-VEGF drugs), fluocinolone improves outcomes for patients. Many patients have improvements (e.g., over 10 or 15 letter gains in BCVA), others have stable VA, but some do lose vision.

2. The FAME trial of fluocinolone in DMO was carried out in eyes that had not failed to respond to anti-VEGF drugs. The MEAD trial recruited a similar population. In both cases, this was because the trials started before anti-VEGF drugs became routinely available.
    a. Therefore, the population in the scope does not match the populations in the trials, which are eyes that that have not responded sufficiently to anti-VEGF drugs.
    b. The definition of *insufficient response* needs consideration. Clinical advisors suggest that insufficient response may mean insufficient treatment due to pressures on the NHS capacity to deliver services to patients.

3. The ITC analysis which focused on the FAME cohort and phakic-only subgroup, indicates a reduction in ESS of ~15% after adjustments for imbalanced effect modifiers.
    a. Despite concerns about potential bias compared to MEAD, the ITC reveals no statistically significant differences between fluocinolone and dexamethasone across six outcomes,

supporting their equivalence in economic assessments for DMO patients.

4. Reduction in ESS in the FAME cohort's phakic-only subgroup, raises concerns about potential bias compared to MEAD-TE subgroup. Therefore, the loss of sample size when considering only the phakic-only subgroup of FAME, should be considered when making comparisons with the MEAD-TE subgroup.
    a. Differences in baseline characteristic highlight the need for exploratory analyses to assess the impact of these variables on treatment effects.
    b. Heterogeneity in retreatment rules poses another challenge and the analysis sets focuses on phakic lenses available in FAME, but not in MEAD, necessitating careful consideration of available subgroup data in both studies.

7.2 *Cost-effectiveness evidence summary*

5. It is not clear from the submission whether the MEAD and FAME completion rates are sufficiently similar so that their dosing frequencies are comparable.
    a. There is little data about the number of fluocinolone and dexamethasone doses beyond 3 years.
    b. Is it best to limit the time horizon to 3 years? If not, what principle should be applied when estimating dosing for years 4, 5 and 6?

6. The RWE studies suggest large proportions of patients revert to anti-VEGF during the first 3 years of treatment.
    a. Clarity is needed as to whether these proportions are the same, and at the same time for fluocinolone and dexamethasone, and if so what proportions switch to anti-VEGF each year?

b. If these proportions or their timings are different between fluocinolone and dexamethasone, it is not clear to the EAG whether this issue can still be handled within a cost comparison analysis.

7. The EAG suggest that is it likely that sequencing and use of dexamethasone first to assess the likelihood of response, with fluocinolone only being used among dexamethasone responders, result in lower total costs.
    a. This was not modelled or included in the company submission.
8. The company do not provide evidence to determine what proportion of monitoring visits also double as administration visits when an administration is indicated.

9. It is not clear which estimates of monitoring frequencies for OP visits, OCT examinations and fluorescein angiograms are more reasonable. The EAG present an alternative estimate to the one contained in the company submission.

8. Additional EAG commentary on service context and additional evidence

Continuation of anti-VEGF drugs

NICE said in TA824;[7] "*If non-corticosteroids do not work well enough, people can keep having anti-VEGFs or laser monotherapy*".

- NICE TA824 noted; "*The other treatments do not work well for these people and are only used because clinicians prefer to offer some treatment rather than nothing at all*."
- The cost-effectiveness of this statement is uncertain. It is unclear what i the cost per QALY is of continuing anti-VEGFs in people who do not respond to these drugs.

TA824 also stated; "*The sham procedure may be considered as a proxy for continued anti-VEGF therapies*."

It is possible that continued anti-VEGF therapies may still be having some effect, whereas improvement on sham is due to natural recovery, which does occur in some patients, perhaps after improvement in glycaemic control. However, in TA824, it is stated that "*the committee accepted that it is appropriate for the sham arm of the MEAD[16] trial to be used as a proxy for continued anti-VEGF therapy*." This suggest that continued anti-VEGF therapy has no effect. Therefore, it may not be an appropriate comparator to dexamethasone.

However, although eyes in the FAME and MEAD trials, and most of the RWE studies had not had a good response to anti-VEGFs, those drugs may still have had some effect. The Vilà González et al study showed that only 6% of eyes had no response at all.[22] So given that the effect of fluocinolone is not dramatic (a mean gain in BCVA of about 5 letters), clinicians may with to add other treatments. In addition, the ERG has not seen evidence as to whether the response to anti-VEGF drugs is improved after steroid treatment.

Laser treatment

The decision problem dismissed laser treatment, for example; "*As per [TA349] clinical experts advised that laser photocoagulation has declined due to associated retinal scarring*". However, the EAG suggests that there is no scarring after subthreshold micropulse laser. We expect the use of macular laser will increase after the DIAMONDS trial (an NIHR commissioned trial) showed that laser is cheap and effective in people with central involving DMO <400 microns in CRT.[88]

The decision problem document also said; "*Laser photocoagulation is only recommended for use in non-centre involving DMO thus it occupies a different position in the pathway of care to FAc implant. It is estimated that this applies to approximately 20% of the total DMO population*." The DIAMONDS trial showed that macular laser is suitable for people with centre involving DMO of less than 400 microns. In addition, macular laser is the treatment of choice for non-central involving DMO.[88] The draft NICE DR guideline recommends laser for centre-involving DMO.[23]

In TA824, the manufacturer stated that;[7] "*Based on UK clinical feedback, laser photocoagulation is only used in people when the macular oedema does not involve the centre (around 20% of the total diabetic macular oedema population) or in people with diabetic macular oedema with no associated visual impairment, because of concerns around safety and long-term clinical efficacy*." The EAG do not consider this appropriate. The DIAMONDS trial showed the macular laser was effective in most eyes with centre-involving DMO and CRT <400 microns, with only about 20% requiring anti-VEGF therapy. Subthreshold laser treatment does not burn the retina and so provides reassurance about safety.[88]

There, once steroid treatment has led to a reductio in CRT, then laser treatment could be used. This might have more cost-saving implications with 6-monthly dexamethasone, with some or all the doses being omitted. Over a

3-year period, there could be a mix of laser and dexamethasone treatment at reduced cost. Whereas once fluocinolone has been given, there is a 3-year "sunk" cost.

Insufficient response or insufficient treatment?

The advent of new drugs for macular conditions, together with an ageing population and the increase is the prevalence of diabetes has put considerable strain on ophthalmology services, and there have been several accounts of problems with delivery. The EAG conducted a rapid search to identify reports of problems with service delivery for people with macular conditions, using the search approach in appendix 1. A brief summary is provided below:

- In an NHS Confederation document,[89] Stephen Scowcroft noted that there were more than half a million people on Ophthalmology waiting lists and 26,000 d had been waiting for more than a year, citing NHS England waiting times data.[90]

- Hogg et al[91] noted "a growing imbalance between clinical demand and capacity", focusing on wet AMD in a large centre in England. They found that patients often experienced delays in treatment and that these delays led to poorer visual outcomes.

- Stratton et al[92] report an audit of 3151 patients in 21 UK centres, looking at frequency of aflibercept injections for DMO. They found considerable variations in the time taken for half the patients to achieve the NICE-recommended loading doses, from 16 weeks to 44 weeks. By 12 months, the proportions who had received five or more injections ranged from 93% to 62% amongst centres.

- Rennie and colleagues from Southampton and Bradford report outcomes in 500 eyes with DMO treated with anti-VEGF drugs.[25] At six

months, 66% had a sub-optimal response, defined as gain of5 or fewer letters or <20% reduction in CRT. Only 108 eyes received the recommended loading dose in the first 6 months. Rennie and colleagues comment on “difficulties in delivering high volume and high frequency treatment in clinical practice.

- A survey of members of The Macular Society found that;[93]
  - Nearly six in 10 (57%) have experienced a delay whilst waiting for an NHS appointment and/or treatment
  - Nearly half (47%) have experienced a loss or decline in vision during this time
  - At the time of the survey one in 10 patients had waited more than a year to be seen or were still waiting
  - Four in 10 patients with macular eye conditions who have experienced NHS delays in the past two years fear losing their sight, with 21% struggling with day-to-day tasks

It is not clear from the summary how Macular Society members were recruited. Those who had experienced problems may have been more likely to respond.

- Foot and McEwen[94] report the results of a survey of UK ophthalmologists showing that delays in care were leading to preventable visual harm.There is a risk that over time, the fluid will become chronic if never fully cleared, response to treatment will be poorer and visual outcomes will not be as good. The difference in outcomes by duration of DMO was reported in the FAME[17] trial.

Switching anti-VEGF drugs

There are several studies of switching anti-VEGF drugs if one is insufficiently effective. The effectiveness of switching has been reviewed by Banaee and colleagues.[95] The rationale for trying aflibercept if ranibizumab or bevacizumab are ineffective, is that ranibizumab binds VEGF-A, whereas

aflibercept binds VEGFs A and B, and PlGF (placental growth factor, which acts in combination with VEGF-A),and so neutralises a larger number of the cytokines that may be involved in the development of retinopathy. Aflibercept also has a longer intra-ocular half-life. Banaee and colleagues report that 8 studies of switching from ranibizumab to aflibercept all showed improvements in central macular thickness, and five showed improvements in vision. One problem is whether the changes reflect a regression to the mean. They found no studies of switching from aflibercept to ranibizumab.[95]

Standards of care

In a recent appraisal, of dapagliflozin (TA775) for chronic kidney disease, NICE recommended its addition only in patients receiving best current care – a "standard of care" requirement.[96] The same approach is likely to be followed with the appraisal of empagliflozin (ID6131).[97] The EAG question whether recommendations for treatment with intravitreal steroids should only be made if patients have received optimal anti-treatment.

Predicting insufficient response

As noted, some eyes with DMO respond well to anti-VEGF therapy, but others respond poorly. There has been research into whether baseline characteristics could identify eyes that are not going to respond. Most eyes with poor response (<5 letter gain) after 12 weeks of anti-VEGF treatment do not get a later good response but a poor response at 12 weeks (no gain in letters) does not preclude some improvement by six months.[15, 24] Similarly Dugel et al found that only about a third of eyes with a reduction of <20% in CRT after 12 weeks of anti-VEGF therapy had reductions of >20% by 52 weeks, with 69% having no significant improvement.[98]

Baseline HbA1cdoes not appear to be a reliable predictor of response to treatment. The frequency of hyperreflective foci on OCT may predict response.[99, 100] The level of some biomarkers such as cytokines in vitreal fluid

may be associated with response.[101] Stem cell work has shown differences in permeability to VEGF between responders and non-responders.[22]
So, there are promising lines of enquiry but overall it is not currently possible to reliably predict final response from baseline characteristics. However, most eyes with a poor response will not have a later good response. Continuing anti-VEGF treatment in eyes with poor response at 12 weeks will lead to slight improvement in a minority at the cost of delaying a switch to potentially more effective steroid treatment in the rest. The cost of continuing anti-VEGF is also considerable. Rennie et al found that anti-VEGF treatment was continued for at least four years even in eyes with a sub-optimal response.[25]

Does this imply that a decision to switch from anti-VEGF treatment should be made at three months, assuming injection frequency has been optimal?
More research is required on prediction of response and the EAG will suggest this to the NIHR programmes.

The search strategy for a rapid search for predictors of responses is included in EAG Appendix.

Other issues

Patients in the trials had better diabetic control than seen in routine clinics. In FAME[17], HbA1c at baseline was 7.9%.[17] In the DIAMONDS trial in macular oedema in UK centres, the average HbA1c was about 9%.[88]

Costs

One issue is reliability of NHS reference costs. In past appraisals, clinical experts have argued that the reference cost is too low to cover all costs of intra-vitreal injections. The EAG consider performing a sensitivity analysis with a 50% uplift in cost. We also need to consider costs of follow-up visits between injections. For example, it is not clear how often is intra-ocular pressure measured between steroid injections? (glaucoma risk)

Another issue in costing is whether patients needing bilateral treatment can have it in both eyes at the same visit. We assume that this can be done.
A third cost issue is that anti-VEGF injections are given by nurses but steroid injections with the larger-bore needle requiring a special technique and given by doctors.

Capacity in clinics and other possible benefits

The capacity problem experienced in ophthalmology clinics have been mentioned above. If capacity constraints mean that timely anti-VEGF treatment cannot be given, then steroids could be considered. The reduced clinic workload may allow other patients to be treated more quickly or more optimally, but the benefits are not quantifiable.

Indications for steroid drugs

The TA824 guidance stated;[7] "Dexamethasone intravitreal implant is recommended as an option for treating visual impairment caused by diabetic macular oedema in adults only if their condition has not responded well enough to, *or if they cannot have, non-corticosteroid therapy*." and, "dexamethasone intravitreal implant is recommended for treating visual impairment due to diabetic macular oedema only if the diabetic macular oedema has not responded well enough to non-corticosteroids, *or non-corticosteroids are unsuitable*, irrespective of whether they have a phakic or pseudophakic lens."

NICE defined people in whom anti-VEGFs were unsuitable as people who are pregnant, have established allergies to anti-VEGFs, or have had a cardiovascular event in the past 3 to 6 months (such as a stroke or myocardial infarction). The term "*non-corticosteroids*" means anti-VEGF drugs or macular laser. The text in italics denotes lack of response to other treatments, the Committee noted that there may be other indications for fluocinolone because it avoids the need for frequent injections.

3.4 "*The clinical experts added that people who are unable to have frequent injections because they cannot get to the hospital, their carers cannot bring them, or the hospital is too far would also be unable to have non-corticosteroids. The clinical experts emphasised that although this is a small group, it is important that they have access to treatment.*"

The draft NICE guideline on diabetic retinopathy includes;[23]
1.5.13 "*If a person does not want to continue with regular anti-VEGF injections, consider switching treatment to a dexamethasone intravitreal implant*."

Mortality

Rajala and colleagues found that people with VI due to diabetic retinopathy had a five-fold risk of mortality compared to the non-diabetic population.[102] The risks of mortality associated with diabetic retinopathy were reviewed in the ERG report for the appraisal of ranibizumab for DMO in 2012. The ERG concluded that the risk of death amongst those with DMO, compared to the non-diabetic population, was in the range 3.3 to 4.0. That ERG report is on the NICE website.[103]

NICE Diabetic retinopathy draft guideline – fluocinolone

The NICE guideline was out for consultation until the end of September 2023. It makes a number of recommendations that are relevant to the forthcoming fluocinolone STA.

On treatment of DMO, the draft guideline says;[23]
"*1.5.9 If anti-VEGF treatment alone does not stabilise or improve the person's vision after the loading phase, consider using macular laser as rescue treatment or changing anti-VEGF treatment*."

1*.5.10 Assess response to treatments after 12 months. Consider switching to a dexamethasone intravitreal implant if the response is suboptimal."*

The choice of dexamethasone is because in the health economics analysis, it is assumed that fluocinolone must be given at 12-monthly intervals. This is based on committee opinion and is contrary to the evidence. The FAME[17] trial showed that the fluocinolone implant provided slow release of the drug for 36 months. The committee assumption trebles the drug acquisition cost and makes fluocinolone not cost-effective.

Para 1.5.4 recommends that laser be considered in people without visual impairment which is welcome. However, the EAG question why clinicians would delay until vision in impaired. Treating people with good vision will appear less cost-effective because they have less to gain in utility terms, however cost-effectiveness should be considered over the whole pathway from good vision to visual loss.

8 References

1. EMC. *Summary of Product Characteristics: ILUVIEN 190 micrograms intravitreal implant in applicator*. 2022. URL: https://www.medicines.org.uk/emc/product/3061/smpc (Accessed 17 November 2023).
2. National Institute for Health and Care Excellence (NICE). *Fluocinolone acetonide intravitreal implant for treating chronic diabetic macular oedema in phakic eyes after an inadequate response to previous therapy: technology appraisal guidance [TA 613].* 2019. URL: https://www.nice.org.uk/guidance/ta613 (Accessed 07 November 2023).
3. National Institute for Health and Care Excellence (NICE). *Ranibizumab for treating diabetic macular oedema: technology appraisal guidance [TA274].* 2013. URL: https://www.nice.org.uk/guidance/ta820 (Accessed 07 November 2023).
4. National Institute for Health and Care Excellence (NICE). *Aflibercept for treating diabetic macular oedema: technology appraisal guidance [TA346].* 2015. URL: https://www.nice.org.uk/guidance/ta346 (Accessed 07 November 2023).
5. National Institute for Health and Care Excellence (NICE). *Faricimab for treating diabetic macular oedema: technology appraisal guidance [TA799].* 2022. URL: https://www.nice.org.uk/guidance/ta799 (Accessed 07 November 2023).
6. National Institute for Health and Care Excellence (NICE). *Brolucizumab for treating diabetic macular oedema: technology appraisal guidance [TA820].* 2022. URL: https://www.nice.org.uk/process/pmg36/ (Accessed 07 November 2023).
7. National Institute for Health and Care Excellence (NICE). *Dexamethasone intravitreal implant for treating diabetic macular oedema: technology appraisal guidance [TA 824].* 2022. URL: https://www.nice.org.uk/guidance/ta824 (Accessed 07 November 2023).
8. Klein R, Klein BEK, Moss SE, Cruickshanks KJ. The Wisconsin epidemiologic study of diabetic retinopathy: XVII: the 14-year incidence and progression of diabetic retinopathy and associated risk factors in type 1 diabetes. *Ophthalmology* 1998;**105**(10):1801-15. http://dx.doi.org/10.1016/S0161-6420(98)91020-X
9. Minassian DC, Owens DR, Reidy A. Prevalence of diabetic macular oedema and related health and social care resource use in England. *Br J Ophthalmol* 2012;**96**(3):345-9. http://dx.doi.org/10.1136/bjo.2011.204040
10. Stitt AW, Curtis TM, Chen M, Medina RJ, McKay GJ, Jenkins A*, et al.* The progress in understanding and treatment of diabetic retinopathy. *Prog Retin Eye Res* 2016;**51**:156-86. http://dx.doi.org/10.1016/j.preteyeres.2015.08.001
11. Yau JW, Rogers SL, Kawasaki R, Lamoureux EL, Kowalski JW, Bek T*, et al.* Global prevalence and major risk factors of diabetic retinopathy. *Diabetes Care* 2012;**35**(3):556-64. http://dx.doi.org/10.2337/dc11-1909
12. Idris I, Warren G, Donnelly R. Association between thiazolidinedione treatment and risk of macular edema among patients with type 2 diabetes. *Arch Intern Med* 2012;**172**(13):1005-11. http://dx.doi.org/10.1001/archinternmed.2012.1938
13. Sander B, Larsen M, Andersen EW, Lund-Andersen H. Impact of changes in metabolic control on progression to photocoagulation for clinically significant macular oedema: a 20 year study of type 1 diabetes. *Diabetologia* 2013;**56**(11):2359-66. http://dx.doi.org/10.1007/s00125-013-3027-5
14. Mitchell P, Bandello F, Schmidt-Erfurth U, Lang GE, Massin P, Schlingemann RO*, et al.* The RESTORE Study: Ranibizumab monotherapy or combined with laser

versus laser monotherapy for diabetic macular edema. *Ophthalmology* 2011;**118**(4):615-25. http://dx.doi.org/10.1016/j.ophtha.2011.01.031
15. Gonzalez VH, Campbell J, Holekamp NM, Kiss S, Loewenstein A, Augustin AJ*, et al.* Early and long-term responses to anti-vascular endothelial growth factor therapy in diabetic macular edema: analysis of Protocol I data. *Am J Ophthalmol* 2016;**172**:72-9. http://dx.doi.org/10.1016/j.ajo.2016.09.012
16. Boyer DS, Yoon YH, Belfort R, Jr., Bandello F, Maturi RK, Augustin AJ*, et al.* Three-year, randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with diabetic macular edema. *Ophthalmology* 2014;**121**(10):1904-14. http://dx.doi.org/10.1016/j.ophtha.2014.04.024
17. Campochiaro PA, Brown DM, Pearson A, Chen S, Boyer D, Ruiz-Moreno J*, et al.* Sustained delivery fluocinolone acetonide vitreous inserts provide benefit for at least 3 years in patients with diabetic macular edema. *Ophthalmology* 2012;**119**(10):2125-32. http://dx.doi.org/10.1016/j.ophtha.2012.04.030
18. Kern C, Fu DJ, Huemer J, Faes L, Wagner SK, Kortuem K*, et al.* An open-source data set of anti-VEGF therapy in diabetic macular oedema patients over 4 years and their visual acuity outcomes. *Eye (Lond)* 2021;**35**(5):1354-64. http://dx.doi.org/10.1038/s41433-020-1048-0
19. Virgili G, Curran K, Lucenteforte E, Peto T, Parravano M. Anti-vascular endothelial growth factor for diabetic macular oedema: a network meta-analysis. *Cochrane Database Syst Rev* 2023(6):CD007419 http://dx.doi.org/10.1002/14651858.CD007419.pub7
20. Brown DM, Nguyen QD, Marcus DM, Boyer DS, Patel S, Feiner L*, et al.* Long-term outcomes of ranibizumab therapy for diabetic macular edema: the 36-month results from two phase III trials: RISE and RIDE. *Ophthalmology* 2013;**120**(10):2013-22. http://dx.doi.org/10.1016/j.ophtha.2013.02.034
21. Egan C, Zhu H, Lee A, Sim D, Mitry D, Bailey C*, et al.* The United Kingdom Diabetic Retinopathy Electronic Medical Record Users Group, Report 1: baseline characteristics and visual acuity outcomes in eyes treated with intravitreal injections of ranibizumab for diabetic macular oedema. *Br J Ophthalmol* 2017;**101**(1):75-80. http://dx.doi.org/10.1136/bjophthalmol-2016-309313
22. Vilà González M, Eleftheriadou M, Kelaini S, Naderi-Meshkin H, Flanagan S, Stewart S*, et al.* Endothelial cells derived from patients with diabetic macular edema recapitulate clinical evaluations of anti-VEGF responsiveness through the neuronal pentraxin 2 pathway. *Diabetes* 2020;**69**(10):2170-85. http://dx.doi.org/10.2337/db19-1068
23. National Institute for Health and Care Excellence (NICE). *Guideline: diabetic retinopathy: management and monitoring: draft for consultation*. 2023. URL: https://www.nice.org.uk/guidance/gid-ng10256/documents/draft-guideline (Accessed 06 November 2023).
24. Bressler NM, Beaulieu WT, Maguire MG, Glassman AR, Blinder KJ, Bressler SB*, et al.* Early response to anti-vascular endothelial growth factor and two-year outcomes among eyes with diabetic macular edema in Protocol T. *Am J Ophthalmol* 2018;**195**:93-100. http://dx.doi.org/10.1016/j.ajo.2018.07.030
25. Rennie C, Lotery A, Payne J, Singh M, Ghanchi F. Suboptimal outcomes and treatment burden of anti-vascular endothelial growth factor treatment for diabetic macular oedema in phakic patients. *Eye (Lond)* 2023. http://dx.doi.org/10.1038/s41433-023-02667-w
26. Amoaku WM, Ghanchi F, Bailey C, Banerjee S, Banerjee S, Downey L*, et al.* Diabetic retinopathy and diabetic macular oedema pathways and management: UK Consensus Working Group. *Eye (Lond)* 2020;**34**(Suppl 1):1-51. http://dx.doi.org/10.1038/s41433-020-0961-6

27. NHS England. *Operational note: updated commissioning recommendations for medical retinal vascular medicines following the national procurement for ranibizumab biosimilars*. 2023. URL: https://www.england.nhs.uk/long-read/operational-note-updated-commissioning-recommendations-for-medical-retinal-vascular-medicines-following-the-national-procurement-for-ranibizumab-biosimilars/#diabetic-macular-oedema-dmo (Accessed 06 November 2023).
28. Scanlon PH, Foy C, Chen FK. Visual acuity measurement and ocular co-morbidity in diabetic retinopathy screening. *Br J Ophthalmol* 2008;**92**(6):775-8. http://dx.doi.org/10.1136/bjo.2007.128561
29. Becker C, Schneider C, Aballéa S, Bailey C, Bourne R, Jick S, Meier C. Cataract in patients with diabetes mellitus: incidence rates in the UK and risk factors. *Eye* 2018;**32**(6):1028-35. http://dx.doi.org/10.1038/s41433-017-0003-1
30. The Age-Related Eye Disease Study Research Group. The age-related eye disease study (AREDS) system for classifying cataracts from photographs: AREDS report no. 4. *Am J Ophthalmol* 2001;**131**(2):167-75. http://dx.doi.org/10.1016/s0002-9394(00)00732-7
31. National Institute for Health and Care Excellence (NICE). *Glaucoma: diagnosis and management: NICE guideline [NG81]*. 2017. URL: https://www.nice.org.uk/guidance/ng81 (Accessed 06 November 2023).
32. Bailey C, Chakravarthy U, Lotery A, Menon G, Talks J. Real-world experience with 0.2 µg/day fluocinolone acetonide intravitreal implant (ILUVIEN) in the United Kingdom. *Eye (Lond)* 2017;**31**(12):1707-15. http://dx.doi.org/10.1038/eye.2017.125
33. Sivaprasad S, Oyetunde S. Impact of injection therapy on retinal patients with diabetic macular edema or retinal vein occlusion. *Clin Ophthalmol* 2016;**10**:939-46. http://dx.doi.org/10.2147/opth.S100168
34. *Yutiq (fluocinolone acetonide intravitreal implant) 0.18 mg*. Watertown, MA, USA: EyePoint Pharmaceuticals Inc.; 2021. URL: https://yutiq.com/ (Accessed 06 November 2023).
35. Cunha-Vaz J, Ashton P, Iezzi R, Campochiaro P, Dugel PU, Holz FG*, et al.* Sustained delivery fluocinolone acetonide vitreous implants: long-term benefit in patients with chronic diabetic macular edema. *Ophthalmology* 2014;**121**(10):1892-903. http://dx.doi.org/10.1016/j.ophtha.2014.04.019
36. Yang Y, Bailey C, Holz F, Eter N, Weber M, Baker C*, et al.* Long-term outcomes of phakic patients with diabetic macular oedema treated with intravitreal fluocinolone acetonide (FAc) implants. *Eye* 2015;**29**(9):1173-80. http://dx.doi.org/10.1038/eye.2015.98
37. Bailey C, Chakravarthy U, Lotery A, Menon G, Talks J. Extended real-world experience with the ILUVIEN® (fluocinolone acetonide) implant in the United Kingdom: 3-year results from the Medisoft® audit study. *Eye (Lond)* 2022;**36**(5):1012-8. http://dx.doi.org/10.1038/s41433-021-01542-w
38. Khoramnia R, Peto T, Koch F, Taylor SR, Castro de Sousa JP, Hill L*, et al.* Safety and effectiveness of the fluocinolone acetonide intravitreal implant (ILUVIEN): 3-year results from the European IRISS registry study. *Br J Ophthalmol* 2023;**107**:1502-8. http://dx.doi.org/10.1136/bjo-2022-321415
39. Chakravarthy U, Taylor SR, Koch FHJ, Castro de Sousa JP, Bailey C. Changes in intraocular pressure after intravitreal fluocinolone acetonide (ILUVIEN): real-world experience in three European countries. *Br J Ophthalmol* 2019;**103**(8):1072-7. http://dx.doi.org/10.1136/bjophthalmol-2018-312284
40. Dobler E, Mohammed BR, Chavan R, Lip PL, Mitra A, Mushtaq B. Clinical efficacy and safety of intravitreal fluocinolone acetonide implant for the treatment of chronic diabetic macular oedema: five-year real-world results. *Eye* 2023;**37**(11):2310-5. http://dx.doi.org/10.1038/s41433-022-02338-2

41. Kaldırım H, Savur F, Kırgız A, Atalay K. Comparison of anatomical and functional outcomes of intravitreal dexamethasone implant between phakic and pseudophakic eyes with diabetic macular edema. *Korean J Ophthalmol* 2020;**34**(5):383-91. http://dx.doi.org/10.3341/kjo.2019.0142
42. Wallsh J, Luths C, Kil H, Gallemore R. Initial ten years of experience with the intravitreal dexamethasone implant: a retrospective chart review. *Clin Ophthalmol* 2020;**14**:3097-108. http://dx.doi.org/10.2147/opth.S264559
43. Singer MA, Sheth V, Mansour SE, Coughlin B, Gonzalez VH. Three-year safety and efficacy of the 0.19-mg fluocinolone acetonide intravitreal implant for diabetic macular edema: the PALADIN study. *Ophthalmology* 2022;**129**(6):605-13. http://dx.doi.org/10.1016/j.ophtha.2022.01.015
44. Lam WC, Albiani DA, Yoganathan P, Chen JC, Kherani A, Maberley DA*, et al.* Real-world assessment of intravitreal dexamethasone implant (0.7 mg) in patients with macular edema: the CHROME study. *Clin Ophthalmol* 2015;**9**:1255-68. http://dx.doi.org/10.2147/opth.S80500
45. Fallico M, Maugeri A, Lotery A, Longo A, Bonfiglio V, Russo A*, et al.* Fluocinolone acetonide vitreous insert for chronic diabetic macular oedema: a systematic review with meta-analysis of real-world experience. *Sci Rep* 2021;**11**(1):4800. http://dx.doi.org/10.1038/s41598-021-84362-y
46. Holden SE, Currie CJ, Owens DR. Evaluation of the clinical effectiveness in routine practice of fluocinolone acetonide 190 µg intravitreal implant in people with diabetic macular edema. *Curr Med Res Opin* 2017;**33**(sup2):5-17. http://dx.doi.org/10.1080/03007995.2017.1366645
47. Alfaqawi F, Lip PL, Elsherbiny S, Chavan R, Mitra A, Mushtaq B. Report of 12-months efficacy and safety of intravitreal fluocinolone acetonide implant for the treatment of chronic diabetic macular oedema: a real-world result in the United Kingdom. *Eye* 2017;**31**(4):650-6. http://dx.doi.org/10.1038/eye.2016.301
48. Faes L, Mishra AV, Lipkova V, Balaskas K, Quek C, Hamilton R*, et al.* Visual and anatomical outcomes of a single intravitreal dexamethasone in diabetic macular edema: an 8 year real-world study. *J Clin Med* 2023;**12**(12). http://dx.doi.org/10.3390/jcm12123878
49. Rehak M, Busch C, Unterlauft JD, Jochmann C, Wiedemann P. Outcomes in diabetic macular edema switched directly or after a dexamethasone implant to a fluocinolone acetonide intravitreal implant following anti-VEGF treatment. *Acta Diabetol* 2020;**57**(4):469-78. http://dx.doi.org/10.1007/s00592-019-01439-x
50. Ahmed M, Putri C, Quhill H, Quhill F. Evaluation of 0.2 µg/day fluocinolone acetonide (ILUVIEN) implant in a cohort of previously treated patients with diabetic macular oedema (DMO): a 36-month follow-up clinical case series. *BMJ Open Ophthalmol* 2020;**5**(1):e000484. http://dx.doi.org/10.1136/bmjophth-2020-000484
51. Fusi-Rubiano W, Mukherjee C, Lane M, Tsaloumas MD, Glover N, Kidess A*, et al.* Treating Diabetic Macular Oedema (DMO): real world UK clinical outcomes for the 0.19mg Fluocinolone Acetonide intravitreal implant (Iluvien™) at 2 years. *BMC Ophthalmol* 2018;**18**(1):62. http://dx.doi.org/10.1186/s12886-018-0726-1
52. Panos GD, Arruti N, Patra S. The long-term efficacy and safety of fluocinolone acetonide intravitreal implant 190 µg (ILUVIEN®) in diabetic macular oedema in a multi-ethnic inner-city population. *Eur J Ophthalmol* 2021;**31**(2):620-9. http://dx.doi.org/10.1177/1120672119898414
53. Young JF, Walkden A, Stone A, Mahmood S. Clinical effectiveness of intravitreal fluocinolone acetonide (FAc) (ILUVIEN™) in patients with diabetic macular oedema (DMO) refractory to prior therapy: the Manchester experience. *Ophthalmol Ther* 2019;**8**(3):477-84. http://dx.doi.org/10.1007/s40123-019-0197-3
54. Augustin AJ, Bopp S, Fechner M, Holz F, Sandner D, Winkgen AM*, et al.* Three-year results from the Retro-IDEAL study: Real-world data from diabetic

macular edema (DME) patients treated with ILUVIEN(®) (0.19 mg fluocinolone acetonide implant). *Eur J Ophthalmol* 2020;**30**(2):382-91. http://dx.doi.org/10.1177/1120672119834474
55. Mansour SE, Kiernan DF, Roth DB, Eichenbaum D, Holekamp NM, Kaba S, Werts E. Two-year interim safety results of the 0.2 µg/day fluocinolone acetonide intravitreal implant for the treatment of diabetic macular oedema: the observational PALADIN study. *Br J Ophthalmol* 2021;**105**(3):414-9. http://dx.doi.org/10.1136/bjophthalmol-2020-315984
56. Kodjikian L, Baillif S, Creuzot-Garcher C, Delyfer MN, Matonti F, Weber M, Mathis T. Real-world efficacy and safety of fluocinolone acetonide implant for diabetic macular edema: a systematic review. *Pharmaceutics* 2021;**13**(1). http://dx.doi.org/10.3390/pharmaceutics13010072
57. Coelho J, Malheiro L, Melo Beirão J, Meireles A, Pessoa B. Real-world retrospective comparison of 0.19 mg fluocinolone acetonide and 0.7 mg dexamethasone intravitreal implants for the treatment of diabetic macular edema in vitrectomized eyes. *Clin Ophthalmol* 2019;**13**:1751-9. http://dx.doi.org/10.2147/opth.S201611
58. Elaraoud I, Quhill H, Quhill F. Case series investigating the efficacy and safety of bilateral fluocinolone acetonide (ILUVIEN®) in patients with diabetic macular edema: 10 eyes with 12 months follow-up. *Ophthalmology and Therapy* 2016;**5**(1):105-9. http://dx.doi.org/10.1007/s40123-016-0049-3
59. Figueira J, Henriques J, Amaro M, Rosas V, Alves D, Cunha-Vaz J. A nonrandomized, open-label, multicenter, phase 4 pilot study on the effect and safety of ILUVIEN® in chronic diabetic macular edema patients considered insufficiently responsive to available therapies (RESPOND). *Ophthalmic Res* 2017;**57**(3):166-72. http://dx.doi.org/10.1159/000455235
60. La Mantia A, Hawrami A, Laviers H, Patra S, Zambarakji H. Treatment of refractory diabetic macular edema with a fluocinolone acetonide implant in vitrectomized and non-vitrectomized eyes. *Int J Ophthalmol* 2018;**11**(12):1951-6. http://dx.doi.org/10.18240/ijo.2018.12.13
61. Massin P, Erginay A, Dupas B, Couturier A, Tadayoni R. Efficacy and safety of sustained-delivery fluocinolone acetonide intravitreal implant in patients with chronic diabetic macular edema insufficiently responsive to available therapies: a real-life study. *Clin Ophthalmol* 2016;**10**:1257-64. http://dx.doi.org/10.2147/opth.S105385
62. McCluskey JD, Kaufman PL, Wynne K, Lewis G. Early adoption of the fluocinolone acetonide (FAc) intravitreal implant in patients with persistent or recurrent diabetic macular edema (DME). *Int Med Case Rep J* 2019;**12**:93-102. http://dx.doi.org/10.2147/imcrj.S191171
63. Schechet SA, Adams OE, Eichenbaum DA, Hariprasad SM. Macular thickness amplitude changes when switching from discontinuous to continuous therapy for diabetic macular oedema. *BMJ Open Ophthalmol* 2019;**4**(1):e000271. http://dx.doi.org/10.1136/bmjophth-2019-000271
64. Rosenblatt A, Udaondo P, Cunha-Vaz J, Sivaprasad S, Bandello F, Lanzetta P*, et al.* A collaborative retrospective study on the efficacy and safety of intravitreal dexamethasone implant (Ozurdex) in patients with diabetic macular edema: the European DME registry study. *Ophthalmology* 2020;**127**(3):377-93. http://dx.doi.org/10.1016/j.ophtha.2019.10.005
65. Mushtaq B, Bailey CC, Chakravarthy U, Lotery AJ, Talks J, Menon G. 6-year outcomes of the United Kingdom Medisoft® audit study following treatment with the ILUVIEN® (fluocinolone acetonide) implant in patients with diabetic macular edema. *Invest Ophthalmol Vis Sci* 2023;**64**(8):2651.

66. Mushtaq B, Bhatnagar A, Palmer H. Real-world outcomes in diabetic macular edema for the 0.2 µg/day fluocinolone acetonide implant: case series from the Midlands, UK. *Clin Ophthalmol* 2021;**15**:2935-43. http://dx.doi.org/10.2147/opth.S283561
67. Alfaqawi F, Sarmad A, Lip PL, Elsherbiny S, Chavan R, Mitra A, Mushtaq B. Three-year outcome of fluocinolone acetonide intravitreal implant (ILUVIEN) in the treatment of chronic diabetic macular oedema: Real-world results in the UK. *Invest Ophthalmol Vis Sci* 2018;**59**(9):4810.
68. Ruiz-Moreno JM, Adán A, Lafuente M, Asencio Durán M, Arias Barquet L, García Layana A, Araiz Iribarren J. Effectiveness and safety of fluocinolone acetonide intravitreal implant in diabetic macular edema patients considered insufficiently responsive to available therapies (REACT): a prospective, non-randomized, and multicenter study. *Int Ophthalmol* 2023. http://dx.doi.org/10.1007/s10792-023-02864-2
69. Parker N, Peto T. Use of iluvien implant for diabetic macular oedema in the belfast health and social care trust, Northern Ireland. *Eur J Ophthalmol* 2019;**29(3)**:NP17-NP8. http://dx.doi.org/10.1177/1120672119847084
70. Putri CA, Quhill F. 36-months real-world experience in patients with refractory chronic diabetic macular edema (DME) treated with the 190 micrograms fluocinolone acetonide intravitreal implant (ILUVIEN). *Invest Ophthalmol Vis Sci* 2018;**59**(9):4844.
71. Chronopoulos A, Chronopoulos P, Ashurov A, Korb C, Pfeiffer N, Hattenbach LO. Switching to intravitreal fluocinolone acetonide implant for refractory diabetic macular edema: 12- and 24-month results. *Eur J Ophthalmol* 2022;**32**(1):443-9. http://dx.doi.org/10.1177/1120672121992982
72. Rousseau N, Lebreton O, Masse H, Maucourant Y, Pipelart V, Clement M*, et al.* Fluocinolone acetonide implant injected 1 month after dexamethasone implant for diabetic macular oedema: the ILUVI1MOIS study. *Ophthalmology and Therapy* 2023;**12**(5):2781-92. http://dx.doi.org/10.1007/s40123-023-00749-2
73. Baillif S, Staccini P, Weber M, Delyfer M-N, Le Mer Y, Gualino V*, et al.* Management of patients with diabetic macular edema switched from dexamethasone intravitreal implant to fluocinolone acetonide intravitreal implant. *Pharmaceutics* 2022;**14**(11):2391.
74. Malclès A, Dot C, Voirin N, Agard É, Vié AL, Bellocq D*, et al.* Real-life study in diabetic macular edema treated with dexamethasone implant: The Reldex Study. *Retina* 2017;**37**(4):753-60. http://dx.doi.org/10.1097/iae.0000000000001234
75. Singer MA, Dugel PU, Fine HF, Capone A, Jr., Maltman J. Real-world assessment of dexamethasone intravitreal implant in dme: findings of the prospective, multicenter REINFORCE Study. *Ophthalmic Surg Lasers Imaging Retina* 2018;**49**(6):425-35. http://dx.doi.org/10.3928/23258160-20180601-07
76. Lau T, Ghareeb AE, Kishikova M, Kotagiri A, Masri I, Smith J*, et al.* Functional and structural outcomes of patients with diabetic macular oedema treated with multiple ozurdex implants at 24 months: real life data. *Invest Ophthalmol Vis Sci* 2021;**62**(8):1046-.
77. Sepetis A, Tsokolas G, Mourtzoukos S. Safety and efficacy of dexamethasone intravitreal implant (Ozurdex) for the treatment of diabetic macular oedema in pseudophakic patients. the Portsmouth experience. *Invest Ophthalmol Vis Sci* 2018;**59**(9).
78. Roth DB, Eichenbaum D, Malik D, Radcliffe NM, Cutino A, Small KW*, et al.* The 0.19-mg fluocinolone acetonide intravitreal implant for diabetic macular edema: intraocular pressure-related effects over 36 months. *Ophthalmology Retina* 2023. http://dx.doi.org/10.1016/j.oret.2023.08.004
79. Sheth VS, Singer M, MacCumber M, Cutino A, Kasper J, Coughlin BA, Riemann CD. Long-term control of retinal thickness variability and vision following the

0.19 mg fluocinolone acetonide implant. *Journal of VitreoRetinal Diseases* 2023;**7**(6):490-7. http://dx.doi.org/10.1177/24741264231201314
80. Eaton A, Koh SS, Jimenez J, Riemann CD. The USER study: a chart review of patients receiving a 0.2 µg/day fluocinolone acetonide implant for diabetic macular edema. *Ophthalmology and Therapy* 2019;**8**(1):51-62. http://dx.doi.org/10.1007/s40123-018-0155-5
81. Downey L, Acharya N, Devonport H, Gale R, Habib M, Manjunath V*, et al.* Treatment choices for diabetic macular oedema: a guideline for when to consider an intravitreal corticosteroid, including adaptations for the COVID-19 era. *BMJ Open Ophthalmol* 2021;**6**(1):e000696. http://dx.doi.org/10.1136/bmjophth-2020-000696
82. Vaz-Pereira S, Castro-de-Sousa JP, Martins D, Prates Canelas J, Reis P, Sampaio A*, et al.* The outcomes of switching from short- to long-term intravitreal corticosteroid implant therapy in patients with diabetic macular edema. *Ophthalmic Res* 2020;**63**(2):114-21. http://dx.doi.org/10.1159/000503036
83. Augustin AJ, Kuppermann BD, Lanzetta P, Loewenstein A, Li XY, Cui H*, et al.* Dexamethasone intravitreal implant in previously treated patients with diabetic macular edema: subgroup analysis of the MEAD study. *BMC Ophthalmol* 2015;**15**:150. http://dx.doi.org/10.1186/s12886-015-0148-2
84. Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. *J Clin Epidemiol* 1997;**50**(6):683-91. http://dx.doi.org/10.1016/s0895-4356(97)00049-8
85. Holden SE, Currie CJ, Owens DR. Health-economic evaluation of fluocinolone acetonide 190 µg implant in people with diabetic macular edema. *Curr Med Res Opin* 2017;**33**(sup2):45-52. http://dx.doi.org/10.1080/03007995.2017.1366663
86. Pochopien M, Beiderbeck A, McEwan P, Zur R, Toumi M, Aballéa S. Cost-effectiveness of fluocinolone acetonide implant (ILUVIEN®) in UK patients with chronic diabetic macular oedema considered insufficiently responsive to available therapies. *BMC Health Serv Res* 2019;**19**(1):22. http://dx.doi.org/10.1186/s12913-018-3804-4
87. Cutino A, Green K, Kendall R, Moore PT, Zachary C. Economic evaluation of a fluocinolone acetonide intravitreal implant for patients with DME based on the FAME study. *Am J Manag Care* 2015;**21**(4 Suppl):S63-72.
88. Lois N, Campbell C, Waugh N, Azuara-Blanco A, Maredza M, Mistry H*, et al.* Standard threshold laser versus subthreshold micropulse laser for adults with diabetic macular oedema: the DIAMONDS non-inferiority RCT. *Health Technol Assess* 2022;**26**(50):1-86. http://dx.doi.org/10.3310/szki2484
89. Scowcroft S. *Eye care services: an urgent call for reformation*. NHS Confederation; 2022. URL: https://www.nhsconfed.org/articles/eye-care-services-urgent-call-reformation (Accessed 06 November 2023).
90. NHS England. *Consultant-led referral to treatment waiting times data 2022-23: incomplete commissioner Apr22*. 2022. URL: https://www.england.nhs.uk/statistics/wp-content/uploads/sites/2/2022/06/Incomplete-Commissioner-Apr22-XLS-7187K-57873.xls (Accessed 06 November 2023).
91. Hogg J, Gkorou O, Duncan HJ, Stone LG, Blyth M, Brandes L*, et al.* The prevalence and impact of treatment delays in exudative age-related macular degeneration. *Invest Ophthalmol Vis Sci* 2021;**62**(8):2941-.
92. Stratton I, Scanlon P, Chakravarthy U, Eleftheriadis H, Bailey C, Mukherjee R*, et al.* Aflibercept injections for diabetic macula oedema: an audit of 3151 patients in 21 centres followed for 12 months. *Diabet Med* 2019;**36**:156.
93. Association of Optometrists. *NHS patient backlogs are leading to life-changing sight loss*. 2023. URL: https://www.aop.org.uk/our-voice/media-

centre/press-releases/2023/03/21/nhs-patient-backlogs-are-leading-to-life-changing-sight-loss (Accessed 06 November 2023).
94. Foot B, MacEwen C. Surveillance of sight loss due to delay in ophthalmic treatment or review: frequency, cause and outcome. *Eye* 2017;**31**(5):771-5. http://dx.doi.org/10.1038/eye.2017.1
95. Banaee T, Ashraf M, Conti FF, Singh RP. Switching anti-VEGF drugs in the treatment of diabetic macular edema. *Ophthalmic Surgery, Lasers and Imaging Retina* 2017;**48**(9):748-54. http://dx.doi.org/doi:10.3928/23258160-20170829-10
96. National Institute for Health and Care Excellence (NICE). *Dapagliflozin for treating chronic kidney disease: technology appraisal guidance [TA775].* 2022. URL: https://www.nice.org.uk/guidance/ta775 (Accessed 06 November 2023).
97. National Institute for Health and Care Excellence (NICE). *Empagliflozin for treating chronic kidney disease ID6131: in development [GID-TA11170]*. 2023. URL: https://www.nice.org.uk/guidance/indevelopment/gid-ta11170 (Accessed 06 November 2023).
98. Dugel PU, Campbell JH, Kiss S, Loewenstein A, Shih V, Xu X*, et al.* Association between early anatomic response to anti-vascular endothelial growth factor therapy and long-term outcome in diabetic macular edema: an independent analysis of Protocol I study data. *Retina* 2019;**39**(1):88-97. http://dx.doi.org/10.1097/iae.0000000000002110
99. Shalchi Z, Okada M, Bruynseels A, Palethorpe D, Yusuf A, Hussain R*, et al.* Effect of glycosylated hemoglobin on response to ranibizumab therapy in diabetic macular edema: real-world outcomes in 312 patients. *Can J Ophthalmol* 2018;**53**(4):415-9. http://dx.doi.org/10.1016/j.jcjo.2017.10.008
100. Schreur V, Altay L, van Asten F, Groenewoud JMM, Fauser S, Klevering BJ*, et al.* Hyperreflective foci on optical coherence tomography associate with treatment outcome for anti-VEGF in patients with diabetic macular edema. *PLoS One* 2018;**13**(10):e0206482. http://dx.doi.org/10.1371/journal.pone.0206482
101. Kwon JW, Jee D. Aqueous humor cytokine levels in patients with diabetic macular edema refractory to anti-VEGF treatment. *PLoS One* 2018;**13**(9):e0203408. http://dx.doi.org/10.1371/journal.pone.0203408
102. Rajala U, Pajunpää H, Koskela P, Keinänen-Kiukaanniemi S. High cardiovascular disease mortality in subjects with visual impairment caused by diabetic retinopathy. *Diabetes Care* 2000;**23**(7):957-61. http://dx.doi.org/10.2337/diacare.23.7.957
103. Cummins E, Waugh N, Lois N, Shyangdan D. *Ranibizumab for diabetic macular oedema: report for NICE rapid review*. 2021. URL: https://www.nice.org.uk/guidance/ta274/documents/macular-oedema-diabetic-ranibizumab-rapid-review-of-ta237-evidence-review-group-report-for-nice-rapid-review2 (Accessed 06 November 2023).

9 EAG Appendix

Search for predictors of response

Database: Ovid MEDLINE(R). Search Strategy:

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1 (diabetic macular oedema or diabetic macular edema).ab,kf,ti. (2905)

2 Macular Edema/ (6644)

3 diabet*.mp. (581602)

4 2 and 3 (3289)

5 1 or 4 (3889)

6 (ranibizumab or bevacizumab or aflibercept or lucentis or avastin or eylea).ab,kf,ti. (14942)

7 (respon* or resistan* or nonrespon* or refractory).ab,kf,ti. (3626355)

8 Drug Resistance/ (45856)

9 7 or 8 (3633803)

10 5 and 6 and 9 (178)

11 limit 10 to (humans and yr="2008 -Current") (167)

Targeted search for service delivery issues relating to treatment for macular conditions in the NHS.

1. Review of references suggested by the EAG team and non-RCTs listed in the company's decision problem form (section 5a):

Date searched: 11/09/23

Including Pubmed search for 'UK EMR users group' (any field) 17 results

2. MEDLINE:

Ovid MEDLINE(R) ALL <1946 to September 11, 2023>

Date searched: 12/09/23

1 (anti-vegf* or anti Vascular endothelial growth factor* or ranibizumab or bevacizumab or aflibercept or lucentis or avastin or eylea).kf,tw. 33062

2 (NHS or national health service or UK or "U.K." or England or Scotland or Wales or Northern Ireland).kf,tw. 260788

3 (real world or routine care or routine treatment or clinic? or cohort or observational study).kf,tw. 1379152

4 observational study.pt. 146011

5 3 or 4 1435768

6 1 and 2 and 5 103

7 limit 6 to yr="2015 -Current" 93

10 results selected as possibly relevant and not already identified.

3. Google:

Date searched: 12/09/23

anti vegf NHS injection frequency OR backlog OR delays OR adequacy *browsed first 30 results*

anti vegf NHS treatment frequency OR backlog OR delays OR adequacy *browsed first 30 results*

anti vegf outcomes NHS OR UK "real world" *browsed first 30 results*

age related macular degeneration NHS treatment frequency OR delays OR workload OR backlog OR adequacy *browsed first 30 results*

diabetic macular oedema NHS treatment frequency OR delays OR workload OR backlog OR adequacy *browsed first 30 results.*

Targeted search for recent (last 5 years) RWE for fluocinolone or dexamethasone implants

[redacted]

[redacted]

Studies excluded by the company

Table 3 of CS Appendix D gives a list of excluded studies and reasons, but does not give full citation details and often not even authors.

The EAG has checked the list and considers that some of the excluded studies may have been useful, as shown in EAG Table 14.

Table 32. Studies excluded by the company that might have been of interest.

Title	Authors, year	Reason given by Alimera and *EAG comments in italics*
Medico Economic Evaluation of Fluocinolone Acetonide Implant Versus Dexametheasone Implant in Resistant Diabetic Macular Oedema	Not given	Publication type/study design not of interest
Safety and Efficacy of Intravitreal Fluocinolone Acetonide Implants in Patients With Diabetic Macular Edema		Publication type/study design not of interest
Sustained low-dose treatment with fluocinolone acetonide (FAc) is effective for treating chronic diabetic macular oedema (DMO)	Cole A, Bailey C 2012	Publication type/study design not of interest *EAG – real-life data from UK?*
Three-year, randomized, shamcontrolled, phase III study of dexamethasone intravitreal implant in patients with diabetic macular edema	Belfort R, Boyer DS, Yoon YH, Bandello F, Maturi RK, Augustin AJ,et al 2014	Population not of interest *EAG – may be from MEAD trial?*
A multicenter, 12-month randomized study comparing dexamethasone intravitreal implant with ranibizumab in patients with diabetic macular edema	Callanan D, Loewenstein A, Patel S, Massin P, Corcóstegui B, Li X, Jiao J, Hashad Y, Whitcup S 2016	"Full text not found" *EAG – full text is available from journal. But may not be relevant to subgroup of poor responders*

A prospective randomised controlled clinical trial comparing a combination of repeated intravitreal Ozurdex and macular laser therapy versus macular laser only in centre-involving diabetic macular oedema (OZLASE study)	Heng L, Sivaprasad S, Crosby-Nwaobi R, Saihan Z, Karampelas M, Bunce C, Peto T, Hykin P 2016	Population not of interest. *EAG – might provide data on eyes resistant to laser and why. Note that eyes with thicker (>400 microns) that do not respond well to laser, might after dexamethasone treatment have reduced CRT and become responsive to laser. So one option for treatment might be a combination of dexamethasone and macular grid laser which would have lower cost.*
A randomized clinical trial comparing fixed vs pro-re-nata dosing of Ozurdex in refractory diabetic macular oedema (OZDRY study)	Ramu J, Yang Y, Menon G, Bailey C, Narendran N, Bunce C, Quartilho A, Prevost A, Hykin P, Sivaprasad S 2015	Population not of interest. *EAG – might have been of interest for costs.*
Long-term outcomes of phakic patients with diabetic macular oedema treated with intravitreal fluocinolone acetonide (FAc) implants	Yang Y, Bailey C, Holz FG, Eter N, Weber M, Baker C, et al 2015	Population not of interest *EAG – population looks relevant. Is this a "real-world" study?*
Sustained intraocular delivery of fluocinolone acetonide slows progression of diabetic retinopathy	Campochiaro PA, Wykoff CC, Kapik B, Green KE 2016	Outcomes not of interest *EAG. Many patients with DMO also have retinopathy, NPDR or PDR, and an additional benefit of fluocinolone could increase cost-effectiveness*
Clinical effectiveness of the fluocinolone acetonide implant in diabetic macular oedema resistant to anti-VEGF therapy	Chalkiadakis, S. E.; Harris, F. J.; Taylor, S. 2016	Publication type/study design not of interest
Long-term Effects of Intravitreal 0.19 mg Fluocinolone Acetonide Implant on Progression and Regression of Diabetic Retinopathy	Wykoff CC, Chakravarthy U, Campochiaro PA, Bailey C, Green K, Cunha-Vaz J.	Outcomes not of interest *EAG – again, benefits to NPDR and/or PDR could have economic consequences which could improve cost-effectiveness*
Fluocinolone acetonide (FAc) intravitreal implants improve visual acuity in chronic diabetic macular edema (DME) for up to 36 months	Kodjikian L, Bandello F, de Smet M, et al.2022	Publication type/study design not of interest *EAG – another real world study?*
Effect of fluocinolone acetonide 0.2 mug/day implant on the decision to drive in patients with diabetic macular oedema: a report from the FAME[17] study	Grewal DS, Fletcher DC, Hariprasad SM, Suner IJ. 2019	Outcomes not of interest *EAG. Driving is very important to patients and losing ability to drive and mobility can affect QoL.*
Comparison of data characterizing the clinical effectiveness of the fluocinolone intravitreal implant	Holden SE, Kapik B, Beiderbeck AB, Currie CJ.2019	Publication type/study design not of interest

(ILUVIEN) in patients with diabetic macular edema from the real world, non-interventional ICE-UK study and the FAME[17] randomized controlled trials		*EAG – looks relevant to the economics. One cost-effectiveness analysis was done by the same authors.*
Effects of Long-Term DME Control With 0.2 microg/Day Fluocinolone Acetonide Implant on Quality of Life: An Exploratory Analysis From the FAME[17] Trial	Singer MA, Wykoff CC, Grewal DS 2020	Outcomes not of interest *EAG – quality of life is of interest.*
Effectiveness of 190 microg fluocinolone acetonide and 700 microg dexamethasone intravitreal implants in diabetic macular edema using the area-under-the-curve method: The CONSTANT analysis	Zarranz-Ventura J, Mali JO. 202-	Publication type/study design not of interest EAG – *does look a useful approach. The authors say'* "Calculations of area-under-the-curve (AUC) provide the average letters gained across the entire treatment period, which may be a better estimate of long-term effectiveness than single time-point outcomes, particularly when it comes to sustained-release therapies." *The Alimera review excluded this study – it favoured fluocinolone.*
Comparison of Concomitant Administration of Dexamethasone in One Eye versus Fluocinolone Acetonide in the Fellow Eye in Patients with Similar Degrees of Diabetic Macular Edema	Akduman YV, Grodsky JD, Rodrigues EB	Publication type/study design not of interest *EAG – looks a useful approach to give direct comparison but should be excluded because of very small numbers of eyes (6)*
The 0.19-mg Fluocinolone Acetonide Intravitreal Implant Reduces Treatment Burden in Diabetic Macular Edema	Merrill PT, Holekamp N, Roth D, Kasper J, et al 2023	Publication type/study design not of interest *EAG – useful data for costing. Article comes from the PALADIN trial.*

Quality assessment of systematic reviews

Table 33. Quality assessment using National Institutes of Health criteria.

Review	Focused question	Eligibility criteria	Searches	Dual review	Validity	Study details	Publication bias	Heterogeneity
Fallico[45]	Y	CD	Y	Y	CD	N	Y	Y
Kojiikian[56]	Y	CD	CD	CD	N	Y	N	NA

Y, yes; N, no; CD, cannot determine; NA, not applicable; NR, not reported.

1. Is the review based on a focused question that is adequately formulated and described?
2. Were eligibility criteria for included and excluded studies predefined and specified?
3. Did the literature search strategy use a comprehensive, systematic approach?
4. Were titles, abstracts, and full-text articles dually and independently reviewed for inclusion and exclusion to minimize bias?
5. Was the quality of each included study rated using a standard method to appraise its internal validity?
6. Were the included studies listed along with important characteristics and results of each study?
7. Was publication bias assessed?
8. Was heterogeneity assessed? (This question applies only to meta-analyses.)

Summary of identified RWE

Table 34. Summary of primary studies included in the Fallico and Kodgikian SLRs, and those identified by EAG additional searches

Primary RWE study	Fallico 2021 SR	Kodgikian 2021 SR
Ahmed et al 2020[50]	✓	
Alfaqawi et al 2017[47]		✓
Alfaqawi et al 2018		
Augustin et al 2020[54]	✓	✓
Bailey et al 2017[32]	✓	✓
Chakravarthy et al 2019[39]	✓	✓
Capone et al 2019		
Coelho et al 2019[57]		✓
Coney et al 2019		✓
Cox et al 2022		
Elaraoud et al 2016[58]		✓
El-Ghrably et al 2017		✓
Figueira et al 2017[59]		✓
Fusi-Rubiano et al 2018[51]	✓	✓
Ghareeb et al 2021		
Holden et al 2017[46]		✓
La Mantia et al 2018[60]		✓
Lau et al 2021,		
Mansour et al 2020[55]	✓	
Massin et al 2016[61]		✓
McCluskey et al 2019[62]		✓
[redacted]		[redacted]
Mushtaq et al 2021		
Mushtaq et al 2023		
Panos et al 2020[52]	✓	✓
Parker and Peto 2019		
[redacted]		[redacted]
Putri et al 2018		
Rehak et al 2020[49]	✓	✓
Schechet et al 2019[63]		✓
Tasiopoulou et al 2019		
Vaz-Pereira et al 2020		✓
Young et al 2019[53]	✓	✓

Studies in italics were excluded by the EAG due to sample size <20 eyes, follow-up <12 months, [redacted]