Cost Comparison Appraisal

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

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

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Contents:

The following documents are made available to stakeholders:

Access the **final scope** and **final stakeholder list** on the NICE website.

1. **Company submission** from Alimera:
   a. Evidence submission
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**

3. **Patient group, professional group, and NHS organisation submission** from:
   a. Diabetes UK
   b. Macular Society
   c. Royal College of Ophthalmologists

4. **External Assessment Report** prepared by Warwick Evidence

5. **External Assessment Report – factual accuracy check**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

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List of abbreviations

AE	Adverse Event
AESI	Adverse event of special interest
AITC	Adjusted Indirect Treatment Comparison
ANOVA	Analysis of Variance
AUC	Area Under the Curve
BCVA	Best-corrected visual acuity
BP	Blood Pressure
BRB	Blood retinal barrier
BRVA	Best-reported visual acuity
CAI	Cataract surgery after implant
CBI	Cataract surgery after implant
CI	Confidence interval
CMH	Cochran–Mantel–Haenszel
CPT	Central Point Thickness
CRT	Central Retinal Thickness
CSR	Clinical Study Report
CST	Central Subfield Thickness
CS	Company Submission
DEX	Dexamethasone intravitreal implant
DM	Diabetes Mellitus
DMO	Diabetic Macular Oedema
DME	Diabetic Macular Edema
DR	Diabetic Retinopathy
DRCR.net	The Diabetic Retinopathy Clinical Research Network
DSMB	Data Safety Monitoring Board
ETD	Estimated Treatment Difference
ETDRS	Early Treatment Diabetic Retinopathy Study
EOS	End of Study
EOT	End of Treatment
ERG	NICE Evidence Review Group
FAc	Fluocinolone Acetonide
FAD	Final Appraisal Document
FDA	Food and Drug Administration
FTH	Foveal Thickness
H0	Null Hypothesis
H1	Alternative Hypothesis

HbA1c	Glycated haemoglobin
HRQoL	Health Related Quality of Life
ICER	Incremental Cost-Effectiveness Ratio
ICH	International Conference on Harmonisation
IOP	Intraocular Pressure
ITC	Indirect Treatment Comparison
ITT	Intention To Treat
IVTA	Intravitreal Triamcinolone Acetonide
LOCF	Last Observation Carried Forward
MD	Mean Difference
MHRA	Medicines and Healthcare products Regulatory Agency
NEI-VFQ	National Eye Institute Visual Function Questionnaire
NHS	National Health Services
NICE	National Institute for Health and Care Excellence
OCT	Optical Coherence Tomography
OWSA	One-Way Sensitivity Analysis
PAS	Patient Access Scheme
PD	Pharmacodynamics
PP	Per Protocol
PRN	*pro re nata* (as needed)
PSA	Probabilistic Sensitivity Analysis
QALY	Quality-Adjusted Life Year
RCT	Randomised Controlled Trial
RWD	Real-World Data
SAS	Statistical Analysis System
SEM	Standard Error of the Mean
SOC	System Organ Class
TA	Technical Appraisal
TD-OCT	Time Domain Optical Coherence Test
TE	Treatment-Experienced
UKPAR	UK Public Assessment Report
VA	Visual Acuity
VEGF	Vascular Endothelial Growth Factor
VFQ	Visual Function Questionnaire

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 Decision problem

Fluocinolone acetonide intravitreal implant 0.19 mg (ILUVIEN®) 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 technology's marketing authorisation only, namely, for the treatment of vision impairment associated with chronic DMO considered insufficiently responsive to available therapies.

NICE technology appraisal (TA)301 recommends fluocinolone acetonide (FAc) intravitreal implant as an option for treating chronic DMO that is insufficiently responsive to available therapies if the implant is to be used in an eye with an intraocular (pseudophakic) lens only.(2) NICE technology appraisal TA613 a part-review of TA301, did not recommend FAc implant for treating chronic DMO in phakic eyes.(3) This does not align with the full marketing authorisation for ILUVIEN in the UK, which does not define or restrict patient eligibility by lens status.(1)

The present technology appraisal is a review of TA613 which, if successful, will resolve a significant unmet need for DMO patients with phakic eyes and confirm the clinical- and cost-effectiveness of FAc implant for the full DMO population in accordance with the marketing authorisation.

The published NICE technology appraisal guidance (TA824) for the comparator recommends dexamethasone intravitreal implant (hereinafter referred to as 'DEX' as an option "for treating visual impairment caused by DMO in adults only if their condition has not responded well enough to, or if they cannot have non-corticosteroid therapy irrespective of whether they have a phakic or pseudophakic lens".(4)

The FAc and DEX implants are both intravitreal corticosteroids of the same therapeutic drug class with similar mechanisms of action. Consequently, a cost-comparison can be made based on the full DMO population that, if successful, will update both TA301 and TA613 recommendations.

The decision problem addressed in this submission is summarised in **Table 1**.

Table 1. The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with chronic diabetic macular oedema that is insufficiently responsive to available therapies who have phakic lenses.	As per scope	
Intervention	Fluocinolone acetonide intravitreal implant	Fluocinolone acetonide intravitreal implant	Not applicable
Comparator(s)	Dexamethasone intravitreal implant	Dexamethasone intravitreal implant	Not applicable
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)	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

	• health-related quality of life, including the effects of changes in visual acuity.		
Special considerations including issues related to equity or equality			As a result of current NICE guidance, an inequality of access persists within the UK DMO patient population. 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.(5)

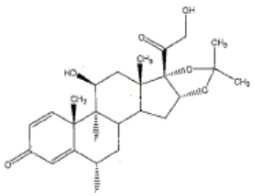
B.1.2 Description of the technology being evaluated

Fluocinolone acetonide intravitreal implant (ILUVIEN®) is a single, sustained release micro-implant, intravitreally-injected and designed to deliver a continuous daily microdose of 0.2 µg/day FAc for up to 36 months. Each implant contains 190 micrograms of FAc, equivalent to a total dose of 0.19 mg.(1) Note that the FAc intravitreal implant was evaluated in the registrational randomised controlled clinical trials (RCTs) at two micro doses, 0.2 µg/day and 0.5 µg/day. The 0.2 µg/day dose (total dose of 0.19 mg) was subsequently approved as the licensed dose. The summary of product characteristics (SPC) and the UK public assessment report (UK PAR) are provided in Appendix C.

The technology for evaluation is described in Table 2.

Table 2. Evaluated technology

UK approved name and brand name	Fluocinolone intravitreal implant (ILUVIEN)
Mechanism of action (1)	The active component in ILUVIEN is fluocinolone acetonide (FAc). FAc is a synthetic corticosteroid (pharmacotherapeutic group: ANTI-INFLAMMATORY AGENTS, corticosteroids, plain, ATC code: S01BA15) that has anti-inflammatory and anti-VEGF properties. Corticosteroids inhibit the inflammatory response to a variety of inciting agents. They inhibit the oedema, fibrin deposition, capillary dilation, leukocyte migration, capillary proliferation, fibroblast proliferation, deposition of collagen, and scar formation associated with inflammation. Corticosteroids are thought to act by the induction of phospholipase A inhibitory proteins, collectively called lipocortins. It is postulated that these proteins control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes by inhibiting the release of the common precursor arachidonic acid. Arachidonic acid is released from membrane phospholipids by phospholipase A_2. Corticosteroids have also been shown to reduce levels of vascular endothelial growth factor, a protein which increases vascular permeability and causes oedema.

	ILUVIEN therefore helps treat the inflammation associated with DMO which in turn helps protect the retina and maintain stable long-term vision for the patient. The chemical name for fluocinolone acetonide is (6α,11β, 16α)-6,9-difluoro-11,21-dihydroxy-16,17-[(1methylethylidene)bis-(oxy)]-pregna-1,4-diene-3,20-dione.[9] Its chemical structure is:  MW 452.50; molecular formula $C_{24}H_{30}F_20_6$ and it has the molecular formula $C_{24}H_{30}F_2O_6$ ILUVIEN has a near zero-order release kinetics for up to 3 years. In a human pharmacokinetic study (C-01-06-002, the FAMOUS Study) fluocinolone acetonide concentrations in plasma were below the lower limit of quantitation of the assay (100 pg/mL) at all time points from Day 1 through to Month 36. The maximal aqueous humour fluocinolone acetonide concentrations were observed on Day 7 for most of the subjects. Aqueous humour fluocinolone acetonide concentrations decreased over the first 3−6 months and remained essentially the same through Month 36 for subjects who were not retreated. Subjects who were retreated experienced a second fluocinolone acetonide peak concentration similar to that following the initial dose. After retreatment, aqueous humour concentrations of fluocinolone acetonide returned to levels approximately similar to those observed at the time of first treatment.
Marketing authorisation/CE mark status	Alimera Sciences Limited was granted a UK marketing authorisation for ILUVIEN from the Medicines and Healthcare products Regulatory Agency (MHRA) for the treatment of vision impairment associated with chronic DMO on 4 May 2012.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	ILUVIEN is indicated for the treatment of: ▪ vision impairment associated with chronic DMO considered insufficiently responsive to available therapies; and ▪ for the prevention of relapse in recurrent non-infectious uveitis affecting the posterior segment of the eye.(1) The present submission relates to the first indication (vision impairment associated with chronic DMO) only.

Method of administration and dosage	The recommended dose is one ILUVIEN implant containing 190 µg (0.19 mg) of FAc in the affected eye. Administration in both eyes concurrently is not recommended on the same visit. Treatment with ILUVIEN is for intravitreal use only and should be administered by an ophthalmologist experienced in intravitreal injections. The intravitreal injection procedure should be carried out under controlled aseptic conditions, that include use of sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent). Adequate anaesthesia and a broad-spectrum microbicide should be given before the injection.(1)
Additional tests or investigations	There are no additional tests or investigations specified in the marketing authorisation.
List price and average cost of a course of treatment	List Price: £5,500 per implant. The confidential Patient Access Scheme (PAS) price is £[redacted] per implant, excluding VAT.
Patient access scheme/commercial arrangement (if applicable)	A confidential PAS arrangement was agreed with NHS England in for TA613 and remains in place.

B.1.3 Health condition and position of the technology in the treatment pathway

B.1.3.1 Health condition

It is estimated that diabetes mellitus (DM) affects over 8% of the world's population. It is associated with significant and major impacts ion mortality and morbidity, and presents a significant challenge to healthcare systems globally.(6) More than 4.8 million people in the UK have DM and this is projected to rise to 5.3 million by 2025.(7) It is estimated that 10% of the entire NHS budget is spent on the care of people with diabetes and, of this, 80% is spent on the consequences and complications of the disease.(8)

Diabetic retinopathy (DR) is a complication of DM and is a leading cause of blindness in adult populations around the world.(9, 10) It is understood that the longer the duration of DM, the higher the prevalence of DR; in patients with DM for 10 years or less the prevalence of DR is 20%, rising to 76% in those with DM for 20 years or more.(11)

DMO is a complication of DR that causes an accumulation of fluid (oedema) within the central portion of the retina, the macula. The macula is responsible for central vision and visual acuity. Centre-involving DMO is a major cause of visual loss in patients with DM and is considered one of the leading causes of severe visual impairment and preventable blindness in the working age population.(12, 13) Swelling of the macula reduces visual acuity. It results from hyperglycaemia-induced activation of pathways which induce oxidative stress with a subsequent release of cytokines. This impairs the inner and outer blood-retinal barriers (BRB).(14) The inner blood-retinal barrier plays a major role in controlling fluid entry into the retina. Fluid regulation is ensured by the tight-junctions between endothelial cells of retinal vessels, dynamically regulated by a neuroglia-vascular crosstalk involving astrocytes and RMG cells.(9) Hyperglycaemia-induced retinal hypoxia and abnormal biochemical pathways increase vitreous levels of VEGF and other inflammatory mediators, and lead to DMO.(15)

Recurrent episodes of DMO can lead to variability in the thickness of the retina which, over time, can result in retinal damage and irreversible sight loss.(11, 16-18) These morphological changes occur in both phakic and pseudophakic eyes. Achieving a dry retina is a critical objective in the therapeutic management of DMO. The build-up of fluid from leakage of damaged or abnormal blood vessels characterises the pathogenesis of DMO, is indicative of compromised retinal structure and can be predictive of a deterioration in function.(19) Persistent oedema compromises the spatial relationships between the retinal neuronal components, over time this can destroy the connection between both photoreceptors and ganglion cells. This anatomical degradation can lead to irreversible vision loss.(20) An unmet need which allows for predictable and consistent resolution of retinal oedema in DMO persists. Recurrence of oedema i.e., repeated cycle of retina expansion and contraction damage the retina and have been linked with worse visual outcome.(19) The FAc implant is designed to protect the retina and is indicated for the treatment of the vision impairment associated with DMO.

The global prevalence of DMO is estimated to be 4.6%.(21) There is a dearth of up-to-date public health estimates specific to the prevalence of DMO in the UK. In 2010,

estimated prevalence of DMO in England was 7.1%.(22) Outputs from a 2016 systematic literature review and meta-analysis on the prevalence and incidence of DR and DMO in Europe estimated, specific to the UK, a clinically significant DMO prevalence rate of 5.2%.(23)

B.1.3.2 Clinical pathway of care

The goal of treatment in DMO is to preserve or improve retinal function by reducing retinal thickening and macula oedema (improve morphological changes) and ultimately improve vision outcomes for the patient.(11, 18)

Standard of care treatment for DMO since the mid-1980s was laser photocoagulation. However, the introduction of intravitreal anti-VEGF injections over the last 15 years has mostly replaced laser photocoagulation and is now considered standard first-line therapy for treatment-naïve patients presenting with DMO in the UK. NICE has recommended the use of four anti-VEGF therapies to date: ranibizumab (TA274), aflibercept (TA346), faricimab (TA799) and brolucizumab (TA820).(24-27) A fifth anti-VEGF option, bevacizumab, is also sometimes used in clinical practice to treat DMO patients, although it does not have a marketing authorisation for this indication.

However, despite the known role of VEGF is the development of DMO, anti-VEGF therapy has been shown to be ineffective in some patients with DMO.(17, 18, 28) A sizeable proportion of DMO patients are unsuitable for anti-VEGF therapy or do not respond sufficiently to treatment and may continue to receive anti-VEGF therapy even though the clinical benefits are sub-optimal.(11, 17, 18, 29) The EARLY trial analysis clearly identified that up to 40% of patients had a <5 letter-change at 3 months following anti-VEGF treatment.(17) The literature confirms that the pathophysiological evolution of DMO is multi-factorial and complex, whereby VEGF is not the only mediator of DMO pathology. Instead, both angiogenesis and inflammation have been shown to underpin disease progression.(16) There is increasing evidence which support the role of the inflammatory process in the pathogenesis of DMO. Clinically it is not possible to determine which pathway is predominating i.e., pro-angiogenic or pro-inflammatory mechanisms.(11, 18) Where

extracellular fluid build-up persists as determined through OCT evaluation following treatment with anti-VEGF agents within 3-6 months it may signal that the inflammatory pathway predominates. As the DMO becomes more inflammatory-driven, it becomes less responsive to anti-VEGF therapy and in some patients the DMO becomes resistant to anti-VEGF therapy.

In these circumstances, changing to a different therapeutic strategy (i.e. an intravitreal corticosteroid regimen), which have been demonstrated to exert an effect in retinal preservation irrespective of lens status, should be implemented as the clinical effect is not being exerted.(18, 30-32) Changing treatment to an intravitreal corticosteroid implant at the appropriate time, whether short-acting or long-acting, may help optimise patient outcomes and reduce injection frequency, thereby reducing treatment burden.

Dexamethasone intravitreal implant (trade name, OZURDEX®) is an intravitreal corticosteroid indicated in the UK for the treatment of adult patients with visual impairment due to DMO who are pseudophakic or who are considered insufficiently responsive to, or unsuitable for non-corticosteroid therapy. DEX is a short-acting corticosteroid, with retreatment (re-implantation) performed after approximately 6 months in DMO patients who have experienced an initial response to DEX and who, in the physician's opinion, may benefit from retreatment without being exposed to significant risk.(33) Retreatment may also be performed after approximately 6 months if the patient experiences decreased vision and/or an increase in retinal thickness, secondary to recurrent or worsening DMO.

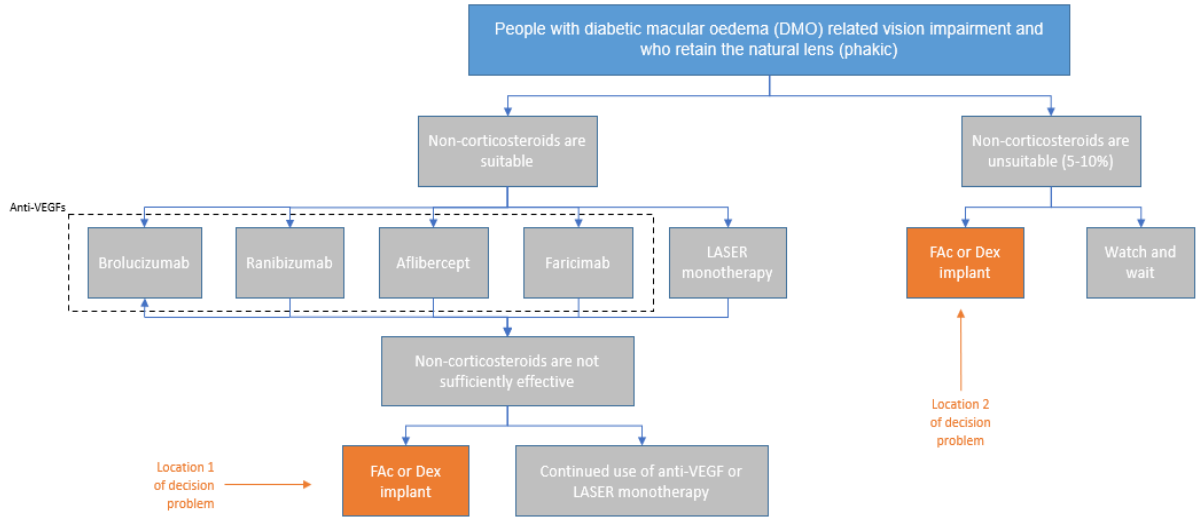
DEX is currently recommended by NICE where patients have had a sub-optimal response to anti-VEGF therapy or in cases where anti-VEGF therapy is contraindicated, irrespective of their lens status.(4)

The FAc implant (ILUVIEN) is another intravitreal corticosteroid implant and an alternative treatment option for DMO patients insufficiently responsive to available therapies. It is currently used at the same point in the treatment pathway as DEX, i.e., where anti-VEGF therapies and/or laser monotherapy have proved ineffective or sub-optimal.

Figure 1 outlines the current pharmacological management of DMO in the NHS and the position of both FAc implant and DEX in the pathway.

However, unlike DEX, the FAc implant is currently only recommended by NICE in patients with a pseudophakic lens.(3) The FAc implant is a long-acting corticosteroid, with the treatment effect lasting for up to 36 months.(1) Consequently, unfair bias in terms of access to available efficacious corticosteroid therapies exists whereby, in clinically-suitable patients, FAc treatment is restricted to those patients having an intraocular lens.

Figure 1. Treatment pathway and position of FAc implant



Abbreviations: FAc implant, fluocinolone acetonide intravitreal implant; Dex, dexamethasone intravitreal implant.
Note. Blue = decision problem population; grey = treatment options; orange = position of comparison in the decision problem.

UK clinical experts consulted by the company have confirmed that the pathway depicted in Figure 1 is representative of clinical practice in the NHS in England and agree that the proposed positioning of FAc implant in the treatment pathway (i.e., for it to be available to be prescribed to DMO patients with either a pseudophakic or phakic lens insufficiently responsive to available therapies) is both appropriate and necessary to address a significant unmet need that persists for longer-acting therapies for DMO patients, irrespective of their lens status, and also to improve the management of ophthalmology/ocular service capacity in the NHS.(34)

The company's clinical advisers further noted that the clinical efficacy, safety and durability of effect of FAc implant demonstrated in both phakic and pseudophakic eyes in the pivotal FAME registration studies has been replicated in real-world practice.(35-37)

With its 36-months duration of action, a single FAc intravitreal implant addresses an unmet therapeutic need by providing a longer-acting protective effect to the retina for DMO patients, irrespective of their lens status, and thereby avoiding loss of vision.

Ocular injections can be a source of fear, stress, and anxiety for patients with retinal diseases, and the frequent clinic visits, injections, and patient monitoring required to achieve optimal long-term outcomes for patients with DMO results in a high burden of treatment for patients and their caregivers.(5) Patients with DMO were found to have a mean of 19.1 appointments over a 6-month period with healthcare professionals, including diabetologists, retina specialists, ophthalmologists, and their GP. For patients with additional comorbidities additional appointments with specialists including neurologists, cardiologists, nephrologists, and podiatrists greatly increase the clinical contact burden for patients.(38) The patient burden is thus significant. With its 36-month duration of action, FAc implant aligns with patient need and preferences outlined in NICE TA824, allowing the patient to maintain the same level of vision as other treatment options, but with even fewer injections. Nationally, ophthalmology services represent the second highest throughput for outpatient attendance relative to other medical and surgical conditions. In a Wessex study, a disproportionate increase in the demand for eye care services is projected for the over-65-year-old cohort.(39) A transformation in clinical care pathways and service delivery is required to address current and projected capacity issues. The use of FAc 0.19 mg can significantly reduce treatment burden in the overall DMO patient population. One consequence of reduced treatment burden is the consequential reduction in clinic burden and freeing-up NHS capacity**.**

B.1.4 Equality considerations

If a person is registered as blind or partially sighted, they are considered disabled, as stated in the Equality Act 2010. Therefore, the patient population addressed in this submission is a protected group under this Act**.**

B.2 Key drivers of the cost effectiveness of the comparator(s)

B.2.1 Clinical outcomes and measures

The comparator in this appraisal, DEX 0.7 mg DEX, was evaluated against anti-VEGF therapies in the cost-effectiveness analysis of NICE TA824 in the same DMO population specified in the present decision problem.(4) The submitting company in TA824 also built on preferences and assumptions used in the earlier NICE technology appraisals of the FAc implant, TA301 and TA613.(2, 3)

The TA824 committee concluded that 'Clinical trial evidence [from MEAD-010 and MEAD-011 RCTs] shows that [DEX] is more effective than a sham (inactive) procedure. The sham procedure may be considered as a proxy for continued anti-VEGF therapies. The resulting cost-effectiveness estimates for [DEX] compared with anti-VEGF therapy are likely to be within what NICE normally considers an acceptable use of NHS resources' (see Section 1.2 of the final appraisal document (FAD)); and

> 'Each of the plausible analyses for [DEX] compared with anti-VEGFs in the population with phakic eyes when non-corticosteroids do not work well enough resulted in ICERs showing that [DEX] dominated anti-VEGFs, or that [DEX] was associated with cost savings per QALY lost in the range normally considered a cost-effective use of NHS resources.'

The clinical outcomes and measures in the final scope of TA824 that were included by the company in their submission were best-corrected visual acuity (BCVA, affected eye and both eyes), central subfield thickness (CST), intraretinal and

subretinal fluid, mortality, adverse effects of treatment and health-related quality of life (HRQoL). However, the primary clinical outcome driving the modelled quality-adjusted life year (QALY) outcome was change in BCVA. The key clinical driver of the cost-effectiveness results relevant to this outcome was HRQoL.

In TA824, the Evidence Review Group (ERG) noted the following uncertainties in the assumptions around, and estimates for, BCVA:

- the company's assumption that sham in the MEAD trials over-estimated the efficacy of anti-VEGF therapy;
- the use of 'last observation carried forward (LOCF)' for computation of missing data in MEAD for changes in BCVA;
- the maximum duration of treatment (5 years versus 3 years in TA349 – the TA prior to TA824 for DEX in DMO, which did not specify lens status);
- the assumed changes in BCVA in years 4 and 5 in the absence of long-term data were improved cost-effectiveness versus a 3-year horizon; and
- assumptions were too simplistic throughout the lifetime horizon to accurately capture [differences in] the consequences of treatment.

Of note, TA824 considered a cost-effectiveness analysis of DEX versus two anti-VEGF therapies using the NICE Single Technology Appraisal route; in contrast, the present evaluation consists of a cost-comparison between FAc and DEX on a premise of equivalence or similarity in health outcomes. This means that measurement of HRQoL is excluded and that some of the uncertainties identified in TA824 are not relevant to the present cost-comparison. Uncertainties that are relevant to this cost-comparison are uncertainty in maximum duration of treatment; use of treatments beyond the 3-year trial follow-ups; and the most appropriate time-horizon.

B.2.2 Resource use assumptions

In relation to resource utilisation, the TA824 FAD described several benefits of DEX and made several statements that are also relevant to this cost-comparison. These are summarised in Table 3.

Table 3. Benefits of DEX described in TA824 relevant to this cost-comparison

DEX benefits described in TA824	Source	Relevant to the present cost-comparison
Treatment burden of frequent injections 'The patient expert highlighted that having frequent eye injections causes fear, but there is no alternative because laser therapy has not been very effective for them. They emphasised that reducing the number of times they need treatment, especially for an eye injection, would be of huge benefit for their quality of life.'	Section 3.1 of the TA824 FAD	Yes
Reduced clinic visits 'Using dexamethasone intravitreal implant would reduce the number of visits to the eye clinics for follow up or treatment. The clinical experts explained that a longer time between treatments will free up the capacity in the NHS as well as improve quality of life for people with diabetic macular oedema.'	Section 3.2 of the TA824 FAD	Yes
Time on treatment '…neither DEX700 nor anti-VEGFs have a predefined treatment regimen where retreatment is defined at regular intervals, rather the need for retreatment is assessed at regular intervals. As such the proportion of patients receiving a DEX700 intravitreal implant, an anti-VEGF injection or laser treatment in a given model cycle is not necessarily reflective of the proportion on continued treatment. Treatment discontinuation is modelled independently of the average number of treatments received by patients on treatment.		The same relationship applies in the present cost-comparison
Number of DEX injections 'The ERG notes that due to the 3 years follow up period of the MEAD trials, the company's estimation of DEX700 administration costs for Years 4 and 5 of treatment was reliant on the company's clinical expert's estimation of the average number of intravitreal implants patients would receive in the two remaining years of treatment. These estimates suggested reduced treatment (1 implant per year) in Years 4 and 5. The ERG's clinical experts instead considered that the average number of intravitreal implants observed in Year 3 (*** implants per year) would be maintained for Years 4 and 5 for those patients remaining on treatment. This is also consistent with company's assumption that the average number of anti-VEGF		This uncertainty also applies to the present cost-comparison.

injections from Year 3 remained constant until the end of Year 5.'		
Resource use assumptions 'The ERG's clinical experts disagreed with some of the company's resource use assumptions. Namely that fluorescein angiography was rarely used in clinical practice (once every 5 years for patients on and off treatment)…', 'the impact of these alternative assumptions was found to be minimal. The ERG's clinical experts also acknowledged that clinical practice is variable and therefore no changes to these resource use assumptions have been made to the ERG's preferred base case.'		Yes
The ERG in TA824 concluded that: 'As for the estimation of unit costs and resource use, the ERG considers the company's methods to be generally reasonable'.		Yes

B.3 Clinical effectiveness

B.3.1 Identification and selection of relevant studies

In order to support the decision problem, and in the absence of direct comparative clinical trial evidence comparing the efficacy and safety of the technology and the comparator as treatment options for DMO, the company needed to generate estimates of comparative efficacy for FAc 0.19 mg in comparison to DEX 0.7 mg in DMO patients with a phakic lens who have insufficient response to, or who are unsuitable for treatment with, non-corticosteroid treatment.

To identify the best available evidence to generate new estimates of comparative efficacy, a systematic literature review (SLR) was conducted with inclusion criteria aligned to the decision problem. The purpose of the SLR was to identify and synthesise clinical evidence describing the efficacy and safety of the FAc implant (ILUVIEN®) and dexamethasone implant (OZURDEX®) or DEX.

The SLR was conducted following the standards set out in the Preferred Reporting Items for Systematic Reviews and Meta-analyses and the Cochrane Handbook for Systematic Reviews of Interventions, as well as guidance issued by NICE.(40-42)

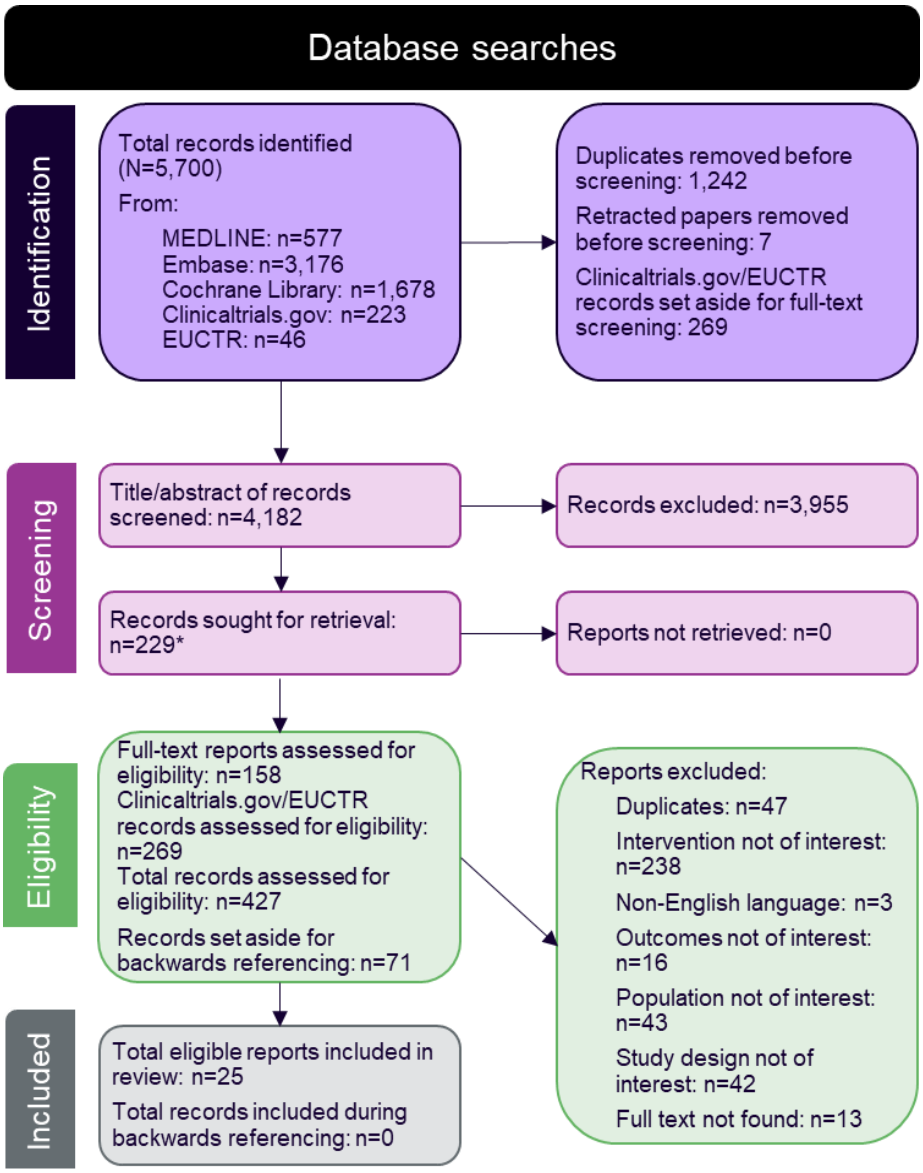
The searches for this SLR were conducted in the following electronic databases:

- MEDLINE®, MEDLINE® In-Process & Other Non-Indexed Citations, MEDLINE® ePub Ahead of Print, and MEDLINE® Daily
- Embase
- The Cochrane Library, incorporating:
    - Cochrane Central Register of Controlled Trials (CENTRAL)
    - Cochrane Database of Systematic Reviews (CDSR)

B.3.1.1 Search results

The database searches conducted on 09 May 2023 yielded 5,700 records, from which 1,242 duplicates and 7 retracted papers were removed. An additional 269 records identified via clinicaltrials.gov and the EUCTR were put aside for full text screening. The remaining 4,182 records were screened based on their title and abstract, excluding 3,955 records and identifying 229 potentially relevant records. Of these, 71 records were set aside for backwards referencing, leaving 158 potentially relevant records alongside the 269 records previously set aside. These 427 records underwent full text screening, resulting in the exclusion of 402 records. Overall, 25 publications, reporting data for 10 unique RCTs, were eligible for inclusion in the SLR (Table 4). The PRISMA flow diagram for the search is presented in Figure 2.

Figure 2. PRISMA diagram



Full details of the process and methods used to identify and select the clinical evidence relevant to the technology being evaluated and the comparator, DEX, are present in Appendix D.

B.3.2 List of relevant clinical effectiveness evidence

A summary of the 10 clinical studies included in the SLR is presented in Table 4.

Table 4. Summary of identified clinical trials

Trial name	N	Patient population	Intervention	Comparator	Follow-up	Efficacy results	Safety results	Trial publications (identified in the SLR)
FAME	956	Adult patients with persistent DMO despite at least 1 macular laser treatment	Fluocinolone acetonide intravitreal implant (0.5 µg/day, 0.2µg/day) (ILUVIEN®)	Sham procedure	36 months	✓	✓	(35, 37, 43-45)
MEAD (NCT00168337 /NCT00168389)	1048	Adult patients with DMO, BCVA of 20/50 to 20/200 Snellen equivalent, and CRT of ≥300 µm by optical coherence tomography.	Dexamethasone intravitreal implant (0.7 mg, 0.35 mg) (OZURDEX®)	Sham procedure	36 months	✓	✓	(31, 46-48)
NCT00502541	196	Adult patients with DMO, visual acuity of ≥20 and ≤68 letters, received at least one macular laser treatment > 12 weeks prior to entry into the study	Fluocinolone acetonide intravitreal implant (Retisert™)	Standard of care	26 weeks	✓	✓	(49-51)

Trial name	N	Patient population	Intervention	Comparator	Follow-up	Efficacy results	Safety results	Trial publications (identified in the SLR)
Pearson, 2003	80	Adult patients with a history of macular laser photocoagulation and refractory or recurrent DMO	Fluocinolone acetonide intravitreal Implant (2mg, 0.5mg, Retisert™)	Standard of care	12 months	✓	✓	(52)
NCT01945866	129	Adult patients with DMO, visual acuity of 24-78 letters, CSF thickness of ≥290µm (female), or ≥ 305µm microns males, and at least 3 injections of an anti-VEGF 20 weeks prior to study entry.	Dexamethasone intravitreal implant + ranibizumab 0.3mg	Sham procedure + ranibizumab (0.3 mg)	24 weeks	✓	✓	(53)
BEVORDEX (NCT01298076)	61	Adult patients with DMO for which laser treatment is unlikely to be helpful, visual acuity of 17-72 letters, and CRT >250µm	Dexamethasone intravitreal implant	Bevacizumab (1.25mg)	24 months	✓	✓	(54-59)
DIME (NCT02471651)	30	Adult patients with DMO, visual acuity of 17-72 letters, and CRT >250µm	Dexamethasone intravitreal implant (0.7mg)	Anti-VEGF injection (Ranibizumab, bevacizumab, or aflibercept)	12 months	✓	X	(60)

Trial name	N	Patient population	Intervention	Comparator	Follow-up	Efficacy results	Safety results	Trial publications (identified in the SLR)
NCT01571232	20	Adult patients with DME visual acuity of 3-78 letters, < 0.1 LogOCT decrease in macular oedema and at least 2 injections of an anti-VEGF prior to study entry.	Dexamethasone intravitreal implant (0.7mg)	Bevacizumab (1.25mg)	6 months	✓	✓	(61)
Maturi, 2015	30	Adult patients with DME with incomplete response to multiple anti-VEGFs	Dexamethasone intravitreal implant (0.7 mg)	Bevacizumab (1.25 mg)	1 year	✓	✓	(62)
NCT02036424	45	Adult patients with DME visual acuity of 24-78 letters, CSF thickness of >340µm and at least 3 injections of an anti-VEGF 20 weeks prior to study entry.	Dexamethasone intravitreal implant (0.7mg)	Bevacizumab (1.25 mg)	10 months	✓	✓	(63)

Abbreviations: BCVA, best-corrected visual acuity, DMO, diabetic macular oedema, CSF, central subfield, CRT, central retinal thickness, OCT, optical coherence tomography, VEGF, vascular endothelial growth factor.

Of the ten RCTs that were identified, only two (FAME and MEAD, the Phase 3 regulatory submission trials for the technology and the comparator, respectively) were assessed as relevant for inclusion in the indirect treatment comparison (ITC) analysis comparing the relative efficacy and safety of FAc 0.19 mg (equivalent to 0.2 µg per day) and DEX 0.7 mg in phakic DMO patients who are unsuitable for, or insufficiently responsive to non-corticosteroid therapies. The rationale for the exclusion of the remaining eight studies is presented in Appendix D.

The RCT clinical effectiveness evidence presented in B.3.2 – B.3.6 is thus confined to the FAME studies for the FAc implant (two phase 3 randomised, sham-controlled trials of identical design, FAME A and FAME B) and the MEAD studies for the dexamethasone implant (two phase 3 randomised, sham-controlled trials of identical design). A summary of the clinical effectiveness evidence relevant to the decision problem (FAME studies for the FAc implant and the MEAD studies for DEX 0.7 mg) is provided in The results of the sub-group analyses reported by Boyer et al., Yang et al., and Augustin et al. are presented in Appendix E.

Table 5.

Additional supportive non-randomised or observational evidence of the efficacy and safety of the FAc implant from real-world studies if presented in Section B.3.6.7 and discussed in Section B.4.

Phakic eye population

Individual patient data from the FAME studies and aggregated published data from the MEAD studies were used to inform the ITC and the cost-comparison model included in this company submission.

Campochiaro et al. [12] present the pivotal 24-month results for the FAME studies, which included only DMO patients who had received at least one prior laser treatment. The FAME study populations were not stratified according to whether subjects had a phakic or pseudophakic lens in the study eye at baseline, nor was there are pre-specified subgroup analysis based on lens status.

Boyer et al. present the pivotal 36-month results for the MEAD studies, which included both treatment-experienced (TE) and treatment-naïve patients, and eyes with a phakic or pseudophakic lens.(31) Boyer et al. also present a subgroup analysis of change in BCVA and central retinal thickness (CRT) from baseline for patients with a phakic lens who experienced a cataract-related adverse event (AE). This subgroup analysis included both TE and treatment-naïve patients. A second analysis of MEAD presented by Augustin et al. presented 36-month results for the TE subgroup of patients in MEAD.

Further information about the trials and clinical outcomes included in the ITC are presented in section B.3.9.

The results of the sub-group analyses reported by Boyer et al., Yang et al., and Augustin et al. are presented in Appendix E.

Table 5. Summary of RCT clinical effectiveness evidence

Study	**FAME A and FAME B** NCT00344968	**MEAD studies** MEAD–010 (NCT00168337) MEAD-011 (NCT00168389)
Study publications	Primary publication: Campochiaro et al. 2011 Key secondary publication: Campochiaro et al. 2012 Phakic DMO subpopulation only: Yang et al. (12, 35, 44)	Primary publication: Boyer et al. Key secondary publication: Augustin et al. (31, 46)
Study design	A Phase 3 randomised, double-masked, parallel group, multi-centre, dose finding comparison of the safety and efficacy of ASI-0001A 0.5µg/day and ASI-001B 0.2 µg/day fluocinolone acetonide intravitreal implants to sham injection in subjects with diabetic macular oedema (DMO).	Two randomised, multi-centre, masked, sham-controlled, phase III clinical trials with identical protocols were conducted.
Population	Subjects with persistent DMO despite at least 1 macular laser treatment.	Patients with DME, best-corrected visual acuity (BCVA) of 20/50 to 20/200 Snellen equivalent, and central retinal thickness (CRT) of ≥300 µm by optical coherence tomography.
Randomisation	1:2:2 to sham injection (n=185), FAc 0.2 µg/day (low-dose) (n=375), or FAc 0.5 µg/day (high-dose)(n=393).	Patients were randomised in a 1:1:1 ratio to study treatment with dexamethasone intravitreal implant (DEX) 0.7 mg (n=351), DEX 0.35 mg (n=347), or sham procedure (n=350) and followed for 3 years (or 39 months for patients treated at month 36) at 40 scheduled visits. Patients who met retreatment eligibility criteria could be retreated no more often than every 6 months.
Intervention(s)	Active treatment consisted of FAc intravitreal implant 0.2 µg/day (low-dose) or 0.5 µg/day (high-dose). The FAc intravitreal implant was implanted through the pars plana into the vitreous of the eye using a 25-gauge needle.	Dexamethasone intravitreal implant (DEX) 0.7 mg (n=351), DEX 0.35 mg (n=347)

Study	**FAME A and FAME B** NCT00344968		**MEAD studies** MEAD–010 (NCT00168337) MEAD-011 (NCT00168389)
Comparator(s)	The sham injection consisted of the needle hub being pressed against the globe of the study eye to simulate injection of an implant.		Sham procedure (n=350)
Indicate if study supports application for marketing authorisation (yes/no)	Yes	Yes	Yes
Reported outcomes specified in the decision problem	The primary outcome was the percentage of patients with improvement from baseline best-corrected visual acuity (BCVA) in Early Treatment Diabetic Retinopathy Trial (ETDRS) letter score of 15 or more at Month 24. Secondary outcomes included other parameters of visual function and foveal thickness (FTH). Safety outcome measures included ocular and non-ocular adverse events (AEs) and intraocular pressure (IOP).		The predefined primary efficacy endpoint for the United States Food and Drug Administration was achievement of 15-letter improvement in BCVA from baseline at study end and average change in CRT from baseline during the study by OCT (AUC, area-under-the-curve approach). Safety outcome measures included ocular and non-ocular adverse events (AEs) and intraocular pressure (IOP).
All other reported outcomes			Secondary efficacy outcomes for the study eye included average change in BCVA from baseline during the study determined with the area under the curve (AUC) method, mean change in BCVA from baseline at each study visit, time to ≥15-letter improvement in BCVA from baseline, percentage of patients with BCVA of >20/40 at each study visit, and average change in CRT from baseline during the study by OCT (AUC approach).

Study	FAME A and FAME B NCT00344968	MEAD studies MEAD–010 (NCT00168337) MEAD-011 (NCT00168389)
		Additional safety outcomes included biomicroscopic and ophthalmoscopic findings, and measures of diabetes control (HbA1c and glomerular filtration rate).

B.3.3 Summary of methodology of the relevant clinical effectiveness evidence

Unless otherwise stated, evidence from the FAME A and FAME B studies were sourced from the primary clinical study reports. Information on the MEAD trials for the comparator, DEX, was sourced from the primary publication, Boyer et al., and from TA824).(4, 31)

B.3.3.1 FAME studies - Study design

The Phase 3 registrational FAME studies (single protocol: NCT00344968) evaluate the safety and efficacy of the FAc implant at two doses (0.5 µg/day and 0.2 µg/day) compared to sham injection in patients with DMO who had received at least one prior macular laser treatment for their DMO. Both FAME A and FAME B studies were conducted under a single protocol as randomised, double-masked, sham injection controlled, parallel-group, multi-centre studies conducted over a 36-month period. FAME A and FAME B were identical in design.

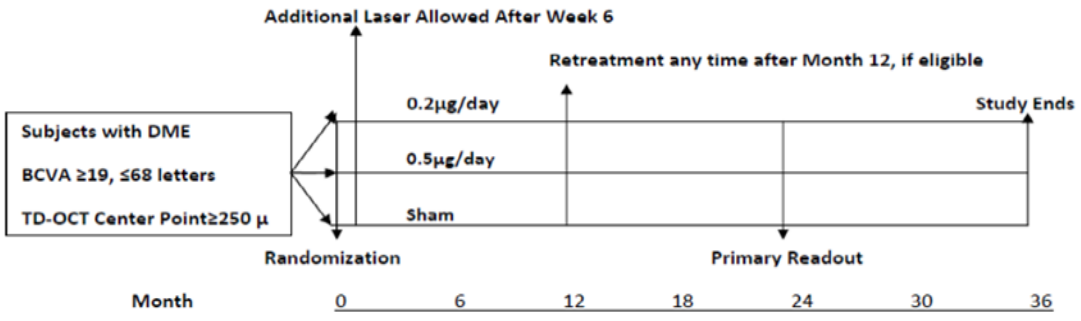
A total of 956 patients with persistent DMO despite having received at least one prior macular laser treatment were randomised 1:2:2 to receive either the 0.2 µg/day FAc implant (n=375), the 0.5 µg/day FAc implant (n=393) or a sham intervention (n=185) in one eye.

Study visits consisted of at least 18 visits over the duration of the study and a 3-year post-treatment period, included a screening visit conducted within 21 days of enrolment, and a baseline visit (Day 0), followed by visits at Week 1, Week 6, Month 3 following initial study treatment and every 3 months thereafter to the end of the study (EOS). Study assessments included best-corrected visual acuity (BCVA), optical coherence tomography (OCT), fluorescein angiography, fundus photography, adverse events, and concomitant medications.

After 6 weeks, all patients were eligible for laser photocoagulation therapy. At the time the FAME studies were conducted laser photocoagulation was the mainstay of treatment for DMO.(64) Nonetheless, despite laser treatment, not all patients were responsive to laser therapy and continued to experience visual loss. After Month 12, all patients were eligible for re-treatment with randomised study drug or the sham intervention if they had lost 5 letters or more of BCVA or experienced an increase in retinal centre point thickness (CPT) of 50 µm or more from their best reading in the previous 12 months. Other therapies, such as anti-VEGF and intravitreal triamcinolone acetonide, now considered part of the standard of care, were not allowed to be included in the protocol because at the time of the trial they were not approved for DMO. Some patients were prescribed these off-protocol therapies to control their disease; these patients were not removed from the statistical analyses and were recorded as protocol deviations.

A schematic of the FAME study design is presented in Figure 3.

Figure 3. FAME Study Design



Source: UK Public Assessment Report ILUVIEN 190 mg 2019.(65)

A summary of FAME A and FAME B study methodologies is presented in

Table ***6***.

Table 6. FAME studies - Summary of study methodology

Study	FAME A NCT00344968	FAME B NCT00344968
Settings and locations where the data were collected	FAME A was conducted at 49 sites in the United States, Canada, 4 countries in the European Union, and India	FAME B was conducted at 52 sites in the United States, India, and three countries in the European Union
Trial design	Randomised, double-masked, sham injection controlled, parallel-group, multi-centre studies	
Eligibility criteria	**Key inclusion criteria** 1. Males and non-pregnant females at least 18 years of age. 2. BCVA of ≥19 and ≤68 letters (20/50 or worse but at least 20/400) in the study eye by an Early Treatment Diabetic Retinopathy Study (ETDRS) chart. BCVA of the non-study eye must have been no worse than 20/400. 3. Diagnosis of diabetes mellitus (type 1 or type 2). Any 1 of the following were considered sufficient evidence that diabetes was present: a. Use of insulin for the treatment of diabetes for at least the 3 months before screening. b. Use of oral antihyperglycemic agents for the treatment of diabetes for at least the 3 months before screening. 4. At least 1 macular laser treatment more than 12 weeks before the screening visit.[+] 5. DMO based on investigator's clinical evaluation and demonstrated on fundus photographs, fluorescein angiograms, and OCT. 6. Mean foveal thickness of at least 250 µm by OCT in the study eye. 7. Ability and willingness to comply with the treatment and follow-up procedures. 8. Ability to understand and sign the ICF. No expectation that subject was moving out of the area of the clinical centre to an area not covered by another clinical centre during the next 36 months. **Key exclusion criteria** 1. Pregnant, lactating females or females of childbearing potential (unless using reliable contraception, i.e., double barrier, surgical sterilisation, oral contraceptives, Norplant, intrauterine device.	

Study	FAME A NCT00344968	FAME B NCT00344968
	2. Laser treatment for DMO within 12 weeks of screening or judged to be necessary within 6 weeks following enrolment. 3. Any ocular surgery in the study eye within 12 weeks of screening. 4. YAG capsulotomy in the study eye within 15 days of screening. 5. Prior intravitreal, sub-Tenon, or periocular steroid therapy within 3 months before enrolment (e.g., triamcinolone acetonide) or prior treatment with intravitreal anti-VEGF treatment within 2 months of enrolment. Systemic treatment with bevacizumab was also not allowed within 3 months before screening. 6. Any change in systemic steroidal therapy within 3 months of screening. 7. Glaucoma, ocular hypertension, intraocular pressure (IOP) >21 mmHg or concurrent therapy at screening with IOP-lowering agents in the study eye. 8. Retinal or choroidal neovascularisation due to ocular conditions other than DR (e.g., presumed ocular histoplasmosis, high myopia [spherical equivalent >8 dioptres], macular degeneration). 9. Any active viral, fungal, or bacterial disease of the cornea or conjunctiva or any history of a potentially recurrent infection which could have been activated by treatment with a steroid, (e.g., ocular herpes simplex virus). 10. Known or suspected hypersensitivity to any of the ingredients of the investigational product or to other corticosteroids. 11. History of vitrectomy in the study eye. 12. History of uncontrolled IOP elevation with steroid use that did not respond to topical therapy. 13. History or presence of any disease or condition (malignancy) that in the investigator's opinion would preclude study treatment or follow-up. 14. Any lens opacity which impairs visualisation of the posterior pole or significantly impairs vision, in the opinion of the investigator. 15. Peripheral retinal detachment in prospective area of insertion. 16. Participation in another clinical trial within 12 weeks before the screening visit or during the study. 17. Resting systolic blood pressure (BP) of greater than 180 mmHg or diastolic BP greater than 105 mmHg at the screening visit.	

Study	FAME A NCT00344968	FAME B NCT00344968
Trial drug	Active treatment consisted of either FAc implant at a dose of 0.2 µg/day or 0.5 µg/day. The FAc intravitreal implant was implanted through the pars plana into the vitreous using a 25-gauge needle. Patients assigned to active therapy received a single FAc intravitreal implant in the study eye.*	
Comparator	The sham injection consisted of the needle hub being pressed against the globe of the study eye to simulate injection of an implant.	
Concomitant / prohibited medications	Patients were eligible for retreatment with their initially assigned study drug at Month 12 if they had lost 5 or more letters in BCVA or there was an increase in foveal thickness of 50 µm or more compared to the subject's best status in the previous 12 months. In the case of retreatment, there were 2 follow-up visits on 1 day and 1 week. Although treatment with out-of-protocol therapies was discouraged, patients treated with other, out-of-protocol rescue therapies were retained in the study and included as part of the analysis population. Concomitant medications were allowed as per protocol.	
Dose adjustments and study drug interruptions	No dose adjustments were facilitated in the trial design for both FAME studies. Due to the long-acting profile of the FAc implant in the FAME studies, patients received a single injection. No drug interruptions were feasible or incorporated into the trial design. Where clinically indicated, in the event of an adverse event patients could have the FAc implant surgically removed at the discretion of the Principal Investigator. No surgical removals of the FAc implant were reported.	

***** The assigned treatment was administered to only 1 eye, referred to as the “study” eye. For patients with unilateral DMO, the “study eye” was the affected eye; for patients with bilateral DMO, the “study eye” was the more severely affected eye fitting the inclusion/exclusion criteria. If both eyes were equally affected and eligible, the “study eye” was determined by the patient number allocated at randomisation (even, right eye and odd, left eye).
+ Per the protocol, initially all patients were required to have had prior macular laser; however, to increase enrolment, the protocol was amended to permit patients with no prior laser into the study (Amendment 4, dated August 3, 2006). This amendment was in force for approximately 7 months before the sponsor amended the protocol again to remove this change because there was concern that the response of the population without prior laser might be significantly different from those with prior laser (Amendment 5 dated March 5, 2007). Twelve patients were enrolled who had not received prior laser.

B.3.3.2 FAME studies - Outcomes

The primary objective of both FAME studies was to determine if either dose of FAc intravitreal implant was superior to the control group measured by the proportion of subjects with a ≥15-letter increase in BCVA at Month 24 compared to baseline. The primary endpoint of the study was the percentage of study subjects with an improvement in BCVA of ≥15 letters at 24 months.

Key secondary endpoints included the mean average reduction in foveal thickness (FTH) at Month 24 and Month 36 compared to baseline, and ocular safety outcomes, including intraocular pressure (IOP) and cataract development.

All study outcomes were pre-specified as per the statistical analysis plan and are presented in Table 7. Results were pooled for analysis across the two studies.

Table 7. FAME studies – Outcomes for evaluation

	Criteria for evaluation FAME A and FAME B
Primary efficacy endpoint	The primary efficacy outcome was the proportion of subjects with a ≥15-letter increase from baseline in BCVA in their study eye at Month 24.
Secondary efficacy endpoints	Secondary efficacy outcomes included mean change from baseline in BCVA, mean change from baseline in the excess average foveal thickness, and the proportion of subjects with ≥3-step worsening in the study eye compared to baseline in the ETDRS Multi-Step Eye Scale of DR.
Exploratory endpoints	There were numerous exploratory variables related to BCVA; ETDRS multi-step eye scale of DR; OCT, colour fundus photographs; fluorescein angiography; contrast sensitivity; use of laser therapy and disallowed treatments; and retreatment.
Health-Related Quality of Life (HRQoL)	Health-Related Quality of Life (HRQOL) was assessed using the 25-item vision function questionnaire (VFQ-25) or the VFQ-39 (at selected sites).
Pharmacodynamics	Pharmacodynamics: Pharmacodynamic (PD) analyses included linear correlations between change from baseline in BCVA at Month 24, centre point thickness, and macular volume and baseline haemoglobin A1c (HbA1c), age, duration of diabetes, baseline BCVA, diastolic blood pressure (BP), and systolic BP.
Safety	Safety was assessed by adverse event (AE) reporting, HbA1c, vital signs, intraocular pressure (IOP) increases and cataract formation, loss of VA, lens opacity measurements, dilated ophthalmoscopy, slit-lamp examination, and specular microscopy

Pre-Planned Sub-Group Analysis	A pre-planned subgroup analysis of long-duration (duration from diagnosis ≥3 years) and short-duration (duration from diagnosis <3 years) DMO was also performed to understand the difference in efficacy and safety with the 0.2 µg /day FAc intravitreal implant.

B.3.3.3 FAME studies - Patient demographics and baseline characteristics

Demographic and baseline characteristics for all patients enrolled to FAME A and B were similar across the 3 treatment groups.(35) To allow for comparison across study groups for continuous variables p-values were derived using ANOVA. Inferential testing for categorical variables, stratified by baseline visual acuity, was carried out using the CMH chi-square test. No statistically significant differences were observed across the treatment groups.

The mean age of study subjects was 62.5 years, and more males than females were enrolled to the studies and randomised across all 3 study arms (57.3 % in the 0.2µg/day FAc treatment arm, 61.8 % in the 0.5 µg/day FAc treatment arm and 58.4 % in the sham treatment arm). Study patients were primarily white (69.8%) and non-Hispanic/Latino in origin (88.7%).

The mean duration of diabetes (Type I and Type II) across all three study arms was 20.5 years. The mean duration of DMO was 3.6 years (Range: 3.5-3.9 years). The mean BCVA was 53.4 (Range: 52.9-54.7). Mean FTH was 469 µm (Range: 451.3–485.1 µm). 47.1% had a report of cataract at baseline which was evenly distributed across the 3 study arms, 16.5% had no cataract, and for 36.4% of patient's physician could not grade or it was not applicable. Mean IOP across all three arms was 15.2 mmHg., with a mean of 15.2 mmHg in the 0.2 µg/day FAc treatment arm, 15.2 mmHg in the 0.5 µg/day FAc treatment arm and 15 mmHg in the sham treatment arm group.

78.5% of patients who received 0.2µg/day FAc and 79.6% received sham treatment had not received previous steroid injection in the study eye. Prior therapeutic use of intravitreal anti-VEGF therapy was reported in 36 of the patients (6.4%) who received either 0.2µg/day FAc or sham treatment. From 953 study patients, two patients on the 0.2µg/day FAc treatment arm, 1 patient on the 0.5µg/day FAc

treatment arm and one patient in the sham treatment arm received systemic treatment with bevacizumab before study entry.

Underlying diabetic history and presentation was similar across the three treatment groups with no statistically significant differences observed. Most patients had type II diabetes (91.9%) and in this group the mean time since diagnosis was 15.9 years (16.1 years in the 0.2µg/day FAc treatment arm, 15.8 years in the 0.5 µg/day FAc treatment arm and 15.9 years in the sham treatment arm). 6.6% had a diagnosis of Type I diabetes and for 1.3% there is uncertainty about diagnosis type. Most patients were receiving oral anti diabetic therapy 44.2% with 27.4% receiving combination therapy (oral and insulin) and 27.4% receiving insulin alone. Mean HbA1c reported at baseline was 7.8% (Range 7.7% - 7.8%). Baseline visual acuity status had no notable effect on diabetes history in any of the study groups.

Patient demographics and baseline characteristics for FAME A and FAME B, pooled across both studies, are presented in Table 8.

Table 8. FAME studies – Patient demographics and baseline characteristics (pooled)

	FAME studies (FAME A and FAME B populations pooled)		
	FA 0.2 µg/day	**FA 0.5 µg/day**	**Sham**
N	375	393	185
Demographics			
Mean age (SD), yrs	63.0 (9.3)	62.2 (9.3)	61.9 (9.6)
Male, n (%)	215 (57.3)	243 (61.8)	108 (58.4)
Race, n (%)			
Asian	85 (22.7)	87 (22.1)	40 (21.6)
Black	22 (5.9)	32 (8.1)	11 (5.9)
Caucasian	264 (70.4)	269 (68.4)	132 (71.4)
Other	4 (1.1)	5 (1.3)	2 (1.1)
Diabetes characteristics			
Diabetes Type, n (%)			
Type 1	29 (7.7)	21 (5.3)	13 (7.0)

Type 2	340 (91.0)	366 (93.1)	170 (91.9)
Not recorded	6 (1.6)	5 (1.3)	2 (1.1)
Mean duration of diabetes, yrs (SD)	17.0 (9.4)	16.2 (8.7)	16.4 (8.5)
Mean Hba1c % (SD)	7.8 (1.6)	7.7 (1.6)	7.8 (1.7)
DMO characteristics			
Mean duration of DMO, yrs (SD)	3.6 (2.92)	3.5 (2.60)	3.9 (3.78)
Mean BCVA letter score	53.3 (12.7)	52.9 (12.2)	54.7 (11.3)
Mean central retinal thickness, µm (SD)	461 (160)	485 (174)	451 (152)
Lens status, n (%)			
Phakic	235 (62.7)	265 (67.4)	121 (65.4)
Pseudophakic	140 (37.3)	128 (32.6)	64 (34.6)
Prior DMO treatment, n (%)			
Laser	375 (100)	393 (100)	185 (100)
Intravitreal corticosteroid	63 (16.8)	61 (15.5)	28 (15.1)
Intravitreal anti-VEGF	26* (6.9)	23* (5.9)	10* (5.4)
No prior DMO treatment, n (%)	0	0	0

Source: Campochiaro et al., 2011.
*Values are unlikely to be representative of the true proportion of patients who had received prior treatment with anti-VEGFs due to a high degree of missing data (~60% of patient responses were missing).
Abbreviations: aVEGF, anti-vascular endothelial growth factor, DMO, diabetic macular oedema, BCVA, best-corrected visual acuity, SD, standard deviation.

B.3.3.4 FAME studies - Participant flow

The disposition and flow of all randomised patients through to Month 36 for FAME A and FAME B are presented in Table 9 and Table 10, respectively.(66, 67)

Table 9. FAME A - Summary of Patient Disposition (Randomised Patients)

	Treatment Group			
Category	**Sham**	**0.2µg/day FA**	**0.5µg/day FA**	**Total**
Total subjects randomised (N)	95	190	196	481
Randomised and not treated (n, %)	0	0	1(0.5)	1(0.2)
Randomised and treated (n, %)	95 (100.0)	190 (100.0)	195 (99.5)	480 (99.8)

Total completed (n, %)	67 (70.5)	141 (74.2)	132 (67.3)	340 (70.7)
Total discontinued (n, %)	28 (29.5)	49 (25.8)	64 (32.7)	141 (29.3)
Adverse event	3 (3.2)	2 (1.1)	14 (7.1)	19 (4.0)
Unsatisfactory therapeutic effect	2 (2.1)	0	1 (0.5)	3 (0.6)
Protocol violation	2 (2.1)	2 (1.1)	3 (1.5)	3 (0.6)
Subject withdrew consent	6 (6.3)	19 (10.0)	13 (6.6)	38 (7.9)
Lost to follow-up	9 (9.5)	14 (7.4)	14 (7.1)	37 (7.7)
Death[1]	6 (6.3)	11 (5.8)	19 (9.7)	36 (7.5)
Unknown	0	1 (0.5)	0	1 (0.2)
1. A total of 37 subjects died during the study. Reason for study discontinuation was not reported as "death" for 1 subject.				

Table 10. FAME B - Summary of Patient Disposition (Randomised Patients)

	Treatment Group			
Category	**Sham**	**0.2µg/day FA**	**0.5µg/day FA**	**Total**
Total subjects randomised (N)	90	186	199	475
Randomised and not treated (n, %)	0	1(0.5)	1(0.5)	2(0.4)
Randomised and treated (n, %)	90 (100)	185 (99.5)	198 (99.5)	473 (99.6)
Total completed (n, %)	59 (65.5)	133 (71.5)	147 (73.9)	339 (71.4)
Total discontinued (n, %)	31 (34.4)	53 (28.5)	52 (26.1)	136 (28.6)
Adverse event	2 (2.2)	2 (1.1)	1 (0.5)	5 (1.1)
Unsatisfactory therapeutic effect	1 (1.1)	0	0	1 (0.2)
Protocol violation	0	0	2 (0.1)	2 (0.4)
Subject withdrew consent	8 (8.9)	12 (6.5)	14 (7.0)	34 (7.2)
Lost to follow-up	15 (16.7)	23 (12.4)	23 (11.6)	61 (12.8)
Death	5 (5.6)	16 (8.6)	12 (6.0)	33 (6.9)

B.3.3.5 MEAD studies - Study design

The MEAD trials (MEAD-010 and MEAD-011) were two large, phase 3 randomised, sham-controlled multicentre studies to evaluate the safety and efficacy of DEX 0.7 and 0.35 mg in patients with DMO. Both studies were identical by design and data were pooled for analysis. Both MEAD studies met their primary endpoint.(31)

Patients with a diagnosis of DMO, best-corrected visual acuity (BCVA) of 20/50 to 20/200 Snellen equivalent, and central retinal thickness (CRT) of ≥300µm determined by OCT were eligible to be enrolled in the studies. Of note, the MEAD studies enrolled treatment-naïve patients who had refused laser treatment or who, in the opinion of the investigator, would not benefit from laser treatment, as well as subjects who were treatment-experienced.

1048 subjects were randomised in a 1:1:1 ratio to either DEX 0.7 mg (n=351, DEX 0.35 mg (n=347), or sham procedure (n=350) and followed for 3 years (or 39 months for patients treated at Month 36) at 40 scheduled visits. Patients who met retreatment eligibility criteria could be retreated no more often than every 6 months.

Study visits were scheduled every 1.5 months during the first year and every 3 months during years 2 and 3. In addition, study subjects were seen at safety visits 1, 7, and 21 days after study treatment or retreatment. After a study protocol amendment in May 2010, patients who had not yet completed the study and who met retreatment eligibility criteria were retreated at Month 36 and followed at an additional study visit at month 39. Over 50% of patients had completed or discontinued the study prior to the protocol amendment.

A summary of the methodology of the MEAD studies is presented in Table 11.

Table 11. MEAD studies - Summary of study methodology

Study	**MEAD (N=554)** **NCT00168337**	**MEAD (N=494)** **NCT00168389**
Settings and locations where the data were collected	The MEAD studies were conducted from February 2005 to June 2012 at 131 study sites across 22 countries.	
Trial design	Randomised, sham-controlled, multicentre	
Eligibility criteria	**Key inclusion criteria** 1. Patients ≥18 years of age diagnosed with type 1 or 2 diabetes mellitus who had fovea-involved macular oedema that was associated with DR and had been previously treated with medical or laser therapy were enrolled in the study. 2. Treatment-naïve patients who had refused laser treatment or who, in the opinion of the investigator, would not benefit from laser treatment were also enrolled. 3. BCVA in the study eye, measured with the ETDRS method, was required to be between 34 and 68 letters (20/200-20/50), and CRT in the 1-mm central macular subfield of the study eye was required to be ≥300 μm by time domain OCT using the OCT2 or OCT3 (Stratus OCT, Carl Zeiss Meditec Inc, Dublin, CA) system. **Key exclusion criteria** 1. Uncontrolled diabetes (glycosylated haemoglobin [HbA1c] >10%) or other systemic disease,	

Study	MEAD (N=554) NCT00168337	MEAD (N=494) NCT00168389
	2. Treatment with intravitreal anti-VEGF within 3 months of study entry, treatment with intravitreal triamcinolone within 6 months of study entry, 3. Current use or anticipated use of systemic steroids during the study, 4. Glaucoma or optic nerve head or visual field damage consistent with glaucoma, 5. History of marked steroid induced intraocular pressure (IOP) increase, and ocular hypertension in the study eye characterised by IOP >23 mmHg without 6. antiglaucoma medication, IOP >21 mmHg treated with 1 antiglaucoma medication, or use of >2 antiglaucoma medications. 7. Patients with aphakia or an anterior chamber intraocular lens in the study eye, a history of intraocular laser or incisional surgery in the study eye within 90 days before study entry, a history of pars plana 8. Vitrectomy in the study eye, or active iris or retinal neovascularisation in the study eye were excluded.	
Randomisation	Patients were randomised in a 1:1:1 ratio to receive either dexamethasone posterior segment drug delivery system 0.7 mg or 0.35 mg, or sham intervention	
Trial drug (n=351 0.7 mg dose; n=347 0.35 mg dose)	Dexamethasone posterior segment drug delivery system at a dose of 0.7 mg or 0.35 mg, injected directly into the vitreous cavity not less than once every 6 months for up to 36 months	
Comparator (n=350)	Sham posterior segment needle-less drug delivery system without study medication not less than once every 6 months for up to 36 months.	
Concomitant / prohibited medications	Treatment with out-of-protocol rescue therapies was prohibited e.g., anti-VEGF therapies, laser photocoagulation and other corticosteroid therapies. Patients treated with other, out-of-protocol rescue therapies were discontinued from the study. As per enrolment criteria and rescue therapies for the treatment of DMO e.g., anti-VEGF therapies, laser photocoagulation, and other corticosteroid therapies. Systemic treatment with steroids and immunosuppressants also was prohibited. Patients were eligible for retreatment with dexamethasone intravitreal implant only if there had been 6 months since the most recent study treatment and there was evidence of residual oedema.	
Dose adjustments and study drug interruptions	No dose adjustments were facilitated for in the MEAD trials. Study drug interruptions were not permitted.	

B.3.3.6 MEAD studies - Outcomes

The primary objective of both MEAD studies was to determine if either dose of the DEX implant was superior to the control group measured by the proportion of

subjects with a ≥15-letter increase in BCVA at year 3 compared to baseline. The primary endpoint of the study was reported as the percentage of patients with improvement in BCVA of ≥15 letters at Month 36.

Secondary efficacy endpoints included average change in BCVA from baseline during the study determined with the area under the curve (AUC) method, mean change in BCVA from baseline at each study visit, time to ≥15-letter improvement in BCVA from baseline, percentage of patients with BCVA of ≥20/40 at each study visit, and average change in CRT from baseline during the study by OCT (AUC approach), all in the study eye.(31)(25).

Ocular safety outcomes of interest included IOP and cataract development (Table 12).

Table 12. MEAD studies - Outcomes for evaluation

	Outcomes for evaluation
Primary efficacy outcome	The primary efficacy variable was the proportion of patients with a ≥15-letter increase from baseline in BCVA in their study eye at Month 36.
Secondary efficacy outcomes	Secondary efficacy outcomes for the study eye included: • Average change in BCVA from baseline during the study determined with the AUC method. • Mean change in BCVA from baseline at each study visit • Time to 15-letter improvement in BCVA from baseline. • Percentage of patients with BCVA of 20/40 at each study visit • Average change in CRT from baseline during the study by OCT (AUC approach).
Health-Related Quality of Live (HRQoL)	Not reported.
Pharmacodynamics	Not reported.
Safety	Safety parameters included adverse events (AEs), IOP, biomicroscopic and ophthalmoscopic findings, cataract development and measures of diabetes control (HbA1c and glomerular filtration rate).
Pre-Planned Sub-Group Analysis	Predetermined subgroup analysis of selected outcome measures was performed in subgroups of patients defined by demographics,

	duration of diabetes, duration of DMO, baseline HbA1c, prior laser treatment, treatment-naïve status, lens status at baseline, and non-proliferative DR severity at baseline.

B.3.3.7 MEAD studies - Patient demographics and baseline characteristics

Demographic and baseline characteristics for all subjects enrolled to the MEAD trials were similar across the 3 study arms (Table 13).(31) The mean BCVA in study eyes was 56.2 letters (approximately 20/80 Snellen equivalent). The mean duration of DMO before study entry was 24.9 months (median, 16 months). Overall, 66.6% of MEAD study subjects had received previous laser treatment for DMO, 17.9% had been treated with intravitreal steroid, 8.6% had been treated with intravitreal anti-VEGF, and 27.8% had received no previous treatment for DMO.

Table 13. MEAD studies – Patient demographics and baseline characteristics

	DEX Implant 0.7mg (n=351)	DEX Implant 0.35mg (n=347)	Sham (n=350)
Mean age (SD), y	62.5 (8.3)	62.3 (9.2)	62.5 (9.5)
Range (y)	33 - 85	25 - 84	26 - 88
Male n (%)	213 (60.7)	206 (59.4)	217 (62.0)
Mean duration of diabetes (SD), y	16.5 (9.0)	15.8 (9.4)	15.9 (9.1)
Mean HbAlc (SD) %	7.6 (1.2)	7.5 (1.1)	7.5 (1.1)
≤ 8%, n (%)	233 (66.4)	237 (68.3)	249 (71.1)
>8%, n (%)	114 (32.5)	108 (31.1)	100 (28.6)
Not available	4 (1.1)	2 (0.6)	1 (0.3)
Mean ETDRS letter score (SD)	56.1 (9.9)	55.5 (9.7)	56.9 (8.7)
Mean CRT (SD) µm	463.0 (157.1)	466.8 (159.5)	460.9 (132.6)
Mean duration of DME (SD), mo	23.6 (26.0)	25.2 (31.4)	25.9 (27.3)
Range (mo)	0 - 163	0-299	0 - 187
Previous treatment for DME, n (%)			
Focal/ grid laser	231 (65.8)	224 (64.6)	243 (69.4)
Intravitreal steroid	58 (16.5)	69 (19.9)	61 (17.4)
Anti-VEGF	25 (7.1)	39 (11.2)	26 (7.4)
None	104 (29.6)	98 (28.2)	89 (25.4)
Severity of NPDR			
Moderate or better	173 (49.3)	170 (49.0)	174 (49.7)
Severe or worse	151 (43.0)	151 (43.5)	149 (42.6)
Not available	27 (7.7)	26 (7.5)	27 (7.7)
DME perfusion status, n (%)			
Ischemic	43 (12.3)	31 (8.9)	27 (7.7)

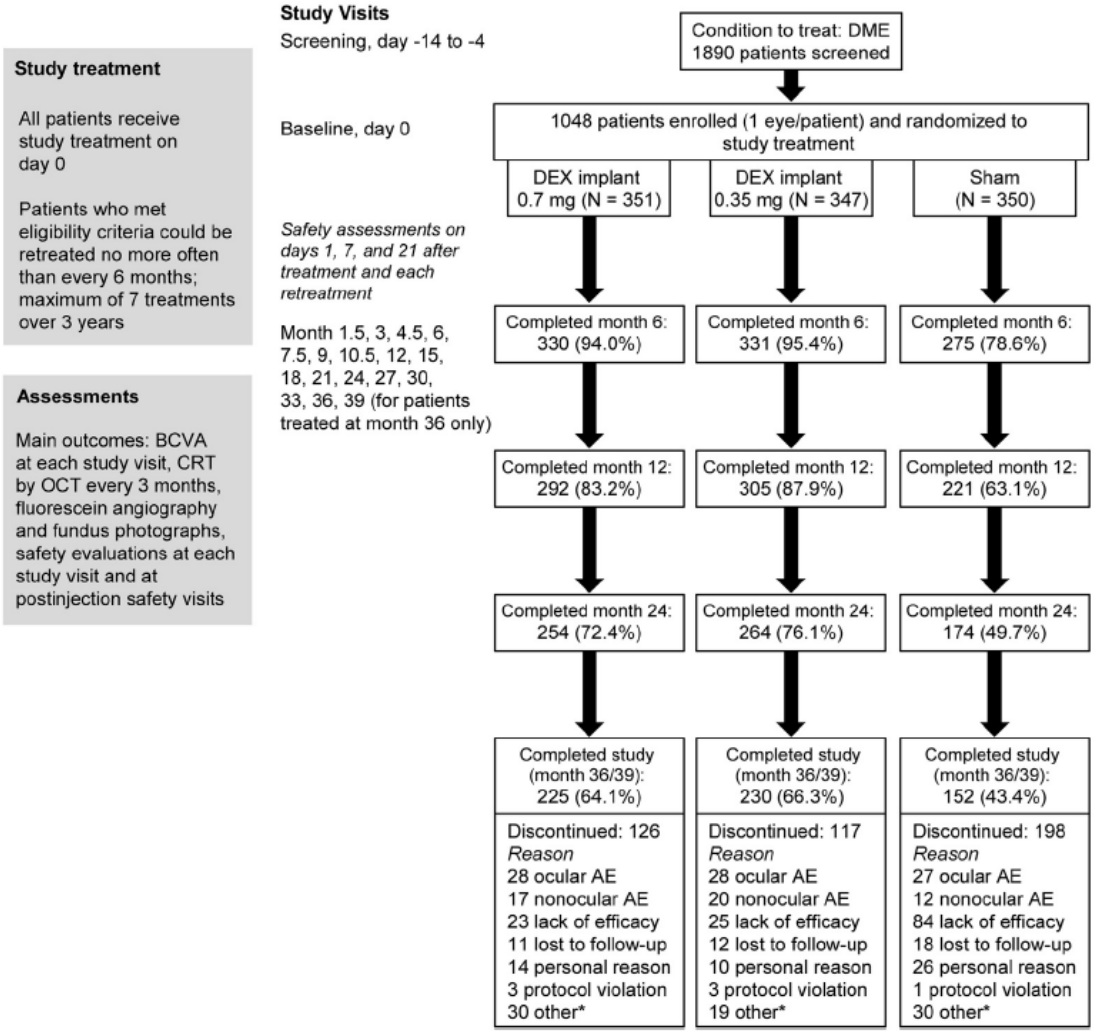
Non-ischemic	257 (73.2)	260 (74.9)	284 (81.1)
Not available	51 (14.5)	56 (16.1)	39 (11.1)
Lens status, n (%)			
Phakic	265 (75.5)	259 (74.6)	249 (71.1)
Pseudophakic	86 (24.5)	88 (25.4)	101 (28.9)
Mean IOP (SD), mmHg	15.3 (2.6)	15.6 (2.8)	15.3 (3.1)
Using IOP-lowering medication, n (%)	12 (3.5)	26 (7.6)	14 (14.0)

Abbreviations: CRT = central retinal thickness; DEX implant = dexamethasone intravitreal implant; DME = diabetic macular edema; ETDRS = Early Treatment Diabetic Retinopathy Study; HbAIc = glycosylated hemaglobin IOP = intraocular pressure; NPDR = non-proliferative diabetic retinopathy; SD = standard deviation; VEGF = vascular endothelial growth factor

B.3.3.8 MEAD studies – Participant flow

The flow of subjects through the MEAD studies is shown in Figure 4.

Figure 4. MEAD studies - Patient disposition



Source: Boyer 2014 (31)

B.3.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

The analysis sets defined in the FAME A and FAME B studies are presented in Table 14.(66, 67)

Table 14. FAME studies - Analysis sets

Data Set Name	Patients Included	Data Excluded	Data Imputation
All Randomised	All randomised and treated	None	LOCF for all missing data
Intent to Treat (ITT)[1]	All randomised and treated	Data after disallowed therapies for DME was set to missing.	LOCF for all missing data
Full Analysis[2]	All randomised[3]	None	LOCF for missing data.
Safety	All randomised and treated	None	None
Per Protocol[4]	All randomised and treated	Data after disallowed therapies for DMO and significant protocol violations set to missing.	None

Notes. [1] The pre-specified primary efficacy data set. [2] Data set was added after key findings of the unmasked 24-month FAME data were made available. [3]The Full Analysis dataset included all randomised patients. The method of last observation carried forward (LOCF) was used to impute for all missing values. This dataset was used on the basis that it most closely follows the intention-to-treat principle. The Full Analysis Set includes data for 3 subjects who were randomised and not treated (1 subject in FAME A and 2 subjects in FAME B). All primary, secondary, and exploratory efficacy variables were analysed using this dataset. [4]Data for all subjects were included in the Per Protocol Analysis unless one or more of the reasons for exclusion were met. The most common reason for exclusion was use of prohibited treatments for DMO, which was more prevalent in FAME A, and much more prevalent in the sham arm of both studies (34.7%, FAME A; 31.1%, FAME B).

All primary, secondary, and exploratory efficacy variables in the FAME studies were analysed using the Full Analysis, All Randomised, ITT and Per-Protocol (PP) datasets. Statistical methods used to compare groups for primary and secondary outcomes relevant to the decision problem.(66, 67)

In the FAME studies, the primary efficacy and safety analysis was based on data at Month 24. The analysis was performed once all patients completed their Month 24 visit or discontinued before Month 24. No interim analysis was planned or performed

by the study sponsor before the Month 24 analysis. All patients continued to receive their masked treatment though the planned study duration of 36 months.

In the MEAD trials for the comparator, DEX, the primary efficacy and safety analysis was based on data at Month 36. The analysis was performed once all patients completed their Month 36 visit or discontinued before Month 36 using the ITT population. The statistical methods use to compare groups for the primary and secondary outcomes in FAME and MEAD are presented in Table 15.

Table 15. Statistical methods used to compare groups for primary and secondary outcomes

	FAME A & B studies (66, 67)	MEAD studies (31)
Hypothesis Testing	The FAME trials were designed to assess for superiority of the intervention over sham control. The following 2 pair-wise comparisons were tested at 24 months to evaluate the between-treatment differences: • 0.2 µg/day FAc versus sham control, and • 0.5 µg/day FAc versus sham control. The corresponding null (H0) and alternative (H1) hypotheses tested for each pair-wise comparison was as follows: • H0: The proportion of patient responders is the same for each group. • H1: The proportion of patient responders is different between groups. Significance level (α) was set to control the probability of Type 1 error. Similarly, the power (β) was set to control the probability of Type 2 error.	The MEAD trials were designed to assess for superiority of the intervention over sham control. Significance level (α) was set to control the probability of Type 1 error. Similarly, the power (β) was set to control the probability of Type 2 error.
Determination of sample size	Study sample size was calculated based on the primary efficacy endpoint for VA i.e., the proportion of patients who had a ≥15 letter increases in BCVA at month 24 when compared to Baseline. Calculations were based on a 2:2:1 randomisation ratio i.e., 0.5 µg/day FAc implant vs 0.2 µg/day FAc implant vs sham control, the Pearson chi-square test for comparing two proportions (each of the FAc implant dosing groups vs sham control), and the Hochberg-Bonferroni multiple comparison procedure to adjust for the comparison of the two FAc implant dosing groups to control.	The planned sample size of 510 patients in each trial (170 in each treatment arm was estimated to provide 80% power to detect a difference of 10% between the Dexamethasone intravitreal implant 0.7 mg group and the sham group in the proportion of patients with 15-letter improvement in BCVA from baseline, assuming a 5% rate for sham and a 2-sided alpha level of 0.025.

	It was estimated that approximately 9% of patients in the sham control group and 25% of patients in at least one of the active FAc implant treatment group would be VA responders. These estimates were derived from the 24-month result of a trial in DMO in patients using a sustained release 0.59 µg/day FA insert. (Pearson. 2006). Under the assumption that both dose groups were equally effective against the control, a total sample size of 400 patients (160 in each FAc implant group and 80 in the sham control group) would provide a power of 89% to detect this difference between groups of 16%, at a significance level of 0.0493. Under the assumption that only 1 dose group was effective, a total sample size of 400 patients would provide 83% power to detect a difference between groups of 16% between the active and control groups at a significance level of 0.02465. (Necessary adjustments for type I error of 0.0001 for each DSMB assessment was determined to be an adequate adjustment and were implemented). The overall sample size was however increased to 450 patients in total in each study, estimated at 180 in each FAc implant group and 90 in the sham control group to adjust for a projected dropout rate of approximately 10%. In the ITT analysis, this adjusted sample size would provide approximately 89% power to detect a difference of 16% between treatment arms at month 24.	
Analysis Population and Data Management	The pre-specified primary efficacy data set was an Intent-to-Treat (ITT) data set and included all randomised patients who received any study drug. Patients treated with non-laser therapy outside the protocol that had potentially confounding effects on DME (e.g., Avastin, intravitreal triamcinolone acetonide, vitrectomy) had all efficacy data collected after the date of treatment set to missing. The method of LOCF was used to impute values for all missing data. At the time the studies were initiated, this data set was selected as the primary efficacy data set because of the anticipated	Efficacy outcomes were evaluated in the intent-to-treat population. of all randomised patients. The last-observation-carried-forward method was used for imputation of missing values, except in the analyses of average change in BCVA and CRT from baseline

	off-label use of non-approved therapies for DME, especially given the 3-year follow up of the study. This was done after discussions and agreement with the US and EU Health Authorities. Following discussions with the regulatory bodies (MHRA and FDA) regarding the unmasked 24-month results of the FAME data it was the position of the regulatory bodies i.e., MHRA and FDA that study results should use a dataset that complied with the intention-to-treat principle as defined in the ICH-E9 guidelines. Specifically, the dataset for FAME would include all data from all patients randomised to study, irrespective of treatment compliance, or exposure to non-approved therapies for DME. This approach to analysis deviated from that specified in the pre-planned statistical analysis plan. To account for analysis set recommendations from the Regulatory Authorities another dataset was added and was named the Full Analysis Population dataset. No data were excluded from the Full Analysis dataset, imputed values, using the LOCF method was applied for all missing data. This method imputed values for missing data by carrying forward through to Month-36 the last measured response occurring just before the missing value, even if this last measure to response was from an unscheduled visit. The LOCF process allowed data to be carried forward from Baseline. The LOCF method was not planned nor performed for the PP analysis of efficacy. It is important to note that Regulatory approval from the MHRA and FDA for ILUVIEN was granted based on the Full Analysis Population data set.	during the study (AUC approach) and time-to-event data, which used observed data. Analysis of the proportion of patients with BCVA improvement of ≥15 letters from baseline and the proportion of patients with BCVA of ≥20/40 used the Cochran-Mantel-Haenszel general association test stratified by study. Analysis of the average change in BCVA or CRT from baseline during the study (AUC approach) used an analysis of covariance model with treatment and study as fixed effects and baseline with the Kaplan-Meier method and log-rank tests. Predetermined subgroup analysis of selected outcome measures was performed. in subgroups of patients defined by demographics, duration of diabetes, duration of DME, baseline HbA1c, prior laser treatment, treatment-naïve status, lens status at baseline, and non-proliferative DR severity at baseline. Safety outcomes were evaluated in the safety population of all patients who were treated during the study. BCVA or CRT as the covariate. Time-to-event data were analysed

Statistical Methods	Pair-wise comparisons between treatment groups were made using a CMH chi-squared test stratified by the baseline VA score in the study eye (≤49 or >49 letters). A 95% confidence interval (CI) around the difference in these percentages between groups was calculated. As a sensitivity analysis, Pearson's unstratified chi-square test was used in lieu of the CMH stratified chi-square test. The Hochberg-Bonferroni correction was used to adjust for multiple comparisons against the control. At Month 24, if both P values for (1) and (2) were ≤0.0491 favouring the FAc groups, then both were considered statistically significant. If either P value was greater than 0.0491, i.e., not significant, then the other P value must have been ≤ 0.02455 (0.0491/2) to declare significance for that group. In terms of safety, the number and proportion of subjects in each treatment group was summarised for ocular AEs, non-ocular AEs, IOP-related AEs, and cataract-related AEs. For continuous safety variables, the observed and change from baseline values were summarised descriptively. For categorical safety variables, change from baseline was summarised using "shift tables". The statistical strategy for all secondary efficacy variables, exploratory efficacy variables, sub-group analyses, HRQoL and safety analysis are summarised in the CSR summary and the CSR reports for both FAME A and FAME B.(66, 67)	Statistical analysis was performed with SAS version 9.3 (SAS Inc, Cary, NC) and a 2-sided alpha level of 0.05. The planned sample size of 510 patients in each trial (170 in each treatment arm) was estimated to provide 80% power to detect a difference of 10% between the Dexamethasone intravitreal implant 0.7 mg group and the sham group in the proportion of patients with ≥15-letter improvement in BCVA from baseline, assuming a 5% rate for sham and a 2-sided alpha level of 0.025.
Analysis Sets	All primary, secondary, and exploratory efficacy variables were analysed using the Full Analysis, All Randomised, ITT and Per-Protocol (PP) analysis sets as per the summary outlined in Table 14.	Information not available.

B.3.5 Quality assessment of the relevant clinical effectiveness evidence

A quality assessment of the FAME and MEAD studies is presented in Table 16 below. The quality assessment of all 10 studies identified in the SLR is described in Appendix D.

Table 16. Quality Assessment of relevant clinical effectiveness evidence

Trial Name	FAME A & B studies (66, 67)	MEAD studies (31)
Was randomisation carried out appropriately?	Yes – Interactive Response Technology utilised for randomisation schedule and patient allocation.	Yes – Interactive Response Technology utilised for randomisation schedule and patient allocation.
Was the concealment of treatment allocation adequate?	Yes – concealment mediated by an automated system.	
Were the groups similar at the outset of the study in terms of prognostic factors?	Demographic and baseline characteristics for all patients enrolled to FAME A & B were analysed and reported as similar across the 3 treatment groups.	Demographic and baseline characteristics for all patients enrolled to FAME A & B were analysed and reported as similar across the 3 treatment groups.
Were the care providers, participants and outcome assessors blind to treatment allocation.	Yes, double-blind trial design.	Yes, double-blind trial design.
Were there any unexpected imbalances in drop-outs between the groups.?	No imbalances reported.	Higher rate of patient withdrawal in the sham arm of the studies in Year 1.
Is there any evidence to suggest that the authors measured more outcomes than they reported.	All outcomes as per the study protocol were reported in the FAME CSR. Unclear whether published authors measured more outcomes than they reported.	Not known.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes and yes. LOCF imputation was used for missing data.	Yes and yes. LOCF imputation was used for missing data.

B.3.6 Clinical effectiveness results of the relevant studies

B.3.6.1 FAME studies – clinical effectiveness results

Data from the Phase III studies FAME A and FAME B were pooled, as the two studies had identical designs and were conducted in parallel. This section provides data from the pooled analysis, reporting results up to Month 36.(35) The results of the primary and secondary outcome analyses for each of FAME A and FAME B individually are presented in Appendix K.

B.3.6.2 FAME studies - Primary efficacy endpoint

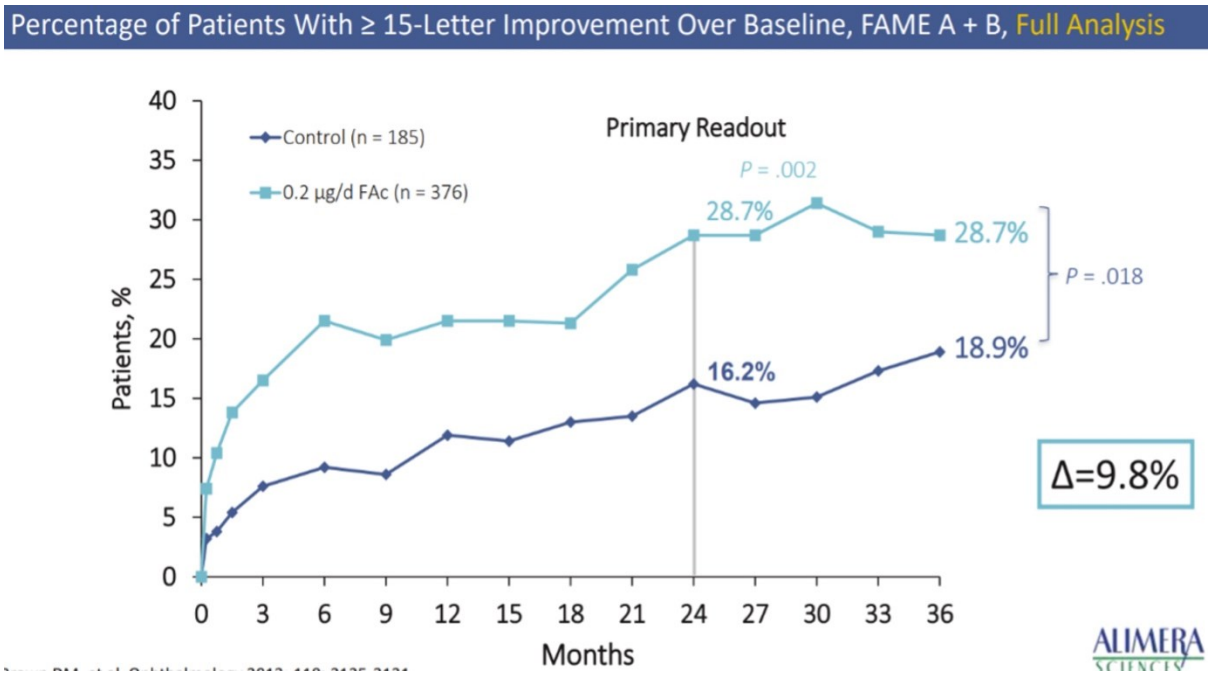
The primary efficacy endpoint as the proportion of patients who experienced an increase from baseline of ≥15 letters in BCVA in their study eye. Following the recommendation of the regulatory bodies (FDA, EMEA) following the release of the 24-month data, the Full Analysis Population was used for the primary efficacy analysis. The primary endpoint was independently met in both FAME studies. The 0.2 µg/day FAc implant was subsequently approved by the regulatory authorities as the licensed dose.

In the pooled analysis, 28.7% of patients receiving the 0.2 µg/day FAc implant achieved a ≥15 letter improvement over baseline (p=0.002) at Month 24, an improvement that was sustained through to Month 36. At Month 36 the percentage of patients with improvement in BCVA letter score of ≥15 letters were 28.7% in the 0.2 µg/day FAc implant group and 27.8% in the 0.5 µg/day FAc implant group (LOCF). In the sham group, 18.9% of the patients had a ≥15 letter improvement. (p=0.018).(Figure 5).

In the Full Analysis Population (LOCF), the mean improvement from baseline BCVA letter score at Month 36 was 5.3 in both FAc implant groups compared with 2.0 in the sham treatment group (P≤0.018). For patients who remained in the trial through to Month 36, the mean improvement from baseline BCVA letter score at Month 36 was

8.1 (0.2 µg/day FAc) 7.1 (0.5 µg/day FAc) compared with 3.1 for the sham group (p=0.0070).

Figure 5. Percentage of Patients with ≥15 Letter Improvement Over Baseline, FAME A + FAME B; Full Analysis Set



Source: Campochiaro et al.(44)

The benefits of the FAc implant were seen quite early, as the percentage of patients with a letter score gain of ≥15 was 10% at Month 1 (Figure 5).(35) At each time point, the percentage of patients achieving this outcome was significantly greater in the FAc implant group compared to the sham group, representing a substantial improvement of the BCVA means. There was a relatively rapid response to treatment over time following administration of the FAc implant injection.

Between Month 9 and Month 18, a gradual decline in BCVA letter score emerged in the FAc implant groups when compared to the sham treatment group. This observed transient decline in mean BCVA in the active FAc treatment group can be attributed to cataract progression, whereby the recovery subsequently seen between Month 18 and Month 24 was attributable to cataract surgery. Within the overall trial cohort, of

the 48% of patients in the 0.2 µg/day FAc implant group who were phakic at baseline did not have cataract surgery by the end of study (EOS) at Month 36. This group of patients had a mean change in BCVA letter score of -6.

A final BCVA of ≥20/40 was observed at Month 36 in 35.1% and 34.9% of patients in the 0.2 µg/day and 0.5 µg/day dose groups, respectively, compared with 26.5% in the sham treatment group (sham vs.0.2 µg/day FAc group, P = 0.016; sham vs 0.5 µg/day FAc groups, P =0.005). A final BCVA of 20/40 or better represents a clinically meaningful outcome, as this level of vision allows for high levels of functioning, including reading and driving, even if the other eye has severe visual impairment**.** A final BCVA of 20/200 or worse is considered blindness in the study eye; this outcome occurred at Month 24 in 14% of patients in the FAc groups compared to 12% in the sham group.

B.3.6.3 FAME studies - Secondary endpoints

Foveal Thickness as assessed by OCT

At baseline the mean FTH was 451, 461 and 485 µm in the sham, 0.2 µg/day FAc implant and 0.5 µg/day FAc implant groups, respectively. These baseline measures are indicative of a relatively severe oedema.

In the pooled analysis, improvements in FTH were observed as early as Week 1. At week 6, the improvement was more pronounced in both FAc implant arms compared to that of the sham treatment group, <350 µm versus < 450 µm, respectively. At Month 6, it was 318 µm in the FAc implant groups and 396 µm in the sham group. After Month 6 this reduction in FTH was observed across all three treatment groups. At Month 24, the mean FTH was observed to be significantly lower in both FAc treatment groups; 293 µm in the 0.2 µg/day FAc implant group (P=0.005), and 308 µm in the 0.2 µg/day FAc implant group (P<0.001) when compared to the sham treatment group, 340 µm. Between Month 24 and Month- 6 the mean FTH declined in all treatment groups. However, the observed decline was greater in the sham group; 309 µm compared with 280 µm and 300 µm in the 0.2 µg/day FAc implant

and 0.5 µg/day FAc implant groups respectively. At Month 36, no significant differences across the three treatment groups were observed.

Repeated Study Treatments

After Month 12, patients with impaired vision or increased retinal thickness due to persistent or recurrent DMO could receive repeat administration of the assigned study treatment if the protocol-defined retreatment criteria were met. In the pooled analysis, the percentage of patients who received 1, 2 or ≥3 study treatments at Month 36 was 66.1%, 27.7% and 6.3% in the sham group, respectively; 76.1%, 18.7% and 5.3% respectively in the 0.2 µg/day FAc implant group; and 68.8%, 24.2% and 7.0% respectively in the 0.5 µg/day FAc implant group (Table 17).(35)

Table 17. FAME pooled analysis - Study Treatments, Supplementary Laser Treatments and Off-Protocol Treatments through Month 36

	Control (n=112)	**0.2 µg/d FAc (n=209)**	**0.5 µg/d FAc (n=215)**
Study treatments (sham injection or ILUVIEN device), %			
1	66.1	76.1	68.8
2	27.7	18.7	24.2
≥ 3	6.3	5.3	7.0
Supplementary laser treatments (at masked physician's discretion after Week 6)			
Patients, n (%)	68 (60.7)	85 (40.7)	75 (34.9)
***P* value**	N/A	0.003	<0.001
IVTA	39 (34.8)	28 (13.4)	34 (15.8)
***P* value**	N/A	<0.001	<0.001
Anti-VEGF	17 (15.2)	7 (3.3)	11 (5.1)
***P* value**	N/A	<0.001	0.002

Statistical comparisons were made between each fluocinolone acetonide (FAc) insert group and the sham group by analysis of variance.
Abbreviations: FAc = fluocinolone acetonide; IVTA = intravitreous triamcinolone acetonide; VEGF = vascular endothelial growth factor.

Mean change in BCVA

The pooled analysis did not extend to the secondary outcome of mean change in BCVA. In FAME A at Month 24 (full analysis population), subjects receiving FAc 0.2 µg/day had a mean change of +3.7 letters (95% CI -1.8 [-6.3,2.8] p=0.444). Those on

sham had a +3.2 BCVA mean letter change. In FAME B at Month 24 (full analysis population) subjects receiving the 0.2 µg/day FAc implant had a mean change of +5.1 letters (95% CI -6.1 [-10.8, -1.4] p=0.011). Those on sham had a 0.0 BCVA mean letter change.

B.3.6.4 MEAD studies – clinical effectiveness results

The MEAD studies evaluated the safety and efficacy of DEX 0.7 mg and 0.35 mg in the treatment of patients with DMO. Results from the trials were pooled and the pooled primary efficacy analysis is reported in Boyer et al. (31) Clinical effectiveness results for the comparator from the MEAD studies are presented in relation to the decision problem only and as reported.

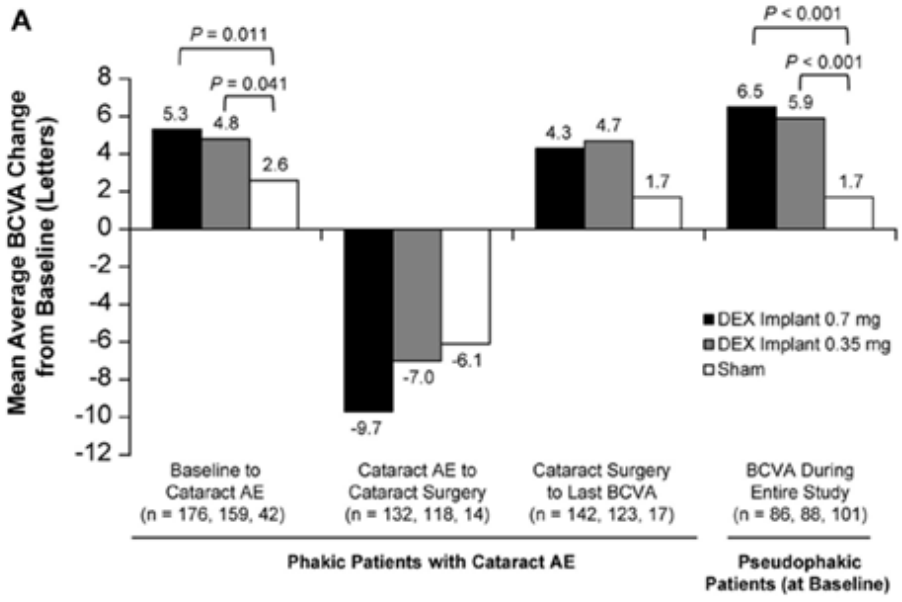
B.3.6.2 MEAD studies - Primary efficacy endpoint

In the primary outcome analysis, both doses of the DEX implant demonstrated statistical superiority to sham procedure (Both doses of DEX showed a more rapid onset of treatment effect when compared to sham. Survival analysis showed a significantly earlier gain of ≥15 BCVA letter gain in both treatment doses when compared to the sham procedure. Proportionally, those patients who gained a ≥15 BCVA letter gain from baseline was significant in both active treatment groups when compared to the sham procedure, was observed as early as day 21 (P<0.003).

Figure *6*). The percentage of patients with a ≥15 BCVA letter improvement from baseline in year 3 or at the final study visit was 22.2%, 18.4% and 12.0% (P ≤0.018) in the DEX 0.7 mg, 0.35 mg and sham procedure respectively. The interaction of treatment effect and study was not significant (P =0.853) in the pooled data analysis, suggesting a consistent effect of treatment across the individual clinical trials.

Both doses of DEX showed a more rapid onset of treatment effect when compared to sham. Survival analysis showed a significantly earlier gain of ≥15 BCVA letter gain in both treatment doses when compared to the sham procedure. Proportionally, those patients who gained a ≥15 BCVA letter gain from baseline was significant in both active treatment groups when compared to the sham procedure, was observed as early as day 21 (P<0.003).

Figure 6. MEAD studies - Mean average change in best-corrected visual acuity (BCVA)



Up to Month 15, both active treatment groups (DEX implant 0.35 mg and 0.7 mg), when compared to sham, demonstrated a greater mean change in BCVA letter gain at most timepoints during this period. After Month 15, it was shown that the initial gain in BCVA letters from both active treatment groups, when compared to the sham procedure was reduced. However, a trend for BCVA letter gain to increase in both active treatment groups resumed at year 3.

In year 2 of the study, the observed increase in cataract AE reports correlated with a reduced effect of treatment on BCVA. These results were suggestive of confounding of the treatment effect after year 1 secondary to cataract formation or disease progression. Additional analyses were thus performed to account for the effect of cataract adverse events and cataract surgery on visual acuity. Subgroup analysis of mean improvement in BCVA letters for both treatment groups relative to the sham procedure in pseudophakic eyes was consistent across time in the 3-year study, with no reduction in visual benefit observed in year 2. This analysis showed an end of study gain of ≥15 letters in BCVA letters from baseline 23.3%, 15.9%, and 10.9% of pseudophakic eyes in the DEX 0.7 mg and 0.35 mg treatment groups, and sham group respectively.

In phakic eyes with an AE report of cataract, the mean average BCVA letter improvement from baseline in the DEX 0.7 mg group was substantial until the time of a cataract AE report. Vision loss was observed after an adverse event report of cataract until the time of cataract surgery. However, the improvement in vision from baseline was restored after cataract surgery. By the end of the study, treatment with DEX resulted in clinically meaningful improvement in BCVA independent of the lens status at baseline. The percentage of patients who gained ≥15 BCVA letters in both active treatment groups, from baseline at study end was similar for both the phakic and pseudophakic subgroups and reflected the results in the total study population.

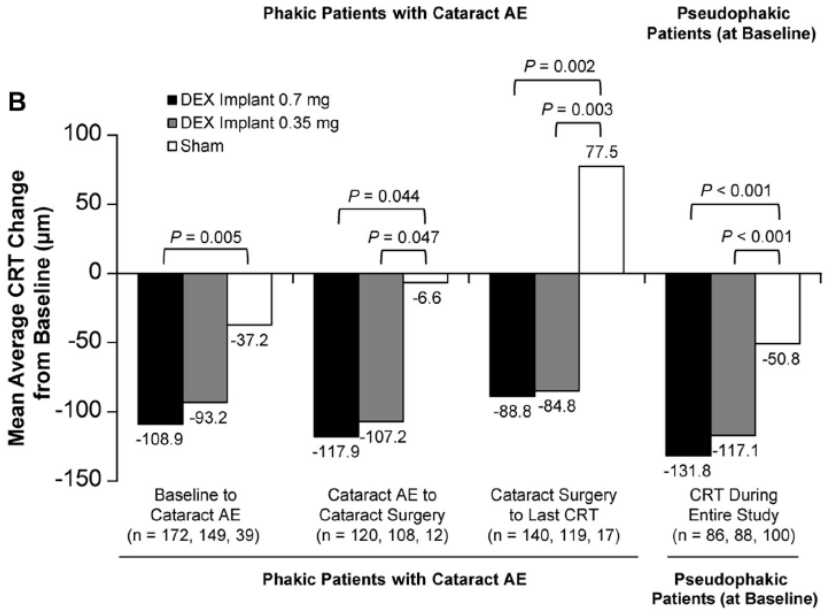
B.3.6.6 MEAD studies – secondary endpoints

Anatomical Outcomes

The mean (SD) average reduction in CRT from baseline during the study was -111.6 (134.1) µm, -107.9 (135.8) µm, and -41.9 (116.0) µm in the DEX 0.7 mg group, DEX 0.35 mg group and sham group, respectively. The mean CRT reduction was significantly greater with DEX 0.7 mg and 0.35 mg when compared to the sham group (P <0.001). The reported decreases in CRT were seen in eyes that had cataract AEs leading to cataract surgery, despite the vision loss in those eyes (

Figure 7). Notably, in the sham procedure group, an increase in CRT after cataract surgery was observed but not in the DEX groups. This is suggestive of a protective effect of dexamethasone intravitreal implant following cataract surgery.(68)

Figure 7. MEAD studies - Central Retinal Thickness (CRT) by lens status



Note. Results were analysed in phakic patients with a cataract adverse event (AE) as well as in pseudophakic patients using an area-under-the-curve approach and observed values in the intent-to-treat population. Dexamethasone intravitreal implant= dexamethasone intravitreal implant.

Retreatment

As per study protocol, DEX retreatment was allowed only if ≥6 months had elapsed since the most recent study treatment, and residual edema was evident. The median number of study treatments received by patients was: 4 in the DEX 0.7 mg group; 5 in the DEX 0.35 mg group; and, 3 in the sham procedure group Table 18. For patients who completed the study, the mean number of study treatments administered was 5.0 and 5.2 in the DEX 0.7 mg and DEX 0.35 mg groups, respectively, and 5.1 in the sham procedure group.(31)

Table 18. MEAD studies - Study treatments through to 3 years

Number of Study Treatments	DEX Implant 0.7 mg (n = 347)	DEX Implant 0.35 mg (n = 343)	Sham (n =350)
1, n (%)	44 (12.7)	34 (9.9)	106 (30.3)
2, n (%)	54 (15.6)	45 (13.1)	63 (18.0)
3, n (%)	39 (11.2)	41 (12.0)	41 (11.7)
4, n (%)	42 (12.1)	40 (11.7)	26 (7.4)
5, n (%)	49 (14.1)	41 (12.0)	29 (8.3)
6, n (%)	88 (25.4)	105 (30.6)	50 (14.3)
7, n (%)	31 (8.9)	37 (10.8)	35 (10.0)
Mean (SD)	41 (2.0)	4.4 (1.9)	3.3 (2.2)
Median	4	5	3
DEX implant = dexamethasone intravitreal implant; SD = standard deviation.			

B.3.6.7 Real-world evidence

B. 3.6.7.1 Real-world evidence for FAc implant

Since the FAME studies were completed, many studies have evaluated the effectiveness and safety of the 0.2 µg/day (0.19 mg total dose) FAc implant in patients with DMO in a variety of real-world settings. Of particular relevance to this NICE appraisal is a meta-analysis,(68) which compared outcomes in 9 real-world studies (69-77) with outcomes from the FAME studies, and 3 studies relevant to the NHS in England.(36, 72, 73, 78) .All of the real-world studies, except IRISS (which did not report anatomical outcomes), report VA and anatomical outcomes, safety outcomes and frequency of injection (both for FAc 0.19 mg and for other supplemental intravitreal therapies).

Visual and anatomical outcomes

The real-world studies report visual outcomes following treatment with the FAc 0.19mg implant consistent with those reported in the FAME studies.(35) Specifically the data consistently demonstrate that a single injection with the FAc 0.19 mg implant can stabilise or improve visual outcomes in most patients with chronic DMO for up to 36 months, again consistent with the outcomes reported in the FAME studies.(35) The results of the meta-analysis conducted by Fallico et al. are presented in Table 19)(68)

Table 19. Results of the meta-analysis conducted by Fallico et al. compared to FAME

Outcome Measure	Fallico Meta Analysis	FAME studies
BCVA Primary Outcome Measure 24-months *	MD of 4.52 BCVA Letters (95% CI, 2.56 - 6.48)	4.4 BCVA Letters (95% CI, 2.64 - 6.16)
BCVA Secondary outcome measures 36-months	MD of 7.89 BCVA Letters (95% CI 6.34-9.86)	8.10 (95% CI 6.34-9.86)
CMT	At 24 months MD = -127.20 µm (95% CI, -175.36 - -79.03) At 36 months MD = -167.76 µm (95% CI, -205 - -133.81)	At 24 Months -167.80 µm (95% CI, -193.28 - -143.33) At 36 months -180.80 µm (95% CI, -205.88 - 155.72)
Pooled Proportions		
Cataract surgery	39% (95% CI, 18 - 62%)	80%
IOP Lowering Drops	27% (95% CI, 19 - 36%)	38.4%
Glaucoma surgery	3% (95% CI, 1 - 5%)	4.8%
Supplementary IVT	39% (95% CI, 31% - 48%)	15.2%

* The primary outcome was mean change of best corrected visual acuity (BCVA) at 24 months. Secondary outcomes were 36-month mean BCVA, mean central macular thickness (CMT) change, rates of eyes receiving supplementary intravitreal therapy, cataract surgery, intraocular pressure (IOP)-lowering drops and glaucoma surgery. MD = Mean Difference (MD).

Moreover, reported real-world outcomes for the FAc 0.19 mg implant are comparable regardless of whether the DMO patient has a phakic or pseudophakic eye at the start of the study. Of note, several real-world studies include phakic and pseudophakic eyes, but the proportion of phakic eyes studied is significantly lower than that of pseudophakic eyes.

In the UK Medisoft study, Bailey et al. reported visual outcomes in the pseudophakic population (n=211) that were comparable with the total (phakic and pseudophakic population (n=253 eyes).(73) (Table 20)

Table 20. BRCVA for all eyes and pseudophakic eyes over 48 months. Medisoft Study

	Baseline	M1	M3	M12	M24	M36	M48
All eyes (n=253)							
Mean VA, letters	52.6	55.8	56.7	56.2	57.6	57.1	57.1
Median VA, letters	55.0	57.5	60.0	60.0	60.0	60.0	60.0
Pseudophakic eyes (n=211)							
Mean VA, letters	52.7	56.0	57.3	56.1	57.5	56.8	57.5
Median VA, letters	55.0	58.5	60.0	57.0	60.0	60.0	60.0
Abbreviations: BRVA, Best-reported VA; M, month; VA, visual acuity							

Dobler et al. conducted a retrospective cohort study of 31 eyes treated with the FAc 0.2 µg/day FAc implant in patients with chronic DMO. BCVA was recorded at baseline and annually up to year 5.(78) The outcomes for the study confirm the effectiveness of the FAc implant in the real-world clinical setting over a 5 year period. Two-thirds of eyes were reported to have improved or stable visual acuity at year 5 (

Table **21**).

Table 21. Change in CRT µm compared to baseline for two categories of baseline CRT (<400 µm and ≥400 µm)

		Number of eyes	Change from baseline			
			1 year	2 years	3 years	5 years
CRT ≥400 µm	CRT (µm)	20	-234.7*	-225.4*	-239.5*	-257.0*
	BCVA (letters)		5.7*	1.4	2	0.3
CRT<400 µm	CRT (µm)	11	-5.5	39.9	52.0	-2.9
	BCVA (letters)		2.0	10.3*	3.3	0.2
*p=<0.05 Abbreviations: BCVA, Best-Corrected Visual Acuity; CRT, Central Retinal Thickness.						

Patients with a thicker baseline CRT (≥400) had a more pronounced decrease in CRT after year 1 which was maintained after 5 years. Patients with a thinner baseline CRT <400 μm had no significant change in CRT at any timepoint. Notably those with a thin baseline CRT had a statistically significant increase in BCVA at year 2 and the group with a thicker baseline had a statistically significant increase in BCVA at year 1. No statistically significant BCVA increases were observed at year 5 (Table 22).(78)

Table 22. Change in BCVA letters compared to baseline in eyes receiving no further intravitreal injections, eyes receiving repeat FAc implant and eyes receiving other rescue intravitreal injections.

Rescue intravitreal injection		Number of eyes	Mean change in BCVA compared to baseline (ETDRS letters)			
			1 year	2 years	3 years	5 years
None		13	+6.0	+5.1	+2.0	+3.8
FAc implant	Including all eyes	5	+4.6	+6.4	+4.2	-5.8
	Excluding 1 eye with retinal detachment at 20-months	4	+5.8	+14.5	+8.0	+1.5
Anti-VEGF and/or DEX implant		13	+2.5	+1.1	+0.9	-1.0
Abbreviations: DEX, dexamethasone intravitreal implant.						

Duration of DMO was reported as a mediator in visual outcomes by Khoramnia et al.; patients with a shorter history of DMO experienced greater visual gains than those with a longer history of DMO.(36) These findings are clinically relevant and can assist in both the identification of suitable DMO patients, irrespective of lens status, who may benefit from treatment with the FAc 0.19 mg implant, and when deciding on the appropriate timepoint to administer treatment to achieve the best outcomes for the patient.

As reported by Khoramnia et al, VA outcomes observed in the IRISS study were largely achieved with a single FAc 0.19 mg implant (93.2% of patients). Visual benefits were particularly evident in eyes with a short-term chronic DMO prior to treatment with the FAc implant, (Table 23 and

Table ***24***) where the data will assist in the identification of patients suitable for treatment with the FAc implant and deciding on the most beneficial time to initiate therapy. A case for earlier treatment to manage inflammation has been reported in the literature.(76)

Table 23. IRISS study - Mean changes in VA from Baseline to Month 48

VA Outcomes	Baseline	M12	M224	M36	M48
Observed eyes (N = 695), N	443	446	371	306	106
Mean (±SD) VA, letters	52.2±19.1	55.6±17.9	56.6±17.9	57.1±18.9	54.8±18.2
Median VA, Letters	55.0	58.5	60.0	60.0	55.0
Changes in mean VVA from baseline were statistically significant at month 12, (P=0.0022) Month 24 (P=0.0040) and Month 36 (P=0.0010) not statistically significant at Month 48 (P=0.2248). Abbreviations: M, month; SD, Standard deviation; VA, visual acuity					

Table 24. IRISS study - VA outcomes in short- and long-term chronic DMO

VA Outcomes	Baseline	M12	M224	M36	M48
Observed eyes with short-term DMO (N = 319), n	210	211	168	136	47
Mean (±SD) VA, letters	52.9±19.3	56.8±17.3	59.8±16.5	59.8±18.6	57.9±16.5
Observed eyes with long-term DMO (N = 322), n	206	204	175	151	49
Mean (±SD) VA, letters	51.6±18.8	54.6±18.6	54.0±18.6	55.5±17.9	50.9±19.9
For short-term DMO: Mean change in VA from baseline was statistically significant at Month 24 (P=0.0071), Month 36 (P=0.0019) and Month 48 (P=0.0228) and reached near significance at month 12. (P=0.0879) For long-term DMO, mean change in VA from baseline was statistically significant at Month 12 (P=0.0288) Abbreviations: M, month; SD, Standard deviation; VA, visual acuity					

As reported by Fallico et al., for CMT at Month 24, most individual effect sizes reported in the real-world studies did not fall within the reported 95% CIs for FAME

and the pooled analysis only partly overlapped with that of FAME.(35, 68) However, at Month 36 the CMT results became more comparable. Outcomes reported at 24-month was characterised by higher heterogeneity, but the authors urged caution in interpreting the result. Specifically, different measurements were used, in the real-world data, CMT change was assessed, in FAME foveal thickness defined as centre point thickness was measured, which is assumed to be the mean thickness at the crossing point of the 6 radial scans. Additionally, time domain OCT was used in FAME whereas spectral domain OCT was used in the real-world studies. In a subset of patients (n=66) mean central foveal thickness was assessed as part of the Medisoft study. A reduction of 20% from baseline to first visit (reduction from 460.3 µm to 368.5 µm).(73) At last visit post-FAc implant a 26% decrease was reported, a reduction to 340.5 µm.

These findings were statistically significant ($p<0.001$). These findings have resonance in clinical practice. The goal of treatment in DMO is to preserve or improve retinal function by reducing retinal thickening and oedema irrespective of lens status.(11, 18) Recurrent episodes of DMO can lead to retinal variability which, over time, can cause retinal damage and irreversible sight loss.(16-18) An unmet need which allows for a consistent resolution of retinal oedema in DMO phakic eyes over an extended duration persists. Available therapies exert effect in retinal preservation independent of lens status. Recurrence of oedema i.e., repeated cycle of retina expansion and contraction damage the retinal and have been linked to worse visual outcomes.(19)

Safety outcomes

Increased IOP and the development of cataract represent two primary safety events in patients receiving an intravitreal corticosteroid therapy. Across all the real-world data reported here, no new safety signals were detected. Across all studies a predictable and manageable safety profile was demonstrated. There were however some differences in real-world reporting on rates of cataract surgery. Some studies reported lower rates of cataract surgery when compared to FAME data.(35) Potential reasons to explain this difference could be an underestimation of these events due to

the shorter follow-up in some of the real-world studies included in the meta-analysis conducted by Fallico et al.(68)

The proportion of phakic eyes who needed cataract extraction after the FAc implantation was lower in the IRISS when compared to the proportion of patients undergoing cataract surgery in FAME.(36) The authors concluded that this was due to the high proportion of pseudophakic eyes included in the study. Of note, the majority of patients evaluated in the IRISS study were from UK sites where the FAc implant is restricted to patients with a pseudophakic eye.(36)

There were some differences in real-world reporting on rates of IOP-lowering medications. In pooled safety analysis of the real-world data done by Fallico et al rates of patients requiring IOP-lowering therapies and glaucoma surgery were lower than those reported in FAME (Table 19).(68)

Bailey et al. reported the proportion of patients on topical IOP-lowering medications increase from 16% at baseline to 29.7% of eyes requiring IOP-lowering medication. (73) This increase is higher than that reported in the FAME studies (23.9%), the IRISS study (23.3%), and the Paladin study (22%).(35, 36, 76) Bailey et al. reported that incisional IOP-lowering surgery was 2.7% at year 3 which aligns with that reported in the FAME studies. These findings were considered by the author to be related to IOP-monitoring in the real-world which was also impacted by the COVID pandemic. Bailey et al. also reported a difference in the incidence of treatment-emergent IOP-lowering medication, and in the incidence of IOP >30 mmHg in eyes with and without a prior history of IOP-related events. ($p<0.001$).(73) Eyes with no prior history of IOP-related events required significantly less treatment-emergent IOP-lowering medications than those with a prior history of IOP (Table 25).

Table 25. Impact of prior IOP-related events. Medisoft Study

	TE IOP-lowering medication	**IOP increase ≥10 mmHg**	**IOP increase >25 mmHg**	**IOP increase >30 mmHg**	**Laser trabeculoplasty [a]**	**IOP - lowering surgery [a]**
All eyes, % (n=256)	29.7	28.9	33.6	18.0	0.8	2.7

Mean time to event (days) ±SD	476.4 ±307.1	438.7 ±332.6	418 .3±323.9	547.3 ±323.7	–	–
Prior history of IOP-related events, % (n=94)	50.0	45.7	56.4	35.1	2.1	5.3
No prior history of IOP-related events, % (n=162)	17.9	19.1	20.4	8.0	0.0	1.2
[a] Time-to-event analyses were not performed for laser trabeculoplasty or IOP-lowering surgery, as the number of events was very small and the data could have been significantly skewed by outliers. IOP intraocular pressure, SD standard deviation. TE treatment emergent.						

Khoramnia et al. reported that, despite the inclusion of patients who would have not matched the FAME enrolment criteria for IOP history, the frequency of events observed remain consistent with those reported in FAME; 38.4% of patients needed IOP-lowering medications and 4.8% required IOP-lowering surgeries.(35, 36) Notably, in the IRISS study, it emerged that patients with short-term chronic DMO (participants with a median DMO duration of ≤3.6 years) had a marginally lower frequency of IOP related events when compared with eyes with long-term chronic DMO duration (>3.6 years).(36) The mean time to the first procedure for IOP events (whether surgery or non-penetrating) was 25.9±10.6 months (median, 23.7 months). The authors concluded this was a relevant finding and could support clinical decision-making for intravitreal corticosteroid therapy in patients with chronic DMO.

Retreatment

Only 3 of the real-world studies evaluated in the meta-analysis by Fallico et al. recorded reinjection with the FAc implant, with few patients, 1-8.6%, having such a retreatment during the follow-up period.(68) This reaffirms the expected treatment duration of up to 36 months. By contrast, in the real world setting the pooled estimates of eyes receiving supplementary intravitreal therapy was higher (39%) than that reported in FAME (15.2%). It was postulated that the difference in reported additional intravitreal therapies could relate to the timepoint the FAME trial was done, where treatment was largely macular laser or off-label corticosteroid therapy. Anti-VEGF therapy was not approved in DMO at that timepoint and rarely used. In FAME, anti-VEGF agents and triamcinolone acetonide were not permitted as rescue

treatments and were only given in cases where patients were not experiencing improvement. These considerations and the imaging techniques used in FAME could reasonably explain why the percentage of FAME patients administered supplementary therapies was lower. Of note, 13% of patients enrolled into FAME received an additional FAc implant during the follow-up period, this additional therapy could have reduced the need for other intravitreal agents. 56.3% of eyes analysed in the IRISS study required no additional treatment.(36)

Dobler et al reported that after 5-years post the FAc implant, 42% of patients remained free of any rescue intravitreal therapy. Mean time to first rescue intravitreal injection was 29.2± 14 months.(78) 5 eyes received a repeat FAc implant over the 5-year period (meant time to second FAc implant was 38 ± 4 months. Consistent with the durability of effect of the FAc implant (

Table ***26***).(1) Eyes required a mean of 2.5 intravitreal injections per year prior to FAc administration. Post FAc administration, the mean number of intravitreal injections per year decreased to 0.78/year in the 5-year follow-up period of this study. This represented a reduction in treatment burden of 69%.(78)

Table 26. Change in BCVA letters compared to baseline in eyes receiving no further intravitreal injections, eyes receiving repeat FAc implant and eyes receiving other supplemental intravitreal injections. Dobler et al.

Supplemental intravitreal injection		Number of eyes	Mean change in BCVA compared to baseline (ETDRS letters)			
			1 year	2 years	3 years	5 years
None		13	+6.0	+5.1	+2.0	+3.8
FAc implant	Including all eyes	5	+4.6	+6.4	+4.2	-5.8
	Excluding 1 eye with retinal detachment at 20-months	4	+5.8	+14.5	+8.0	+1.5
	Anti-VEGF and/or DEX implant	13	+2.5	+1.1	*+0.9*	-1.0
Abbreviations: BCVA, best-corrected visual acuity; DEX, dexamethasone intravitreal implant; ETDRS, Early Treatment Diabetic Retinopathy Study; FAc. Fluocinolone intravitreal implant.						

Reduced clinic burden

Real-world evidence is an indicator of the outcomes that should be expected in clinical practice should practice fail to achieve the same results in RCTs.(68) This can result in a gap between treatment efficacy, as reported in the controlled environment of an RCT, and the effectiveness of the same treatment in a real-life clinical setting. This is particularly relevant in the management of DMO, a chronic condition that requires continuous and intensive treatment.(68). Notably, the 'efficacy-effectiveness gap' for anti-VEGF therapies in DMO is well-recognised.(68, 79) The onerous RCT treatment regimens and conditions associated with the anti-VEGF therapies cannot always practically be implemented in a real clinic. NICE resource impact analysis from TA820 references between 16-18 injections are required across 3 years treatment for the main anti-VEGFs. Consequently, visual gains for anti-VEGF therapies observed in real-world practice are sub-optimal when compared to RCT outcomes as injection frequencies may not be possible.(68, 79) Clinical consensus and the UK literature speak to the need for DMO therapies with an extended durability of effect, to reduce burden and improve treatment regimen adherence.(18, 80, 81). Reduced clinical burden due the reduced injection frequency associated with the FAc implant was reported across all the real-world evidence

assessed here whilst concomitantly reporting visual outcomes consistent with those reported in the FAME trials.

Conclusions

The data from the real-world studies synthesised in the meta-analysis conducted by Fallico et al. represent important supportive evidence to the FAME studies demonstrating the real-world experience of the FAc 0.19 mg implant. The key visual, anatomic and safety outcomes reported by Fallico et al. were all highly consistent with those reported in the FAME studies.(35)

DMO is a chronic disease. Reaching a steady-state concentration is generally necessary for effective pharmacological management of diseases, which is the ability to deliver continuous exposure of therapeutic levels of the active molecule, while remaining below the threshold of safety issues that would lead to an unacceptable benefit to risk profile. A key and unique advantage of the FAc 0.19 mg implant over DEX rests in its near zero-order pharmacokinetic profile which allows for a stable and predictable release of drug over an extended duration of up to 36 months.(1, 30) Real-world reported outcomes confirm the 36-month duration of effect in the real-world. The extended duration of effect reduces the burden on the DMO patient, as well as the burden on the clinic and an ocular service already at capacity in the NHS. The conclusions of a recent study assessing trends of intravitreal injections at Moorfields Eye Hospital, UK, noted that the “demand for intravitreal injections has increased substantially over the last decade and is predicted to further increase. Healthcare systems will need to adapt to accommodate the high demand. Other solutions may include longer-acting therapies to reduce the treatment burden”.(80)

B.3.6.8.2 Real-world data – dexamethasone intravitreal implant

Four real-world studies evaluating clinical outcomes following treatment with the DEX implant were considered. All the real-world studies of DEX 0.7mg considered here report on lens status i.e., phakic or pseudophakic lens at baseline. The proportions of phakic to pseudophakic eyes was consistently lower in all the real-

world studies assessed. All studies except for Singer et al. report on outcomes relative to lens status.(37) Across all studies mean duration of follow-up was variable. Reported outcomes relative to lens status i.e., phakic and pseudophakic eyes are consistent. This is particularly salient to the population under consideration for decision problem of this review i.e., population with a phakic lens.

Kaldirim et al. reported a statistically significant change in BCVA from baseline at Months 1, 3 and 6 for patients treated with DEX($p<0.001$).(82) Comparison between groups showed no statistical differences between BCVA at any timepoint except Month 3 ($p=0.04$). In this study, the authors compared the anatomical and functional outcomes of pseudophakic and phakic eyes with DMO after a single intravitreal dexamethasone implant and concluded that there were no significant effects of lens type on outcomes at the end of the Month 6.

Wallsh et al. reported on a cohort of 43 patients (62 eyes) with DMO with 18 having a phakic lens and 44 having a pseudophakic lens prior to treatment with DEX 0.7 mg.(83) Eyes had mainly been treated with a prior course of anti-VEGF (91%). The duration of DEX treatment was 247.4 ± 35.30 days [mean ± SEM]) and 1.53 implants were administered. BCVA was recorded at baseline and on final visit and outcomes compared based on lens status (pseudophakic throughout, phakic throughout, or underwent cataract surgery (n=5/18 with a phakic lens at baseline). Note that those eyes that underwent cataract surgery did so after an average of 1.6 ± 0.2 DEX implants. Comparison between groups revealed no statistical differences (i.e., pseudophakic vs. phakic, $p=0.60$; pseudophakic vs. cataract surgery, $p=0.83$; and, phakic vs cataract surgery, $p=0.62$). The authors concluded that the population experienced similar improvements in both BCVA and CMT over the study course whether they were pseudophakic or phakic at initiation of the study, although they an important limitation was the small sample of phakic eyes with DMO at initiation. Another study was conducted by Lam et al. This was a retrospective cohort study in patients with macular oedema secondary to retinal disease treated at ten Canadian retina practices, including one uveitis centre.(84) From the 120 eyes identified, 34 had DMO. 67.6% of DMO eyes (n=23) were pseudophakic and 32.3% (n=11) were

phakic lens. During follow-up three of the eleven phakic eyes underwent cataract surgery. In terms of outcomes, when BCVA analysed by lens status at baseline, there was a peak mean loss of 0.6±0.6 lines in phakic eyes and a statistically significant ($p<0.05$) peak mean gain of 1.4±0.5 lines in pseudophakic eyes. The authors mentioned that data revealed that the improvement in BCVA was more pronounced in pseudophakic eyes than in phakic eyes and that these findings were in line with results from clinical trials of the DEX implant for the treatment of patients with DMO.

Retreatment

In terms of reinjection rates observed, Singer et al. report that the DEX implant was administered repeatedly with a mean re-injection interval of 5 months.(37) This was a phase 4, prospective, multicentre (18 USA sites), observational study involving 177 DMO patients (180 eyes; 93.8% previously treated) conducted between August 2014 and May 2016. Of the 180 eyes, 29.4% were phakic, 60.6% were pseudophakic and the remaining eyes were aphakic or the lens status was not recorded. Mean maximum BCVA changes from baseline after the first three DEX implants were +9.1 letters, +7.7 letters, and +7.0 letters, respectively ($p<0.001$). BCVA changes were reported by lens status with pseudophakic eyes being numerically greater (no statistics were reported) following administration of the first and third DEX implant, and BCVA changes being numerically greater after the second DEX implant (Table 27).(37)

Table 27. Re-injection Rates of the Dexamethasone Intravitreal Implant per Phakic and Pseudophakic Lens Status

Baseline lens status	Injection 1	Injection 2	Injection 3
Phakic BCVA letter gain	+8.6 to +11.5 (n = 52)	+8.5 to +14.8 (n = 29)	+5.2 to +17.8 (n = 13)
Pseudophakic BCVA letter gain	+ 9.4 to +11.6 (n = 100)	+7.4 to +11.1 (n = 60)	+7.6 to +12.4 (n = 37)
p-values (between groups)	Not reported		
Mean BCVA changes from baseline for total population were +9.1, +7.7 and +7.0 letters after injection 1, 2 and 3, respectively.			

The authors did not make conclusions regarding lens status as the study was conducted to better understand the usage and outcomes of the dexamethasone implant in DMO patients in a clinical practice setting. The authors did conclude that treatment with DEX 0.7 mg alone or in combination with other DMO therapy was effective in improving both visual and anatomic outcomes in this real-world population of patients, who typically had chronic, treatment refractory DMO.

B.3.7 Subgroup analysis

The ITC described in this CS (see section B3.9, Appendix D and Appendix I), demonstrates that treatment with FAc 0.19 mg provides similar health benefits at a similar or lower cost to DEX 0.7 mg in the full population for whom the comparator is recommended by NICE.

As noted previously, there was no pre-specified analysis in the FAME studies based on lens status; thus, there is no sub-population of treatment-experienced subjects with a phakic lens at baseline in FAME. Because this appraisal relates specifically to the DMO population with phakic eyes, however, the company presents here a post-hoc analysis of the sub-group of patients in the FAME trials who had phakic eyes and who were treated in line with the current marketing authorisation for ILUVIEN. The sub-group analysis is reported in Yang et al.(12). It has not been used to inform the ITC or the cost-comparison economic model in this appraisal. However, it presents important supportive evidence of the consistency of visual outcomes achieved with FAc implantation in DMO patients, irrespective of their lens status.

As noted previously, the MEAD studies for the comparator enrolled DMO patients with both phakic and pseudophakic eyes, both treatment-naïve and treatment-experienced. A post hoc subgroup analysis was by Augustin et al. in DMO patients who had received prior treatment (laser or medical treatment) prior to enrolment in the MEAD RCTs.(46) This sub-group analysis in a cohort of treatment-experienced (TE) patients represents a relevant cohort for comparative purposes in this decision problem. The post hoc analysis reported by Augustin et al. is used to inform the ITC

in this appraisal and the cost-comparison economic model (see Section B.4). Full details are presented below in section B.3.7.2 and Appendix E.

B.3.7.1 FAME studies – Subgroup analysis of patients with phakic eye at baseline

The objective of the post hoc sub-group analysis conducted by Yang et al. was to compare visual and anatomical outcomes between subjects in the FAME studies who had a pseudophakic lens at baseline and those who had a phakic lens at baseline and were subsequently treated for cataract during the study period.(12) The analysis is therefore of direct relevance to the population of interest in the decision problem.

Only patients treated with the 0.2 µg/day implant were included in the analysis. Patients who were phakic at all times during the study were excluded from the analysis; many of them had dropped out of the FAME studies. The number of patients treated with sham injections undergoing cataract surgery was small (n=32); these subjects were also excluded from the analysis.

Patients included in the analysis were divided into two main sub-groups according to whether the study eye had cataract surgery before (cataract before implant (CBI) group) or after (cataract after implant (CAI) group) receiving the 0.2 µg/day implant. Each of these two sub-groups were further sub-divided based on the duration of DMO, categorised as non-chronic if DMO duration was <3 years and chronic if DMO duration was ≥3 years. No imputation for missing data was applied. Comparisons were not tested for significance because of the post hoc nature of the analyses.

Outcomes for evaluation included both functional and anatomical outcomes at Month 36 in phakic patients who underwent cataract surgery during follow-up versus those who were already pseudophakic at baseline.

In this reported population who received the 0.2 µg/day implant, 348 patients were pseudophakic. Of these 348 patients; 140 were in the CBI group and 188 in the CAI group. The mean age of patients in the CBI group was 67.7 years, and the mean age

for patients in the CAI group was 60.5 years (p<0.0001). Baseline characteristics for BCVA, CPT, duration and type of diabetes, and glycosylated haemoglobin were reported as similar across all four sub-groups assessed in the analysis. In the CBI group, the median time to development of cataract was 12 months; the median time to cataract extraction was 18 months.

The results of the analysis showed that the proportion of patients with ≥15-letter improvement at 36 months was slightly higher overall in the CAI group (35.1%) than in the CBI group (29.3%). When the change in BCVA letter score from baseline to Month 36 was evaluated, patients in the CAI group experienced a decline in BCVA between Months 6 and 18. This is expected, as vision loss is a consequence of cataract formation. This decline in BCVA was transient and was not observed in the CBI group; visual gain from Month 3 was maintained. However, at month 36, the change in BCVA letters was numerically greater in the CAI group.

Subjects in the CAI group with chronic DMO were more likely to have a ≥15 letter BCVA improvement than those with non-chronic DMO (42.3% versus 27.5%, respectively). Improvements in mean BCVA letter score were also greater in chronic versus non-chronic patients (11.1 BCVA letter gain versus 4.3 BCVA letter gain, respectively.

In terms of anatomical outcomes, patients treated with the FAc 0.2μg implant who underwent cataract surgery had a small increase in CPT immediately after surgery. However, patients with chronic DMO recovered by Month 3 and were stable at Month 12 (mean CPT of 287 µm at the last visit before cataract surgery, 365 µm 1 month post operatively and 297 µm 3 months post operatively). In patients with non-chronic DMO, CPT stabilisation did not occur until Month 9 post operatively. Non-chronic patients had a mean CPT of 308 µm at the last visit before cataract surgery, and 355 µm 1 month post operatively, returning to pre-surgical values by Month 9.

Overall, the results from the post-hoc analysis conducted by Yang et al are clinically meaningful in terms of demonstrating that visual outcomes of phakic eyes treated with the 0.2 µg/day implant were no worse and possibly better than visual outcomes

seen in patients with pseudophakic eyes. Phakic eyes with chronic DMO treated with the FAc implant and requiring subsequent cataract surgery had particularly favourable visual outcomes.

Because the analysis was conducted post-hoc, it has limitations. The analysis was not powered to detect differences between patients receiving the 0.2 µg/day implant and those receiving the sham intervention. Nonetheless, the reported data support the use of the 0.2 µg/day FAc implant in both phakic and pseudophakic eyes in patients with both chronic and non-chronic DMO.

B.3.7.2 MEAD RCTs – Subgroup analysis of pre-treated patients

Augustin et al. conducted a post-hoc subgroup analysis of the MEAD registrational studies for the comparator, DEX 0.7 mg, in subjects who had received prior treatment for their DMO (laser and/or medical therapy) before to enrolling in the MEAD study (i.e. treatment-experienced patients).(46)

Only patients treated with DEX 0.7mg (n=247) and sham procedure (n=261) who had prior treatment for DMO at study enrolment were included. Key efficacy endpoints evaluated included the proportion of patients achieving a ≥15 BCVA letter gain from baseline in the study eye at end of study, mean change in BCVA from baseline during the study, and mean change in CRT from baseline during the study. The safety outcomes evaluated included ocular events.

The post hoc analysis reported by Augustin et al was used to inform the ITC in this appraisal (see Section B.3.9 and Appendix D) and the cost-comparison economic model (see Section B.3.4).

The baseline characteristics of treatment-experienced subjects included in the Augustin et al. sub-group analysis, together with the reported outcomes, are presented in Appendix E.

B.3.8 Meta-analysis

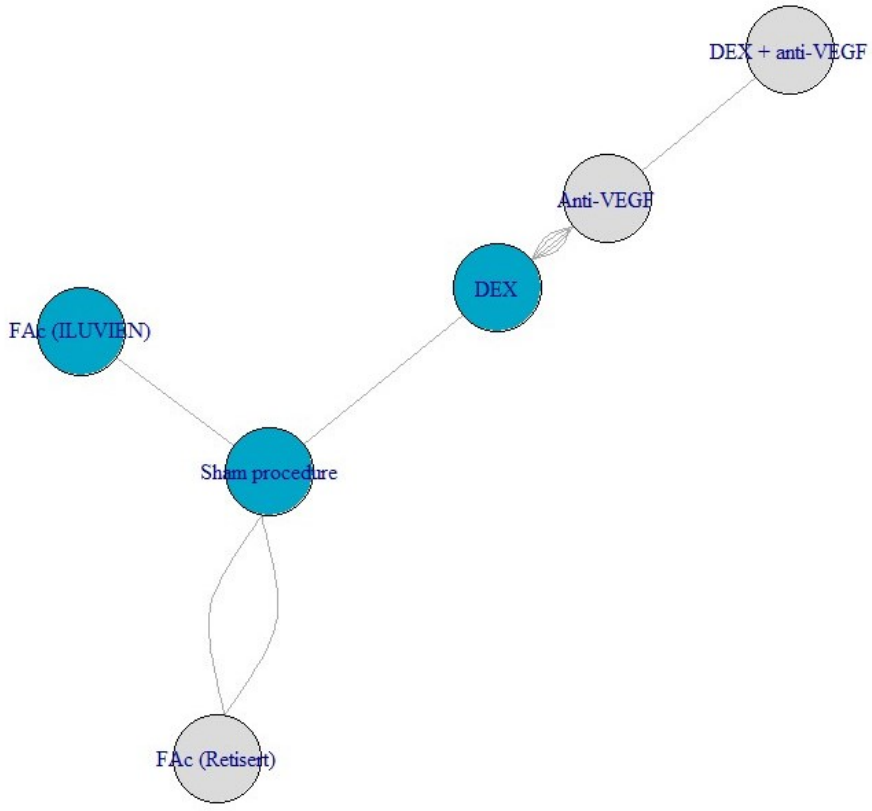
As no further Phase 3 RCTs studying the efficacy and safety of FAc 0.19 mg for DMO were found, no meta-analysis was conducted.

B.3.9 Indirect and mixed treatment comparisons

B.3.9.1 Overview

An ITC was conducted to provide estimates of comparative effectiveness between FAC 0.19 mg implant and DEX 0.7 mg implant. Information from the 10 RCTs identified in the SLR (see section B3.1 and Appendix D) were used to an extended comparison network, including FAc, DEX, DEX used in combination with anti-VEGF, anti-VEGF alone, laser, and sham procedures, as shown in Figure 8.

Figure 8. Overall network of treatments identified in the SLR, blue nodes indicate the proposed ITC network based on FAME (FAc versus sham) and MEAD (DEX versus sham)



Of the ten RCTs that were identified in the SLR, only two (FAME and MEAD, Phase 3 regulatory submission pivotal trials for FAc and DEX intravitreal implant, respectively) were assessed as relevant for inclusion in the ITC analysis comparing the relative efficacy and safety of FAc (equivalent to 0.2 µg per day) and DEX 0.7 mg in phakic DMO patients who are unsuitable for, or insufficiently responsive to non-corticosteroid therapies. The rationale for the exclusion of the remaining eight studies is presented in Appendix D (Table 3, Appendix D).

See Appendix D for full details of the methodology for the indirect comparison or mixed treatment comparison.

B.3.9.2 Outcomes considered in the ITC

B.3.9.2.1 Treatment efficacy outcomes

The primary efficacy outcome for assessment in the ITC of FAc and DEX 0.7mg was the proportion of subjects considered 'VA responders' in their study eye, with VA response defined as an increase from baseline of 15 or more in BCVA as measured with the ETDRS letters score. The VA responder analysis featured as a primary efficacy endpoint in both the FAME and MEAD trials. A ≥15-point increase in BCVA is commonly acknowledged as clinically significant endpoint in ophthalmology trials and thought to reflect a meaningful alteration in visual acuity. In both trials, VA responder analyses were evaluated at end of trial (EOT), with the LOCF method used to impute values when data was missing. Outcomes of the responder analyses were presented as the absolute proportion of responders in each treatment group and the proportional difference between the active treatment group (FAc 0.19 mg total dose or DEX 0.7 mg) versus sham.

Secondary efficacy outcomes assessed in the ITC analyses included the mean change in BCVA letter score from baseline to EOT; this endpoint was also common to both trials. Notably, there were some differences in how the outcomes were evaluated, particularly in relation to the statistical methods used. In FAME, changes from baseline BCVA values were analysed using an analysis of variance model (ANOVA), with treatment group and baseline visual acuity strata (≤49 or >49 letters)

as fixed effects. Missing data were imputed using the LOCF method. In contrast, MEAD adopted an area-under-the-curve (AUC) approach, with mean change from baseline analysed using an ANOVA model with treatment and study as fixed effects and baseline BCVA; missing values were not imputed.

A further secondary efficacy outcome assessed in the ITC analyses was the mean change in CRT from baseline to EOT. While this was evaluated as a key endpoint of the MEAD trial, FAME examined change from baseline in excess average CRT, with excess CRT calculated by subtracting a value of 180 μm from the average CRT for each subject. Again, analytical methods between the two trials differed. In MEAD, excess average foveal thickness change from baseline values were analysed using an ANOVA model with treatment group and baseline visual acuity strata as fixed effects and baseline excess average foveal thickness as the covariate. Missing data were imputed by the method of LOCF. In MEAD, an AUC approach was used, with mean change from baseline analysed using an ANOVA model including variables for treatment, study, and baseline CRT; missing values were not imputed.

B.3.9.2.2 Treatment safety outcomes

In addition to the efficacy outcomes assessed in the ITC analyses, several safety outcomes were also considered:

- Proportion of patients reporting serious ocular AEs
- Proportion of patients reporting IOP-related AEs (any AE related to increased intraocular pressure or glaucoma).
- Proportion of patients reporting cataract-related AEs (assessed only in patients with a phakic lens at baseline)

B.3.9.3 Results of the ITC

B.3.9.3.1 Comparison of baseline characteristics

A total of 339 patients were included within the indirect treatment comparison (ITC) cohort of FAME (FAc 0.2 ug/day; n=221; sham: n=118), and 508 patients were

included in the TE cohort of MEAD (DEX 0.7mg: n=247; Sham n=261). Demographic and baseline data for the two cohorts are summarised in Table 28.

In general, patient characteristics were well aligned between the trials, but there were some differences were observed in DMO characteristics at baseline: patients in FAME had a greater central retinal thickness (CRT) than those in MEAD (495µm versus 474µm), fewer had a phakic lens (63.1% versus 71.1%), and a higher proportion had received prior laser therapy (100% versus 93.3%).

Table 28. Demographic and baseline characteristics, FAME (ITC cohort) and MEAD (TE cohort)

	FAME (ITC cohort)			MEAD (TE cohort)			p-value[1]
	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)	0.521
Gender - Male, n (%)	134 (60.6)	73 (61.9)	207 (61.1)	150 (60.7)	168 (64.4)	318 (62.6)	0.705
Race-Caucasian, n (%)	172 (77.8)	89 (75.4)	261 (77.0)	188 (76.1)	192 (73.6)	380 (74.8)	0.519
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)	0.336
Type 2	197 (89.1)	112 (94.9)	309 (91.2)	220 (89.1)	238 (91.2)	458 (90.2)	0.716
Not recorded	4 (1.8)	-	4 (1.2)	-	-		-
Mean duration of diabetes, yrs (SD)	16.4 (9.8)	15.2 (8.9)	16.0 (9.5)	16.4 (8.7)	16.2 (9.7)	16.3 (9.2)	0.531
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)	0.104
DMO characteristics							
Mean duration of DMO[2], yrs (SD)	2.5 (2.8)	3.2 (4.4)	2.8 (3.4)	2.3 (2.2)	2.7 (2.4)	2.5 (2.3)	0.134

	FAME (ITC cohort)			MEAD (TE cohort)			p-value[1]
	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)	0.737
Mean CRT, µm (SD)	494 (128)	495 (125)	495 (127)	478 (153)	472 (131)	474 (142)	**0.003**
Lens status, n (%)							
Phakic	139 (62.9)	75 (63.6)	214 (63.1)	182 (73.7)	179 (68.6)	361 (71.1)	**0.019**
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)	**<0.001**
Intravitreal corticosteroid	41 (18.6)	20 (16.9)	61 (18.0)	58 (23.5)	61 (23.4)	119 (23.4)	0.071
Intravitreal anti-VEGF	NE*	NE*	NE*	25 (10.1)	26 (10.0)	51 (10.0)	-

[1]P-values were based on one-sample t-tests for continuous variables and chi-square tests for categorical variable, comparing values for the "All" cohort of both trails.

*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.

B.3.9.3.2 Study completion rates

3-year study completion rates for the FAME ITC cohort were similar in both the FAc 0.19 mg and sham treatment groups: [redacted]% and [redacted]%, respectively. After censoring at the point of receiving additional therapy, completion rates were substantially reduced: [redacted]% in the FAc 0.19 mg group and [redacted]% in the sham group. In the TE cohort of MEAD, [redacted]% of patients in the DEX 0.7mg treatment group completed the 3-year study period, compared to [redacted]% in the sham group.

B.3.9.3.3 Direct estimates of treatment efficacy and safety

Direct estimates of treatment efficacy and safety for FAc 0.19 mg versus sham, as calculated using patient-level data from FAME, are shown in Appendix J. Reported efficacy and safety estimands for DEX 0.7 mg versus sham for the MEAD trial (TE cohort) are also included at Appendix J.(46)

Population weighting and ESS

Matching on baseline imbalance EMs did not substantially reduce the ESS of the FAME ITC cohort (n= 294; [redacted]% reduction). Neither did matching on all EMs (N=286, [redacted]% reduction). Demographic and baseline characteristics for the re-weighted ITC cohorts are shown in Appendix J. Re-estimated efficacy and safety estimands for FAc 0.19 mg versus sham based for the ITC cohort are also shown in Appendix J.

B.3.9.3.4 ITC analyses for the proportion of patients achieving ≥15-letter improvement in BCVA from baseline to EOT

In the base-case matching-adjusted indirect comparison (MAIC) analysis (adjusting for imbalanced EMs and censoring patients at the point of additional therapy) no significant differences were observed in the proportion of patients who gained ≥15 letters between the FAc 0.19 mg and DEX 0.7 mg groups. While directionality of the point estimate tended slightly towards FAc, the confidence intervals were wide and included the null (estimated treatment difference ([redacted]). Similar results were obtained from the MAIC when adjusting for imbalanced but not including censoring ([redacted]),) and from analyses employing alternative ITC methods (

Figure ***9***).

Figure 9. ITC analyses of FAc 0.19 mg versus DEX 0.7mg for the proportion of patients achieving ≥15-letter BCVA improvement from baseline to EOT

Abbreviations: AITC, adjusted indirect treatment comparison, BCVA, best-corrected visual acuity, CI, confidence interval, DEX 0.7 mg, dexamethasone intravitreal implant 0.7 mg, EOT, end of treatment, EM, effect modifier, ETD, estimated treatment difference, FAc 0.19 mg, fluocinolone acetonide intravitreal implant 0.19 mg, ITC, indirect treatment comparison, MAIC, matching-adjusted indirect comparison.

B.3.9.3.5 ITC analyses for the mean change from baseline in BCVA letter score from baseline to EOT

For mean change from baseline in BCVA letter score, results from the base-case MAIC analysis demonstrated numerical but non-significant favourability for FAc 0.19 mg over DEX 0.7 mg, with an ETD of [redacted] letters (95% CI: [redacted]; p = [redacted]). The results obtained from the non-censored matched analysis were consistent with this, with estimates achieving borderline significance (ETD: [redacted] letters (95% CI: [redacted]; p = [redacted])); results from those matching for all EMs, the AITC, and the naïve analysis were also consistent (Figure 10).

Figure 10. ITC analyses of FAc 0.19 mg versus DEX 0.7mg for the mean change in BCVA from baseline to EOT

Abbreviations: AITC, adjusted indirect treatment comparison, BCVA, best-corrected visual acuity, CI, confidence interval, DEX 0.7 mg, dexamethasone intravitreal implant 0.7 mg, EOT, end of treatment, EM, effect modifier, ETD, estimated treatment difference, FAc 0.19 mg, fluocinolone acetonide intravitreal implant 0.19 mg, ITC, indirect treatment comparison, MAIC, matching-adjusted indirect comparison.

B.3.9.3.6 ITC analyses comparison for the mean change in CRT from baseline to EOT

For mean change from baseline in CRT, estimates derived from the base-case MAIC demonstrated equivalence of FAc 0.19 mg and DEX 0.7 mg. While directionality of the point estimate slightly favoured DEX 0.7 mg, it was accompanied by a wide confidence interval (ETD: [redacted])). Similar results were obtained from the MAIC when adjusting for imbalanced EMs but not including censoring (ETD [redacted] (95% CI: [redacted]; p = [redacted])). and from analyses employing alternative ITC methods (Figure 11).

Figure 11. ITC analyses of FAc 0.19 mg versus DEX 0.7mg for the mean change in CRT from baseline to EOT

Abbreviations: AITC, adjusted indirect treatment comparison, CRT, central retinal thickness, CI, confidence interval, DEX 0.7 mg, dexamethasone intravitreal implant 0.7 mg, EOT, end of treatment, EM, effect modifier, ETD, estimated treatment difference, FAc 0.19 mg, fluocinolone acetonide intravitreal implant 0.19 mg, ITC, indirect treatment comparison, MAIC, matching-adjusted indirect comparison.

B.3.9.3.7 Indirect treatment comparison of the proportion of patients experiencing ocular AEs

The incidence of ocular AEs in the ITC cohort of FAME and the TE cohort of MEAD are summarised in Table 29. When comparing the DEX 0.7mg treatment group of MEAD and the FAc 0.19 mg treatment group of FAME (with censoring), a lower proportion of patients experienced serious ocular AEs (10.9% versus 6.9%), but a higher proportion experienced IOP-related AEs (24.9% versus 38.1%) and cataract-

related AEs (57.6% versus 70.3%). Comparative estimates of treatment safety for FAc 0.19 mg and DEX 0.7 mg versus sham are presented in Appendix J.

Table 29. Proportion of patients experiencing ocular AEs, FAME (ITC cohort) and MEAD (TE cohort)

	FAME				MEAD	
	ITC cohort censored		ITC cohort non-censored		TE cohort [1]	
	FAc 0.19 mg	Treated Sham	FAc 0.19 mg	Treated Sham	DEX 0.7 mg	Treated Sham
N	221	221	221	118	247	261
Serious ocular AE, n (%)	24 (10.9)	1 (0.8)	34 (15.4)	9 (7.6)	17 (6.9)	2 (0.8)
IOP-related AE*, n (%)	55 (24.9)	1 (0.8)	73 (33.0)	11 (9.3)	94 (38.1)	12 (4.6)
Cataract-related AE (incidence in phakic eyes), n (%)**	80 (57.6)	11 (14.7)	113 (81.3)	33 (44.0)	128 (70.3)	36 (20.1)

[1] Values were taken from Augustin et al. The publication presented incidence as a proportion of patients experience ocular AEs, absolute values were back calculated using reported patient numbers.
*Any AE related to increased intraocular pressure or glaucoma
**Proportion calculated using baseline phakic population as the denominator
Abbreviations: AE, adverse event, 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, IOP, intraocular pressure, ITC, indirect treatment comparison, TE, treatment experienced.

ITC analyses for the proportion of patients reporting ocular AEs (serious ocular AEs, IOP-related AEs and cataract-related AEs [phakic eyes only]) for FAc 0.19 mg versus DEX 0.7 mg demonstrated comparability of the two therapies (see Appendix J: Figures 7, 8 and 9).

In the base-case MAIC, no significant differences were observed in the proportion of patients reporting serious ocular AEs between FAc 0.19 mg and DEX 0.7 mg (ETD: [redacted]% (95% CI: [redacted]; p = [redacted])), IOP-related AEs (ETD: [redacted]% (95% CI: [redacted]; p = [redacted])), or cataract-related AEs (ETD: [redacted](95% CI: [redacted]; p = [redacted]))(**Error! Reference source not found.**). The results obtained from the matched analyses (imbalanced EMs) without censoring were consistent with this (Table 30).

Table 30. ITC analyses of FAc 0.19 mg versus DEX.07 mg for the proportion of patients reporting ocular AEs

	MAIC CENSORED			MAIC UNCENSORED		
	FAc 0.19 mg vs sham (SE)	DEX 0.7 mg vs sham (SE)	FAc 0.19 mg vs DEX 0.7 mg ETD [95%CI; P-value]	FAc 0.19 mg vs sham (SE)	DEX 0.7 mg vs sham (SE)	FAc 0.19 mg vs DEX 0.7 mg ETD [95%CI; P-value]
Serious ocular AE	10.9 (2.49)	6.1 (1.70)	[redacted]	8.6 (3.80)	6.1 (1.70)	[redacted]
IOP-related AE*	25.5 (3.84)	33.5 (3.35)	[redacted]	26.1 (4.54)	33.5 (3.35)	[redacted]
Cataract-related AE (in phakic eyes)	41.5 (6.52)	50.2 (4.52)	[redacted]	38.4 (6.88)	50.2 (4.52)	[redacted]

*Any AE related to increased intraocular pressure or glaucoma
Abbreviations: AE, adverse event, DEX 0.7 mg, dexamethasone intravitreal implant 0.7 mg, DMO, diabetic macular oedema, ETD, estimated treatment difference, FAc 0.19 mg, fluocinolone acetonide intravitreal implant 0.19 mg, IOP, intraocular pressure, ITC, indirect treatment comparison, TE, treatment experienced.

B.3.9.4 Discussion

Main findings

In this report, comparative analytical approaches were used to quantify the relative effectiveness of FAc 0.19 mg and DEX 0.7 mg in the treatment of patients with DMO who insufficiently responsive to non-corticosteroid treatment or when non-corticosteroids are unsuitable or inappropriate. Analyses utilised patient-level data from FAME and aggregated published data from MEAD to evaluate the treatments in terms of change in BCVA, the proportion of patients achieving ≥15 letter improvements in BCVA, and improvement in CRT, as well as a range of safety outcomes.

Results from the base-case analyses, which adjusted for imbalances in EM variables between the two trials, demonstrated the broad equivalence of FAc 0.19 mg and

DEX 0.7 mg in terms of visual acuity improvements. No significance differences were observed in the proportion of patients achieving VA response (ETD of [redacted]% (95% CI: [redacted]; p = [redacted])) or in the mean change from baseline in BVCA letter score (ETD of [redacted] letters (95% CI [redacted]; p = [redacted])). Similarly, the two therapies were shown to be comparable in reducing CRT, a key anatomical measure of disease activity for DMO.

FAc 0.19 mg and DEX 0.7mg are both sustained-release corticosteroid implants, which operate through a similar mode of action; both exhibit anti-inflammatory and anti-oedematous effects as well as decreasing VEGF synthesis and so similarities in the observed benefits of the two therapies are expected.(85) It also follows that the safety profile of two therapies would be similar. In the base-case MAIC analyses examining the incidence of ocular AEs for both therapies, no statistically significant differences were observed between FAc 0.19 mg and DEX 0.7 mg in the proportion of patients reporting serious ocular AEs, IOP-related AEs, or cataract-related AEs.

Results from the comparative analyses of both efficacy and safety were robust to censoring of patients at the point of additional therapy. While censored analyses are likely to be biased in favour of FAc and uncensored analyses are likely to be biased in favour of DEX 0.7mg, consistency between the results of the analyses suggests that differences in the design of trials regarding the allowance of additional therapy had little effect on the estimated relative treatment effects of the two treatments.

Strengths

A key strength of the conducted analyses was the use of patient-level data from the FAME. A requirement of ITCs is that either the populations are inherently similar in terms of EMs, or that they are appropriately adjusted to remove any differences so that unbiased estimates can be obtained. Access to patient-level data for FAME allowed for the resolution of imbalances in EM variables between the trials, as well as the resolution of cross-trail difference with respect to study design, eligible criteria, and analytical methods.

Another strength of the analyses was the number of outcomes examined in the ITC analyses, with 3 related to treatment efficacy, and 3 related to treatment safety, providing a comprehensive view of the comparative health benefits of the two therapies.

Limitations

In general, ITCs are associated with a series of limitations which make them less robust than directly observed head-to-head trial data. The presence of observed and unobserved confounders to the estimated treatment effect has the potential to introduce significant bias into the comparison. While efforts were made to adjusted for imbalanced EMs, we did not have data on the proportion of patients with cataract at baseline, which was identified as important by clinicians. Instead, we adjusted for lens status as a proxy variable, given its inherent correlation to cataract presence. It is possible that this approach may be associated with residual confounding.

A further limitation of our analyses was the fact there were only 2 studies available which were relevant to the decision problem, and that the sample size of these studies was limited. This adds uncertainty to estimates, and when population adjustments are necessary, the population sample contributing the patient-level must be large enough to accurately estimate the treatment effects in the comparator population. The total sample size for FAME-enrolled patients in the patient-level data used in the MAIC was 339, with an ESS post-adjustment for imbalanced EMs of 294 (approximately a 13% reduction). Application of censoring following receipt of additional therapy in FAME reduced the sample size even more for analyses of changes from baseline (BCVA and CRT).

There were also notable limitations with respect to the ITC population in comparison with the decision problem, with the target patient population being phakic lens patients who are unsuitable for, or insufficiently responsive to non-corticosteroid treatment. Due to data restrictions, the ITC analyses were conducted in a combined phakic and pseudophakic patient population. To better understand the impact of this deviation, additional analyses using patient-level data from FAME were carried out

evaluating the treatment effect of FAc versus sham in phakic and pseudophakic populations (see Appendix J). Outcomes of these analyses demonstrated broad consistency in treatment effect, irrespective of lens status. Similar findings were also reported for DEX 0.7mg, by Boyer, noting the percentage of patients who gained ≥15 letters from baseline at study end was consistent in phakic and pseudophakic subgroups and reflected the results in the total study population.(31) As such, while there may be some heterogeneity between these groups, we would expect the estimated effects of FAc and DEX relative to sham to change concordantly. Thus, in the context of this ITC comparing FAc and DEX, it is expected that as long as the proportion of patients with a phakic lens is consistent between the two trials, the relative treatment effects would remain consistent with the joint population, and therefore that this limitation is not expected to bias the results of the ITC.

Conclusion

In conclusion, our ITC analyses quantify the relative effectiveness of FAc 0.19 mg and DEX 0.7 mg. Naïve, population-adjusted, and matched methods were considered. 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.

B.3.10 Adverse reactions

For the purposes of addressing the decision problem, the company presents and describes the following AEs as the safety outcomes included in the ITC between FAc implant and dexamethasone implant:

- 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)

B.3.10.1 FAME Studies - Treatment Exposure

Intravitreally-administered FAc was evaluated in 768 subjects (375 in the 0.2 µg/day FAc implant group; 393 in the 0.5 µg/day group) with DMO across the FAME A and FAME B studies.(1) Overall, treatment exposure in all treatment arms and across the two FAME studies was balanced. All patients randomised to the active treatment arms of the trials received a FAc intravitreal implant. The FAc implant has a durability of effect of up to 36 months.(1, 35) The mean number of treatments administered per patient in both FAME A and FAME B was 1.2 in the 0.2 ug/day FAc treatment group.

Details of the treatment exposure for each of the FAME A and B studies individually are provided in Appendix F.

B.3.10.2 Overview of safety profile for FAc implant

FAc intravitreal implants were generally safe and well-tolerated. The most frequently reported adverse drug reactions included cataract operation, cataract and increased IOP. These adverse events are commonly observed with intravitreal corticosteroid therapies; it is well-documented and well understood that the long-term use of corticosteroids may cause cataracts and increased IOP. These ocular AEs can therefore be considered a class effect of intravitreal corticosteroid therapies that

pertains to both FAc and its comparator, the dexamethasone intravitreal implant. This AE class profile is well understood by clinicians and easily-managed in clinical practice. All reported adverse events were generally manageable with no new safety signals identified.

As per the decision problem, ocular serious AEs, cataract-related AEs and IOP-related adverse events are presented in this section.

As noted previously, data from the FAME A and FAME B studies were pooled for analysis. Sections B.3.10.3 – B.3.10.5 describe the AE and safety profile based on the integrated safety analysis. Adverse events and safety outcomes for each of the the FAME studies individually are presented in Appendix F.

B.3.10.3 Treatment-Emergent Adverse Events

In the integrated safety analysis, the most common ocular adverse event was cataract.(35) It was reported in 42.7% of the low-dose group, 51.7% of the high-dose group and 9.7% of the sham group. This constituted 81.7%, 88.7% and 50.7% of patients in each of the study groups that had not had cataract surgery in the study eye at baseline. The median time for cataract reported as an adverse event was month-12 and the median time for cataract surgery was 18-months.(35) Cataract surgery was completed on almost all patients by the end of year 2; consequently, visual outcomes in year three were free of confounding by cataract.(43)

For those patients who had a phakic eye at study baseline, cataract surgery was performed in 80% of those in the low-dose treatment group, in 87% of those in the high-dose treatment group, and in 27.3% of those in the sham procedure group (see Table 31). Comparing patients with pseudophakic eyes at baseline with phakic eye patients who were treated with 0.2 µg/day FAc and who subsequently became pseudophakic, no significant difference in long-term vision outcome was seen in patients with non-chronic DMO. However, in chronic DMO patients, a benefit in favour of the FAc implants was observed.

Table 31. FAME studies (pooled analysis) - Cataract and Intraocular pressure-related Adverse Events

Phakic Patient, % (Study Eye)	Sham (n=121)	0.2 µg/day FAc (n=235)	0.5 µg/day FAc (n=256)
Cataract related events			
Cataract considered an AE	50.4	81.7	88.7
Cataract extraction	27.3	80.0	87.2
All Patients, % (Study Eye)	**Sham (n=185)**	**0.2 µg/day FAc (n=375)**	**0.5 µg/day FAc (n=393)**
IOP Related events			
AE of increased IOP	11.9	37.1	45.5
Any IOP lowering meds*	14.1	38.4	47.3
Trabeculoplasty	0.0	1.3	2.5
Incisional glaucoma surgery	0.5	4.8	8.1

AE adverse event, FAc fluocinolone acetonide.
The percentage of patients in each treatment group with the listed adverse event is listed.
*For a minimum of 7 days.

Source: Campochiaro et al 2011(35)

B.3.10.4 Serious Adverse Events

Overall, ~45% of patients in the FAME studies had at least 1 drug-related serious AE (SAE), with much higher incidence in the active treatment groups compared to the sham group. All drug-related SAEs were ocular in nature. The most common drug-related SAE overall was cataract operation, which primarily occurred in the two active treatment groups (0.2 µg/day group and 0.5 µg/day group). Few subjects discontinued the study due to an ocular event.

Table 32. Frequencies of non-fatal ocular SAEs and drug-related SAEs FAME A and B

	Non-fatal ocular SAEs		Drug-related SAEs	
	FAME A	**FAME B**	**FAME A**	**FAME B**
0.2μg FAc	60%	54%	56%	45%
0.5μg FAc	67%	68%	47%	58%
Sham group	26%	27%	5%	16%
Abbreviations: FAc, Fluocinolone Acetonide; SAE Serious Adverse Event				

Source. FAME A and FAME B (66, 67)

B.3.10.5 Cataract-mediated AEs

A pre-planned subgroup analysis of chronic and non-chronic DMO in the FAME population was undertaken.(12) Safety outcomes evaluated also considered lens status. Reported outcomes pertain to the 36-month timepoint of the FAME trials. On the basis of cataract-mediated adverse events and cataract surgery, the 36-month timeframe is sufficiently long to represent visual recovery post-surgery to inform clinical practice. Most patients with a phakic lens who received the FAc 0.2 ug/day implant demonstrated a cataract, and most cataracts were removed by Month 24, this allowed for visual outcomes in year 3 to be assessed, free from confounding by cataract. In the chronic DMO subgroup evaluated, it was determined that 36-month visual outcomes in patients who received the FAc 0.2 ug/day implant were numerically higher in patients who became pseudophakic during the study i.e., had a phakic lens at the time of FAME study enrolment. These patients had an improvement in BCVA letter score of +11 when compared to those patients with a pseudophakic presentation at baseline, this cohort had a +7 letter improvement in BCVA letters. However, this difference was not observed in the non-chronic DMO cohort evaluated. Patients with a pseudophakic presentation at baseline had an improvement in BCVA letter score of +3.3, versus a +4.3 BCVA letter improvement for patients with a phakic baseline presentation. The relationship between cataract surgery and long-term visual outcomes in patients with chronic DMO are thus not compromised. Evaluation of patients who presented with a pseudophakic lens at baseline, the treatment differences in gaining ≥15 letter between the FAc 0.2 ug/day

implant and sham control groups were similar to those in the full population. Among patients with chronic DMO who were pseudophakic at baseline, 31.6% of patients in the FAc 0.2 ug/day implant group and 17.4% in the sham procedure group experienced a gain of ≥15 BCVA letters at month 36 (p=0.043). Among pseudophakic patients with non-chronic DMO, 25% in the FAc 0.2 ug/day implant group and 16.7% in the sham procedure group, had a gain of ≥ 15-letter at month 36 (p=0.672). These findings demonstrate that differential treatment effects noted between both chronic and non-chronic patients is not an artifact of cataract surgery. In conclusion, cataract is a known and modifiable AE associated with intravitreal corticosteroid therapy and yet treatment with the FAc implant improves patient's visual outcomes in the long-term. Overall, this is suggestive that the FAc implant exerts a protective effect for vision recovery in patients with chronic DMO undergoing cataract surgery.(12)

B.3.10.5 Intra-ocular pressure

In the integrated FAME population, elevation of IOP was one of the primary AEs that was considered drug-related. In the FAME trials a dose response for IOP was seen but did not correspond to a similar increase in efficacy across both FAc doses. Hence, the 0.2 ug/day dose was chosen as the licensed dose. Overall IOP-related adverse events were more frequent in the FAc implant treatment groups than in the sham procedure group (0.2 ug/day 37.1%; 0.5 ug/day; 45.5%, sham 11.9%). In cases where elevated IOP levels are severe, prolonged, and unresponsive to pharmacological treatments, laser trabeculoplasty or incisional IOP lowering surgery is undertaken. Laser trabeculoplasty was carried out in 2.5% of patients in the 0.5 ug/day FAc implant group, 1.3% of patients in the 0.2 ug/day FAc implant group and 0% in the sham procedure group. Incisional IOP-lowering surgery was done in 8.1% of patients in the 0.2 ug/day FAc implant group, 4.3% of patients in the 0.2 ug/day FAc implant group and 0.5% in the sham procedure group.(35)

B.3.10.6 Safety reporting for the dexamethasone intravitreal implant 0.7mg

As specified in the decision problem, the patient population under consideration is patients with a phakic lens who had insufficient response to, or are ineligible for treatment with non-corticosteroid options (i.e., are TE).(3) The patient population enrolled in FAME were all considered TE, having received at least one macular laser therapy 12 weeks prior to enrolment. In contrast, MEAD enrolled both TE and treatment-naïve patients into the trial. With regards to lens status, both trials enrolled patients with phakic and pseudophakic lenses at baseline.

To align with the ITC methods safety reporting on ocular SAEs, and treatment emergent IOP and cataract related adverse have been derived from a post-hoc subpopulation of TE patients conducted by Augustin et al.(46) Table 33 presents the safety events specific to the decision problem in both the pre-treated sub population and from the full analysis population as reported by Boyer et al for the MEAD registration trials.(31) The reported frequencies of safety events listed in the pre-treated population were used to inform the ITC and are reported in Appendix D.

Table 33. Incidence of adverse events safety population. Augustin et al post-hoc analysis of the DMO pre-treated sub-population from MEAD

Incidence %	Previously Treated Patients		Total Study Population	
	DEX 0.7	Sham	DEX 0.7	Sham
	n=247	n=261	n=347	n=350
Serious ocular AE	6.9	0.8	6.9	1.1
IOP related AE[a]	38.1	4.6	36.0	5.1
Cataract related AE (incidence in phakic eyes)	70.3	20.1	67.9	20.4

[a] Any adverse event (AE) related to increased intraocular pressure or glaucoma
AE adverse event, DEX 0.7 dexamethasone intravitreal implant 0.7mg IOP intraocular pressure

The anchored ITC between FAc implant and the dexamethasone intravitreal implant includes eyes with both phakic and pseudophakic lenses. This patient population is the best available option for an informative ITC between FAc implant and the dexamethasone intravitreal implant in the target patient population of treatment-experienced patients with phakic lens. This patient population provides the least

biased comparison of FAc implant and the dexamethasone intravitreal implant, as the proportion of phakic and pseudophakic eyes are broadly consistent between studies (65.2% phakic patients in FAME; 71.1% phakic patients in the treatment-experienced subgroup in MEAD), which means that the presence of pseudophakic eyes should not bias estimates of comparative safety. The ITC enabled the generation of new estimates of comparative safety for both FAc and dexamethasone intravitreal implants.

The incidence of ocular AEs in the ITC cohort of FAME and the TE cohort of MEAD are described in Section B.3.9 and summarised in Appendix D.

ITC analyses for the proportion of patients reporting ocular AEs in FAc 0.2 µg/day versus the dexamethasone intravitreal implant have been presented in Section B.3.9 and demonstrated comparability of the two therapies.

B.3.10.3 Summary Conclusion of the Safety of the Technology

FAc implant was generally well-tolerated across the FAME A and FAME B studies. The most frequently reported AEs included cataract operation, cataract and increased intraocular pressure. Further details are provided in Appendix F. The safety outcomes observed in the FAME RCTs have been replicated in the real-world as described in Section B.3.6.7. The IRISS study, a 6 year Post-Approval Safety Registry Study comprising data from 556 patients (695 eyes), was completed and did not show any additional safety risks to those identified in the FAME studies.(1)

The most frequently reported AEs reported in the MEAD studies in patients who received DEX 0.7mg were cataract and elevated IOP in the study eye.(33) Cataract is a modifiable risk factor that is well-recognised as being associated with intravitreal corticosteroid therapies.

Clinically, the risk-benefit profile of intravitreal corticosteroid therapies in general is understood and it is considered medically acceptable to treat phakic eyes at risk of vision loss due to DMO in patients who have an insufficient response to non-

corticosteroid therapies, or where non-corticosteroids are not suitable or appropriate. The dexamethasone intravitreal implant is already recommended by NICE as a treatment option for DMO patients presenting with a phakic lens.(4)

Because of its long-acting duration, treatment with the FAc implant reduces the number and frequency of intravitreal injections compared to the dexamethasone implant and reduces the treatment burden for both the patient and NHS by design. ILUVIEN releases FAc as a continuous micro dose for up to 36 months with near zero-order kinetics, providing a consistent anti-inflammatory effect in the eye that protects the retina from damage and preserves vision.

B.3.10.3. Similarities and differences between the technology and its comparator

The comparative safety profiles of 0.2 µg/day FAc implant and the dexamethasone intravitreal implant 0.7 mg in the treatment of patients with DMO who are insufficiently responsive to non-corticosteroid treatment, or where non-corticosteroid treatment is not suitable or appropriate have been quantified using ITC methodology (see section B.3.9, Appendix D and Appendix J).

Analyses utilised patient-level data from FAME and aggregated published data from MEAD to evaluate the treatments in terms of a range of safety outcomes.(31, 46) The ITC analyses quantified comparable risk of cataract events, IOP and SAE in both the FAc and dexamethasone intravitreal implants.

In the base-case MAIC, no significant differences were observed in the proportion of patients reporting serious ocular AEs between FAc 0.2 ug/day and the dexamethasone intravitreal implant 0.7 mg (ETD: 4.8 % (95% CI: -1.1, 10.7; p = 0.111)), IOP-related AEs (ETD: -8.0% (95% CI: -18.0, 2.0; p = 0.116)), or cataract-related AEs (ETD: -8.7 (95% CI: -24.2, 6.8; p = 0.273)). The results obtained from the matched analyses (imbalanced EMs) without censoring were consistent with this. ITC analyses for the proportion of patients reporting ocular AEs in FAc 0.2 ug/day versus DEX 0.7 mg demonstrated comparability of the two therapies (see Section B.3.9 and Appendix J: Figures 5, 6 and 7).

The incidence of ocular AEs in the ITC cohort of FAME and the treatment-experienced (TE) cohort of MEAD is summarised in Table 29. When comparing the dexamethasone intravitreal implant 0.7mg treatment group in MEAD and the FAc µg/day FAc implant group in FAME, with censoring, a lower proportion of patients in the dexamethasone group experienced ocular SAEs (6.9% versus 10.9%), but a higher proportion of dexamethasone-treated patients experienced IOP-related AEs (38.1% versus 24.9%) and cataract-related AEs (70.3% versus 57.6%). Comparative estimates of treatment safety for FAc 0.2 ug/day and DEX 0.7 mg versus sham are presented in Table 30.

The results from the comparative analysis of safety were robust to censoring of treatment-experienced patients at the point of additional therapy. It is considered that censored analyses are likely to bias in favour of the FAc implant, whereas uncensored analyses are likely to bias in favour of the dexamethasone intravitreal implant.

The consistency between the results of the analyses suggests that differences in the FAME and MEAD trial designs specific to the introduction of additional DMO therapy had little effect on the estimated relative treatment effects of the two treatments. The utilisation of individual patient level data from FAME allowed for adjustment for differences between the two trials for unbiased estimates. Additionally, the use of FAME patient level data allowed for the resolution of imbalances in effect modifier variables and cross-trial differences with respect to the study design, eligibility criteria, and analytical methods. The ITC presented in section B.3.9 and Appendix D therefore provides a comprehensive and robust evaluation of the comparative safety profile of both the FAc implant and the dexamethasone intravitreal implant.

In the absence of a head-to-head comparison, the presented safety findings can reliably inform assessment of cost effectiveness between the FAc and dexamethasone corticosteroid intravitreal implants for the treatment of patients with DMO who are unsuitable for, or insufficiently responsive to non-corticosteroid treatment.

In terms of clinical decision making, these outputs are meaningful. Safety outcomes are comparable between the two implants.

A critical limitation of the DEX implant relates to its short duration of action.(86, 87) The duration of effect of the DEX implant is up to 6 months; however, both the literature and NHS clinicians consulted by the company indicate that the clinical effect of the DEX implant can decline after anywhere between 3-6 months.(31, 33, 86, 87) The literature describes marked fluctuation in the reduction in CST at consecutive study visits, most notable during year one of treatment, thus creating a saw-tooth pattern of treatment effect.(19, 52, 88) The fluctuations in retinal oedema potentiate the risk of cumulative retinal damage. The use of the DEX implant imposes a 'treat, recurrence and repeat' cycling of care which has distinct limitations in terms of anatomical outcomes and variable visual outcomes. This imposes a burden of care to both DMO patients and the NHS as DEX requires multiple injections in contrast to a single FAc implant lasting for up to 3 years with continuous microdosing, as described in previous sections.

B.3.11 Conclusions about comparable health benefits and safety

One requisite for using cost-comparison methodology is that comparable or similar efficacy must be established between the technology and the comparator.

In the present decision problem, the population of interest is DMO patients with sub-optimal response to prior therapies who have a phakic lens. In the absence of a head-to-head comparison between FAc implant and DEX in this population, ITCs were conducted to quantify the relative effectiveness of FAc 0.2 µg/day implant and DEX 0.7mg. Naïve, population- adjusted, and matched-adjusted comparisons were all considered (see section B.3.9, Appendix D and Appendix J) using the primary and key secondary efficacy outcome measures from the Phase 3 randomised, double-blind, sham-controlled FAME and MEAD studies. Treatment-related ocular and serious adverse events were also included in the ITC. The common comparator for both treatments was sham intervention. The ITC accounted for and adjusted for trial

heterogeneity and differences in how outcomes were assessed and quantified to enable robust and reliable estimates of relative effectiveness and safety. Comparable efficacy and safety were established with no significant differences observed between the two therapies across any of the examined outcome measures.

The strengths and limitations of the ITC approach and potential areas of uncertainty when evaluating the phakic eye population have been identified and discussed in section B.3.9.4. These include trial heterogeneity, lack of access to individual patient-level data for patients enrolled in the MEAD studies and a paucity of published reported data sources for the phakic only population for the comparator. Treatment-experienced patients with both phakic and pseudophakic lens were therefore analysed and included in the ITC. This patient population provides the least biased comparison of FAc and DEX, as the proportion of phakic and pseudophakic eyes are broadly consistent between studies (65.2% phakic in FAME, 71.1% phakic in treatment-experienced subgroup of MEAD), which means that the presence of pseudophakic eyes should not bias estimates of comparative efficacy. The impact of residual imbalance between the studies in the proportion of patients with phakic eyes has also been assessed with a matched adjusted ITC. Furthermore, efficacy results from FAME were generally consistent across phakic and pseudophakic subgroups.

In contrast, conducting the analysis in phakic eyes only is likely to present a biased estimate of comparative efficacy, as there were no treatment-naïve patients included in FAME, and as such, imbalance between the two trials in the proportion of treatment-experienced patients cannot be adjusted for post-hoc. Experts consulted during the development of the ITC have also stated that treatment experience is likely to be a treatment effect modifying factor for both FAc and DEX intravitreal implants, meaning that this imbalance is highly likely to bias ITC results.

In addition to comparability of efficacy and safety outcomes observed in the clinical trial data and the results of the ITC, comparable efficacy and safety between the two treatments has been demonstrated in several real-world studies. Studies reported by

Bailey et al., Fallico et al., Khoramnia et al. and Dobler et al. confirm that the visual and anatomical outcomes reported for DMO patients treated with FAc implant in real-world clinical settings are comparable to the outcomes observed in the FAME registrational trials, and that there is no demonstrable difference in outcomes between patients with a phakic or pseudophakic lens.(36, 68, 73, 78) Similarly, real-world evidence of the dexamethasone intravitreal implant reports comparable treatment outcomes in phakic and pseudophakic eyes.(37, 82-84)

FAc implant and DEX are both corticosteroid therapies, intravitreally-injected, with similar chemical structures and modes of action. The key differentiator rests in their respective duration of effect (up to 36 months for FAc implant, whereas retreatment with DEX is permitted after 6 months), mediated by proprietary release technologies.

The key drivers of the cost-comparison are the acquisition cost of implants and the cost of administering the FAc and DEX implants, which in turn are determined by the frequency of injection. Treatment with FAc is associated with long-term clinical outcomes secondary to the extended durability of effect of the FAc implant.(35) Medically, the goal of therapeutic management of chronic disease is centred around the attainment steady state pharmacokinetics, which is the ability to deliver continuous exposure to therapeutic levels of the active molecule (with and acceptable safety profile) in chronic disease management. The FAc implant is the only available intravitreal therapy in DMO, a chronic disease, which allows for “steady state” pharmacokinetics, enabling continuous micro-dosing which preserves both anatomical and functional outcome in DMO over an extended period, i.e., up to 36-months.(1, 35) In contrast, the dexamethasone implant has up to 6 months duration of effect.(33, 86, 87) The extended duration of effect of the FAc implant offers more consistent anatomical outcomes in terms of fluid resolution and improves visual outcomes in DMO eyes, both phakic and pseudophakic.

The Paladin study confirms that better control of retinal fluctuations with ILUVIEN can lead to significant improvements in vision.(37) A post hoc analysis of the DRCR. net protocol T and Protocol V by Starr et al., using the standard deviation of CST

measurements in individual eyes to quantify CST fluctuations over time, concluded that increased fluctuations in macular oedema as determined by OCT '*appear to be associated with worse visual outcomes.'*(19) A pooled analysis of data from the MEAD trials was the first to examine the long-term retinal changes associated with the visual acuity for DEX. OCT findings for eyes treated with DEX demonstrate marked fluctuation in the reduction in CST at consecutive study visits, particularly during year 1, creating a saw-tooth pattern of treatment effect. This observed effect is in keeping with previous studies suggesting that the efficacy of the dexamethasone intravitreal implant on CST peaks at approximately 1–3 months before gradually declining.(47) The fluctuations in retinal oedema potentiate the risk of cumulative retinal damage. The use of DEX therefore creates a 'treat, recurrence and repeat' cycle of care which has distinct limitations in terms of anatomical outcomes and burden of disease in DMO.

NHS clinical experts in the treatment of DMO have indicated that the clinical effect of DEX can decline anytime from 3-5 months. Less frequent DEX administration in the real-world was discussed as part of NICE TA824, where it was presented that IOP adverse events are less frequent in the real-world than those described in the pivotal MEAD studies because, in real-world clinical practice, DEX is administered less frequently than in the MEAD RCTs.

Thus, the frequency of administration represents an important clinical differentiator between the two therapies. NHS clinicians have pointed to a need to adapt current working practices and adopt changes to improve patient care, while also easing pressure on clinic capacity, reducing hospital visits and maintaining patient safety.(18) Notably, Downey and her co-authors identified that ensuring continuity of treatment during exceptional circumstances, such as the COVID 19 pandemic, highlights the importance of preparing for the unexpected when timely retreatments may not be possible.(18)

As noted above, the body of real-world evidence for FAc implant confirms that the visual outcomes reported in FAME are replicated in the real-world. However, FAc reimplantation in the real-world is somewhat less frequent than that observed in FAME. Fallico et al report 1-8.6% re-administration rate of the FAc implant.(68) In the IRISS study, VA outcomes were achieved with a single implant in 93.2% off patients (Khoramnia et al) and the mean time to second implant was 38±4 months, consistent with the durability of effect noted in the FAME primary publication and the ILUVIEN SmPC.(78) Dobler et al reported that, prior to FAc implantation eyes required a mean of 2.5 intravitreal injections per year. Post FAc administration, the mean number of intravitreal injections per year had decreased to 0.78/year over the course of the 5-year follow-up period of this study, a reduction in treatment burden of 69%. The UK literature speaks to this need for more efficacious intravitreal therapies with an extended duration of effect so that healthcare systems can adapt to high ocular service demand in the face of scare resources.(18, 80)

Overall, the results of the post-hoc analysis of the FAME studies conducted by Yang et al. are clinically meaningful in terms of demonstrating that visual outcomes of phakic eyes treated with the 0.2 µg/day implant were no worse and possibly better than visual outcomes seen in patients with pseudophakic eyes.(12) Phakic eyes with chronic DMO treated with the FAc implant and requiring subsequent cataract surgery had particularly favourable visual outcomes. Because the analysis was conducted post-hoc, it has limitations. The analysis was not powered to detect differences between patients receiving the 0.2 µg/day FAc implant and those receiving the sham intervention. Nonetheless, the reported data support the use of the 0.2 µg/day FAc implant in both phakic and pseudophakic eyes in patients with both chronic and non-chronic DMO.

Treatment with the FAc implant could have a substantive effect on patients' quality of life. Ocular injections can be a source of fear, stress, and anxiety for patients with retinal diseases, and the frequent clinic visits, injections, and patient monitoring required to achieve optimal long-term outcomes for patients with DMO results in a high burden of treatment for patients and their caregivers.(5)

Changes in VA over a 10-year interval were reported as the most important predictor for a reduced NEI-VFQ-25 score. Workforce participation negatively impacted by DMO and other systemic comorbidities were found to be strongly predictive of lower scores in most NEI-VFQ-25 domains.(23) The frequency of treatment injections in DMO is correlated to visual outcomes. Nonadherence was found to correlate with a loss of up to 15 BCVA letters.(90) Failing vision influences the patient's ability to undertake critical diabetic disease management as it makes the tasks difficult. Liu et al reported how a 1-line average improvement was associated with "clinically meaningful changes in Health-Related Quality of Life".(23) The ability to drive is impacted directly by underlying DR, causing further reduction in independence and HRQoL. In addition to impaired visual acuity and loss of visual field, impairment in colour vision, contrast sensitivity, dark adaptation, and increased glare sensitivity are all associated impairments. Szlyk et al evaluated the relationship between retinal thickness measurements and driving simulator variables.(91) Conclusions illustrate a relationship between CRT and driving function in patients with DR which could, by extension, be applied to the DMO population. The findings were suggestive of an overall latency in visual processing independent of letter score and other static measures of visual functioning.

Because of its long-acting duration, treatment with the FAc implant reduces the number and frequency of intravitreal injections compared to the dexamethasone implant and reduces the treatment burden for both the patient and NHS by design. ILUVIEN releases FAc as a continuous micro dose for up to 36 months with near zero-order kinetics, providing a consistent anti-inflammatory effect in the eye that protects the retina from damage and preserves vision. At the clinical interface, the FAc implant concomitantly improves patient outcomes and reduces resource use burden in in an already constrained healthcare system. The FAc implant represents a highly innovative technology in the management of patients with DMO, irrespective of lens status.

B.3.12 Ongoing studies

None of relevance to the decision problem.

B.4 Cost-comparison analysis

B.4.1 Changes in service provision and management

Displacement of DEX with FAc for the treatment of patients with DMO is expected to reduce the frequency of intravitreal corticosteroid injection and therefore reduce the burden of this procedure on NHS ophthalmology services and patients.

As presented in Section B.3., one implant of FAc has a longer treatment effect compared to one implant of DEX. According to literature sources and expert clinical opinion provided to the company for this evaluation, FAc provides extended stability of vision compared to DEX due to a longer sustained release of a micro dose of FAc and duration of treatment effect up to 36 months.(19, 52, 88)

For these reasons, a treatment strategy of FAc requires relatively fewer face-to-face outpatient visits for both drug administration and for disease monitoring compared to a strategy of DEX. Fewer intravitreal injections are also associated with fewer administration-related adverse events, e.g., endophthalmitis, vitreous haemorrhage, and retinal detachment.

B.4.2 Cost-comparison analysis inputs and assumptions

B.4.2.1 Features of the cost-comparison analysis

The objective of the cost-comparison is to quantify and cost the resource use associated with the two corticosteroid treatment strategies FAc and DEX for a pairwise cost-comparison. Costs are compared on a premise equivalence [of FAc] in health outcomes, which is supported by the findings of the ITC presented in section B.3.9. The ITC showed equivalence across efficacy and safety outcomes, supporting equivalent risk-benefit. Expert clinical advice provided to the company confirmed plausibility of the ITC results in the clinical setting (Section B.3.9).

Insufficient published evidence for DEX prohibited an ITC in only phakic eyes. Available data allows a comparison of phakic eyes with cataract, but this adverse

event is confounding, and sample size was diminished. The efficacy of FAc is consistent across phakic and pseudophakic eyes, so the ITC includes eyes without the natural lens (section 3.7.1).

The key features of the cost-comparison are presented in Table 34.

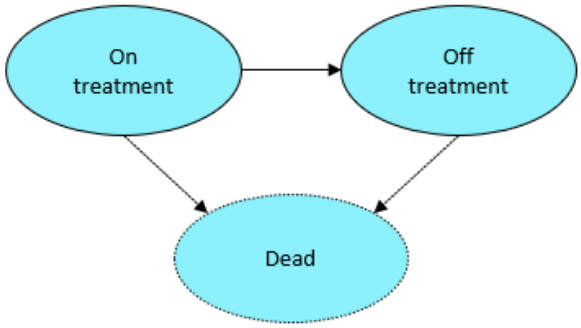
Table 34. Key features of the cost-comparison

Objective	To quantify and cost the resource use associated with the two corticosteroid treatment strategies FAc and DEX for a pairwise cost-comparison.
Main outcome	The per person incremental 6-year total cost to the NHS and Personal Social Services payer in England in 2022. Costs per phakic eye are scaled to costs per person.
Main differentiator of cost	A course of treatment with the FAc intravitreal implant (IVI) required fewer implants than a course of DEX IVI.
Resource use included	steroid implant acquisition, steroid implantation administration, treatment and procedures for adverse events and complications of disease, and the routine management of disease.
Cost of additional and subsequent treatment	Not included. The need for, and timing of, other treatment for DMO is assumed to be null based on the premise of equivalent health outcomes. IVI retreatment estimates elicited from the literature do not adjust for a phakic lens only [eye] population. It is assumed that the need and timing of retreatment in the phakic eye is the same as the pseudophakic eye (section B.4.2.3).
Time horizon	The modelled time horizon is 6 years, by which time no patients are expected to remain on treatment.

B.4.2.2 Model structure

The analysis adopts a three-state cohort transition structure (Figure 12). This facilitates transition off-treatment and introduces mortality - if it is not implicit from retreatment estimates. Retreatment estimates from trials and real-world-studies account for discontinuation including death, however, mortality is applied in an alternative scenario in the model to long-term retreatment estimates (those after year 3) brought forward from TA824 for DEX. Transitions are allowed every three months, to retain consistency with prior DMO models evaluated by NICE, but also because the DEX implantation interval could be less than 6 months.

Figure 12. Model diagram



Key: Ovals are representative of states which simplify DMO status into two dimensions; treatment status (on/off) and mortality (dead/alive). Arrows represent permitted transitions between states. Dead is an absorbing state but is not used in the base case, denoted by the dashed boarder, and dashed arrows.

B.4.2.3 Modelled population

The decision problem specifies the population as people with chronic diabetic macular oedema that is insufficiently responsive to available therapies who have phakic lenses. Notwithstanding the ITC population, this is the population for the costing exercise.

Indeed, it is the same population as NICE TA824, the evaluation of the dexamethasone intravitreal implant (DEX) for treating DMO in people without a pseudophakic lens. Therefore, TA824 is the starting point for multiple estimates of resource utilisation. As two years have passed since the publication of TA824 from an NHS payer perspective, unit costs were appropriately updated using the same source.

Age and gender at baseline inform mortality risk, if used, so must represent the population. Individual patients from the FAME studies were censored in the ITC to match the published means of the MEAD studies. Therefore, the mean age and gender proportion of participants of MEAD at randomisation (DEX 0.7 mg cohort) were used for the baseline cycle. Mean age = 62.5 years, proportion male = 60.7%. 75.5% of eyes in the DEX 0.7 mg treatment arm were phakic. Further detail of

baseline characteristics of patients and study eyes are presented in section B.3.3.3 and in the literature.(31)

Note that costs were assemble on a per eye basis, so to attain costs per person they were uplifted by the fraction that is people who are treated for DMO in a second phakic eye. Individual patient-level analysis of FAME for lens status in non-study eyes revealed that 24 of 191 participants had phakic DMO in both eyes. This produced an uplift of 112.6%.(92)

B.4.2.4 Mortality

Mortality was not applied in the base case because sources of retreatment count already included study drop-out and therefore censored for death. An explicit DMO mortality risk was applied in a scenario analysis. In the scenario, the age-matched and gender-weighted all cause risk of death from the general population of England was adjusted for the additional relative mortality of DMO.(93) Adjustment used the standardised mortality ratio (SMR) accepted for the evaluation of DEX in TA824. This was the product (2.45) of the hazard ratio for additional mortality of diabetes mellitus relative to the general population (1.93) and the hazard ratio for additional mortality of DMO versus the general population (1.27).(89, 94) If mortality were applied from baseline, 83.7% would survive 6 years to age 68.5.

B.4.2.5 Treatment effect

The effect of treatment on visual outcomes, or any difference in effect between treatments, is not considered in the cost-comparison. The model does not directly consider changes in vision, patient utility or estimate quality-adjusted life-years (QALYs). Treatment effect is considered indirectly in respect to the need and timing of retreatment, this is a function of loss of vision and discontinuation, which may be independent.

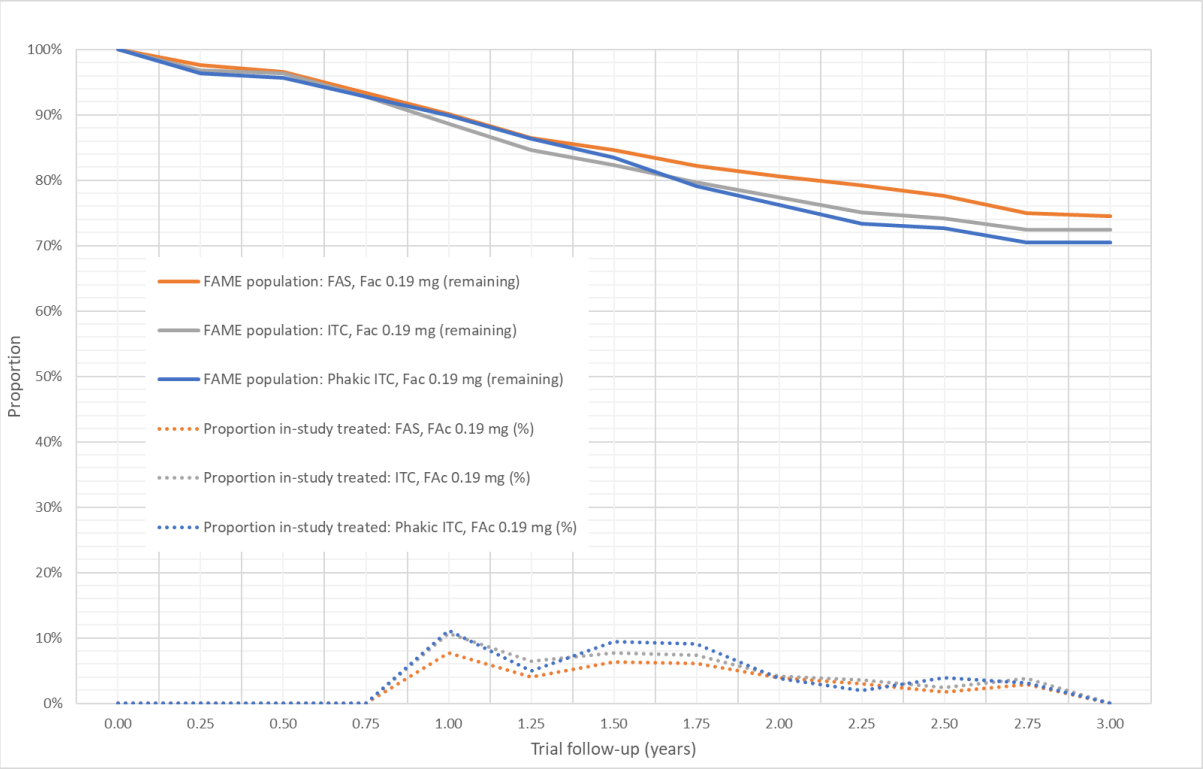
Retreatment with steroids in DMO is considered for patients who have experienced an initial response but later experience decreased vision or an increase in retinal thickness secondary to recurrent or worsening DMO.(1, 33) Whilst retreatment is not

considered for those who do not attain a sufficient initial response, reasons for discontinuation are varied and may include loss of initial response, adverse events, morbidity, mortality, or preference. Quite when discontinuation is defined is complex given the pharmacokinetics and pharmacodynamics and of the sustained-release mechanism. Indeed, if for some the treatment effect is enduring, or if secondary causes of DMO relent, then the time to retreatment reported in trials may be truncated since they typically follow outcomes for three years, yet real-world studies of FAc 0.19 mg have shown the retreatment interval to surpass 3 years.(72) In all, in the case of steroid implants for DMO, it is challenging to estimate when >95% of patients are no longer in need of retreatment. In TA824 the submitting company argued that DEX would not continue past 5 years. Feedback from UK clinical experts argued that 5 years was sufficiently long enough to capture key differences in treatment costs for dexamethasone or anti-VEGFs (specified in the AbbVie company submission section B.3.2.2.1).(4) However, given the prolonged release of FAc 0.19 mg, a time horizon approximating two treatment cycles was chosen, i.e., 6 years. A very small minority of patients ever receive a third FAc implant, in controlled trial and in the real-world (see section B.4.2.7). In the only identified long-term (>3 years follow-up) real-world study in DMO patients in the UK, the mean number of FAc implants over 5-years (1.16) was comparable to the mean number of FAc implants over 3-years (1.14) in the large UK observational study (Medisoft).(73, 78), suggesting that it is rare to receive more than one FAc implant. In FAME, only 8/395 patients (2%) had more than one reimplantation. However, the durability of response was not fully understood until the completion of the dose-finding FAMOUS trial, which reported in 2013 and after the recruitment for FAME was started.(30, 35)

The view of the NICE ERG in their summary of Time on Treatment (page 132) as part of their TA824 evaluation is that DEX *has no predefined treatment regimen where retreatment is defined at regular intervals, rather the need for retreatment is assessed at regular intervals* i.e., retreatment is considered as needed, *pro re nata* (PRN). The ERG went on to state that *the proportion of patients receiving a steroid intravitreal implant in a given model cycle is not necessarily reflective of the*

proportion on continued treatment. Treatment discontinuation was modelled independently of the average number of treatments received by patients on treatment.(4) Figure 13 illustrates the proportion of patients remaining in the FAME study and the proportion of eyes being retreated.

Figure 13. FAME study drop-out and the proportion of eyes administered retreatment.



In the same way, this analysis also distinguishes the number of re-treatments administered in any cycle from treatment discontinuation. In the base case, FAc discontinuation is estimated to be at 5.25 years, that is 9 cycles or 2.75 years after the final implant in cycle 12, 2.75 years after the first implant. DEX discontinuation is estimated to be at 5.0 years, that is 3 cycles or 0.75 years after the final occasion of implant, which is in cycle 17, 4.25 years after the first implant.

The model time horizon is 6 years, but 5.0 years (DEX) and 5.25 years (FAc) mark the times at which no one is expected to receive further retreatment in clinical practice. They are approximately equal, and this is an assumption of the model. The

number of retreatments after three years, a post-RCT extrapolation period, is described in section B.4.2.7.

B.4.2.6 Posology of treatments

The FAc summary of product characteristics states than an additional ILUVIEN® implant may be administered after 12 months if the patient experiences decreased vision or an increase in retinal thickness secondary to recurrent or worsening diabetic macular oedema.(1) It goes on to state that the maximal aqueous humor fluocinolone acetonide concentrations were observed on Day 7 for most of the subjects. Aqueous humor fluocinolone acetonide concentrations decreased over the first 3−6 months and remained essentially the same through Month 36 for subjects who were not retreated.

The EURETINA European guidelines state about FAc that pharmacokinetic studies showed that it provides sustained delivery in the eye for at least one year.(95) Therefore, repeated treatment may be given after a year according to evidence of central fluid and visual acuity parameters. However, this is unlikely in real world clinical settings as outlined below and in previous sections. Whilst the official product label in Europe recommends additional treatments after one year and does not recommend administration to both eyes concurrently, this is not observed in real world studies, which confirm the efficacy of 1 implant across 36 months.(68)

The DEX summary of product characteristics states that patients treated with OZURDEX® who have experienced an initial response and in the physician's opinion may benefit from retreatment without being exposed to significant risk should be considered for retreatment.(33) Retreatment may be performed after approximately 6 months if the patient experiences decreased vision and/or an increase in retinal thickness, secondary to recurrent or worsening diabetic macular oedema. There is currently no experience of the efficacy or safety of repeat administrations in DME beyond 7 implants. It goes on to state that in a 6-month monkey study following a single intravitreal injection of OZURDEX the dexamethasone vitreous humour Cmax

was 100 ng/mL at day 42 post-injection and 5.57 ng/mL at day 91. Dexamethasone remained detectable in the vitreous at 6 months post-injection.

The EURETINA European guidelines state that the DEX implant releases the corticosteroid into the vitreous over a period of ≤ 6 months.(95) Therefore, the official product label in Europe recommends retreatment after approximately 6 months, and does not recommend administration to both eyes concurrently. Newer data support the reinjection of the dexamethasone implant earlier than the recommended retreatment interval. The CHROME study, a retrospective real-world study, included patients with DME, retinal vein occlusion, and uveitis. The mean reinjection interval in this study was 2.3–4.9 months.(84)

B.4.2.7 Retreatment

Evidence from RCTs

The number of FAc retreatments in FAME over 3 years was reported as the proportion of eyes receiving 1, 2 or ≥3 study treatments.(30) This is inadequate for the model so an analysis of the individual patient data was required to specify the timing and number of retreatments at 3-monthly intervals (Table 35). The table shows the proportions remaining in the study, and proportions receiving treatment (uncensored for drop-out). Figures for FAc in the full analysis set are compared to FAc in the ITC any eye population and the ITC phakic eye population. Note that in FAME, patients were eligible for retreatment after month 12, and there was no specified minimum retreatment interval, but retreatment was disallowed after 33 months follow-up. Compare this to the MEAD retreatment protocol, which applied a minimum retreatment interval of 6-months, and no retreatment after 36 months. Given that real-world studies have shown DEX retreatment intervals of less than 6 months, it is more likely that estimates from MEAD are subject to protocol bias than those from FAME.(84, 96, 97) Real-world studies of FAc retreatment have shown intervals in excess of 3 years.(73, 78)

Table 35. Timing and number of retreatments at 3-monthly intervals

Years	FAME population: FAS, FAc		FAME population: ITC, FAc		FAME population: Phakic ITC, FAc	
	Remaining in-study (%)	Retreated (uncensored), %	Remaining in-study (%)	Retreated (uncensored), %	Remaining in-study (%)	Retreated (uncensored), %
0.00	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.50	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.75	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1.00	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1.25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1.50	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1.75	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2.00	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2.25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2.50	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2.75	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3.00	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The number of DEX retreatments in MEAD over 3 years was reported as a mean 4.1 (SD, 2.0) and as the proportions requiring from 1 to 7 implants. Mean time to retreatment was not reported, but if it were assumed that the mean follow-up was 36 months then 1,427 injections in 347 eyes equates to a best-case mean interval of 8.75 months.

Comparison of FAc retreatment in the FAME ITC and FAME ITC phakic only cohorts shows a close alignment. This supports the assumption that the inclusion of pseudophakic eyes in estimates of retreatment rates for a phakic only population is reasonable. This was a necessary assumption for parameterising the base case

DEX strategy given a lack of phakic specific rates. Table 36 compares the proportion of patients receiving retreatment in the FAME and MEAD studies as reported in the included studies.(31, 44)

Table 36. Reported number of eyes administered retreatment with intravitreal steroid implant

Number of study treatments	MEAD. All DEX patients (n=347)(31)	FAME. All FAc patients (n=376)(44)
1, n (%)	44 (12.7)	- (74.4)
2, n (%)	54 (15.6)	- (21.6)
3, n (%)	39 (11.2)	- (4%) *
4, n (%)	42 (12.1)	-
5, n (%)	49 (14.1)	-
6, n (%)	88 (25.4)	-
7, n (%)	31 (8.9)	-
Mean (SD)	4.1 (2.0)	
Median	4	
* received ≥3 study treatments		

The advantage of incorporating evidence from the real-world setting is that is not restrained by the trial protocol specifications. So, a targeted search for any retreatment-related outcomes was conducted to find the retreatment estimates most generalisable to the modelled setting, the NHS in England in 2022. Note that since FAc is not recommended for in the NHS for patients with DMO in phakic eyes, real-world evidence about retreatment in this setting relates mostly to pseudophakic eyes.

The FAc intravitreal implant in real-world studies

The targeted search began with an assessment of the 2021 systematic review of real-world experience with FAc reported by Fallico and colleagues; nine real-world studies were identified (listed).(68) Three studies identified in the systematic review

(Augustin 2020, Rehak 2020, and Mansour 2020) were not considered generalisable to the NHS:

1. Panos et al. (2020) observed 24 eyes at a single English NHS centre with up to 3-years follow-up. 50% phakic eyes.(69)
2. Fusi-Rubiano et al. (2018) observed 29 eyes at a single English NHS centre for an average of 792 days (2 years and 2 months).(70)
3. Augustin et al. (2020) reported the three-year results of the Retro-IDEAL study of 81 eyes in the German healthcare setting.(71)
4. Chakravarthy et al. (2018) report on the ILUVIEN Registry Safety Study (IRISS) of FAc in 593 eyes, as experienced in three European countries (15 NHS sites) over 24-month follow-up.(72) This was updated by Khoramnia in 2022 when follow-up was a minimum of 3 years.(36)
5. Bailey et al. (2017, updated in 2022) reported on the Medisoft registry of 256 eyes at 14 NHS clinical sites, with a mean follow-up in the update of 4.28 years.(73)
6. Rehak et al. (2020) conducted a retrospective single centre 5-year chart review of 49 previously treated eyes in the German healthcare setting.(74)
7. Young et al. (2019) observed 21 eyes at a single English NHS centre with up to 3 years follow-up.(75)
8. Mansour et al. (2020) reported the 24-month interim analysis of the PALADIN study of 118 eyes in the US setting.(76)
9. Ahmed et al. (2020) observed 26 eyes at a single English NHS centre with over a 3-year follow-up. But this study did not report on retreatment.(77)

Since this systematic review, targeted searching identified two further UK NHS observational studies.

10. Holden et al. (2017) reported the outcomes of the ICE-UK trial, a multicentre study of medical records including 233 eyes one year prior and one year after treatment with FAc.(98)

11. Dobler et al. (2023) studied 31 eyes at a single NHS centre, reporting 5-year results.(78)

Table 37 presents study detail for those set in the NHS. Augustin 2020, Rehak 2020 and Mansor 2020 were set outside the NHS, and Young 2019 and Ahmed 2020 did not report on retreatment, so are omitted.

Table 37. Real-world studies of FAc treatment in the UK setting

Study	UK patients	Eyes treated with FAc (% phakic)	Follow-up	Mean FAc implants	Number (%) of eyes receiving one, two, three retreatments	Time until supplementary treatment
Panos 2020 (London) (69)	24	24 (50%)	Up to 3 years, minimum of 2 years	1.00	1=Nil	Mean 13.5 months until subsequent therapy
Fusi-Rubiano 2018 (Birmingham) (70)	27	29 (3%)	Minimum 1 year, 6 patients with ≥3 years	1.00	1=Nil	Mean 12 months until subsequent therapy
Khoramnia 2022 and Chakravarthy 2018 (IRISS) (36, 72)	387/556 (70%) *	695 (16%)	Mean 3 years 2 months (range 0.7-65 months)	1.07	1=4 (0.6%) 2=1 (0.1%)	2 years and 8 months until second FAc implant (n=4)
Bailey 2022 (Medisoft) (73)	227 (100%)	256 (11%)	Minimum 3 years; Mean 4.3 years	1.14	37 (14.5%) No third implants	Mean 3.2 years until second FAc implant
Dobler 2023 (Birmingham) (78)	31	31 (0%)	5 years, 6 weeks	1.16	5/31 (16.1%)	3.2 years (±0.3 years) until second FAc implant

Abbreviations: NR, Not reported. *Not reported in the paper; figure obtained from the author

Panos et al. reported in 2020 a single-centre retrospective analysis of patients with persistent DMO, despite previous anti-vascular endothelial growth factor and/or steroid treatment.(69) The purpose of this study is to report the long-term efficacy and safety of FAc in pseudophakic eyes with DMO in a multi-ethnic patient cohort.

All 24 eyes (24 patients) completed at least 24 months of follow-up, of which 9 completed 36 months of follow-up. Supplementary treatment for persistent or recurrent DMO was necessary in 13 eyes (54%) over the total study period of 3 years. Supplementary treatment was intravitreal triamcinolone (n=2), aflibercept (n=4), ranibizumab (n=8) or Ozurdex (n=1). The choice of medication was left to physicians' discretion. Of the 13 eyes, 2 eyes received more than one supplementary treatment. No further laser treatment or additional FAc implant was administered.

Fusi-Rubiano et al. reported in 2018 a single centre retrospective evaluation of patients with DMO unresponsive to conventional treatment treated with the FAc implant according to UK guidelines.(70) The objective was to compare visual function and structural improvements in pseudophakic eyes with DMO. Twenty-nine eyes were included (97% pseudophakic), with mean (SD) follow up of 792 (270) days. Supplementary treatment for persistence or recurrence of DMO was necessary in 18 eyes over the total study period of 3 years with mean time to supplementary treatment being 12 months (range 2-22 months), with a mean of 2.6 retreatments (range 1 to 9) during the follow-up. Supplementary treatment was with one or more of laser (n=4), intravitreal triamcinolone (n=3) or anti-VEGF agent (aflibercept n=11; bevacizumab n=4; ranibizumab n=3). No patients had retreatment with the FAc implant.

Khoramnia et al. reported complete 3-year follow-up results for IRISS in 2022.(36) Outcomes for 695 eyes (1% known phakic) in 556 patients treated with 0.2 ug FAc were followed up for 1,151 days (SD 357 days), with a minimum of three years in all eyes. The study enrolled from 31 sites in the UK (70% of patients), 11 in Germany and 5 in Portugal. A mean of 1.07 FAc implants per eye were administered over the duration of the study. Most eyes (N=648; 93.2%) received only one implant during the study. A small number of eyes (N=46; 6.6%) received two implants and a single patient (N=1; 0.1%) received three implants. In those that received a second implant, this occurred after 986.1 (2.7 years) ± 318.0 days (range 224–1742). The mean follow-up time for the 47 eyes with ≥2 implants was 1,387 (3.8 years) ± 219.3 days

and the mean follow-up time for the 648 eyes with 1 implant was 1,142 (3.1 years) ± 357.8 days.

Bailey et al. reported in 2022 the larger and generalisable Medisoft study, which aimed to assess the long-term effectiveness of the 0.19 mg FAc implant over ≥3 years for DMO patients in the UK.(73) It was a retrospective audit of pseudo-anonymised data from Medisoft electronic medical records (Medisoft, Leeds, UK) from 14 NHS clinical sites. Data were available for 256 (89% pseudophakic) eyes in 227 patients with a minimum of 3 years of follow-up and mean follow-up duration of 4.28 years. 11% of eyes were phakic. Most patients received macular laser and/or intravitreal treatments prior to FAc implant injection. Overall, a mean of 1.14 FAc implants were used per eye (293 injections) over the entire course of follow-up. The mean time to the injection of the second implant was 1160.7 days (~3.2 years; range 357–1842 days). No patient received more than two FAc implants during the period of follow-up.

Dobler et al. (2023) report a recent small study of 31 eyes (all pseudophakic) treated at the Birmingham and Midlands Eye Centre (NHS). This a retrospective study of a cohort of patients who had been treated for chronic DMO with an 2 ug/day FAc intravitreal implant, which reports 5-year results.(78) The mean follow-up period was 1867 (±122) days, which is equivalent to 5 years and 6 weeks. Five eyes received one repeat FAc implant (mean of 1.16 implants per eye), with a mean time to repeat FAc of 38 ± 4 months (3.2 years). Eyes required a mean of 2.5 intravitreal injections per year prior to FAc, vs. 0.78 intravitreal injections per year in the 5 years post FAc, representing a reduction in treatment burden of 69%.

The DEX intravitreal implant in real-world studies

The targeted search began with the 2018 systematic literature review by Bucolo and colleagues.(99) This was a review of long-term efficacy and the safety of multiple injections of DEX in people with DMO identified 21 peer-reviewed publications, none of the identified studies were conducted in the NHS or UK setting. However, further

searching identified four relevant studies, the final being most generalisable to the model setting.

Fraser-Bell et al. reported in 2023 a prospective study of DEX in the Australia health system.(96) This was larger than any identified in the 2018 systematic review. The AUSSIEDEX study tracked the outcomes of 200 eyes (29% treatment naïve; 73% pseudophakic) over 52 weeks. The mean number of DEX injections was 2.5, with a mean treatment interval of 4.8 months.

Rosenblatt et al. reported in 2022 the European DMW Registry Study, a collaborative retrospective study on the efficacy and safety of DEX implant in patients with DME.(97) This study enrolled 340 eyes (40% pseudophakic) from 8 European countries and all intravitreal implants were administered with an interval of 3 to 6 months (±2 weeks). The mean number of injections in the first, second, and third years were 2.39±0.5, 0.18±0.6 and 0.03±0.2. The mean interval between injections was 145 days ±24.5 days (4.76 months ± 0.8 months).

Lam et al. reported in 2015 the CHROME study, which evaluated the real-world use, efficacy, and safety of one or more DEX implant(s) 0.7 mg in patients in patients with macular oedema.(84) It was a retrospective cohort study of 120 eyes (57% pseudophakic) with macular oedema secondary to retinal disease, at 10 Canadian practices. 34/101 patients had a diagnosis of DMO (32% phakic lens). The mean number of DEX injections was 1.6±0.1 in the DMO eyes; 42.2% of eyes had repeat DEX injections. In this cohort, the reinjection interval to the first re-implantation was 5.8±0.5 months, and the reinjection interval between second and third re-injections was 5.6±1.0 months.

Faes et al. reported in 2023 a large 8-year real-world study of DEX for people treated for DMO at Moorfields Eye Hospital NHS Foundation Trust was published.(100) Intravitreal dexamethasone was used as per treatment guidance provided by NICE TA824. 240 patients met the inclusion/exclusion criteria, with one eye randomly selected in cases where two were involved (240 eyes included, 71% pseudophakic). Criteria: ≥2 hospital visits following initial injection (≥1 beyond 6 months) and no

previous ocular corticosteroid treatment or missing assessment at baseline. 30% of included eyes had a phakic lens. The median time to retreatment in the cohort was 10.4 months (95% CI 8.5–13.3), but for only 46% (55/119) of those who failed to sustain a positive response was retreatment anticipated and administered before the VA benefit was lost. Retreatment was with DEX in 58% (n=32/55) of these cases. For the 130/240 who attained ≥5 ETDRS letters, the probability of sustaining this response beyond 4 months after the event was 50% (failure to sustain their positive visual response was observed for 119/130).

Interpretation of steroid implant retreatment real-world evidence

The large studies of FAc in the NHS, Medisoft and IRISS, which together reported on 951 treated eyes, show that only about 10% of eyes are re-implanted with FAc. In those who were re-implanted with FAc, retreatment followed 3 years after the initial implant. The smaller studies indicated that other treatments were administered sooner, on average approximately 1 year after the first FAc treatment.

The single large observational study of DEX in the NHS setting showed an average retreatment interval of 10.4 months, longer even than a conservative estimate of 8.75 months for MEAD which assumes all patients completed 3 years. However, the authors indicated delay in retreatment since over half of those responders who subsequently failed to sustain response were retreated before all benefit was lost. Are the findings at this single London hospital indicative of health system capacity pressures preventing treatment on a true *pro re nata* basis. In contrast, the studies of eyes treated in other health systems reported mean injection intervals of 4.8, 4.8 and 5.6 months. These estimates may represent the closest real-world proxy to the trial setting outcomes achieved in MEAD.(31)

Retreatment imputed into the model

The ocular outcomes of the full analysis set participants of MEAD and the ITC adjusted cohort of FAME informed the equivalence of effect premise of the cost-comparison. The timing and number of treatments in the same populations are

chosen for the base case analysis, this data is applied to the first 3 years of the 6-year time horizon. Individual patient data used in the ITC was censored for pseudophakic lens status, then the timing of the second FAc administration in the remaining phakic eyes was analysed to estimate the number of FAc 0.19 treatments per eye per cycle. It is assumed that no further second FAc implants are administered after three years. This is explored in a scenario analysis in which a proportion of 3% is used for the first three cycles of year four.

In the absence of individual patient data to inform the timing of DEX administration, it was necessary to assume that implants were administered at consecutive 6-monthly intervals. This soonest possible implantation assumption is based on the study protocol minimum 6-month retreatment interval. For example, for the 11.2% who received two retreatments over 3 years, their administration was modelled at 6 months and 12 months. In a scenario analysis, DEX administration timing was set according to an evenly spread administration on a 6-monthly interval basis. For example, for the 15.6% who received two implants over 3 years, the single retreatment was administered half-way through follow-up, at the fourth possible administration opportunity, which is at 18 months. Administration of DEX after year 3 follows the assumption of TA824, that the equivalent of 1 implant per year is administered in years 4 and 5. With treatment not expected beyond year 5, no DEX is applied in the sixth year. This long-term use of DEX is reduced by half in a scenario analysis.

The number of FAc administrations per eye per cycle for the base case (option label FAME_1) and for alternative scenarios is presented in Table 38. The number per eye per cycle for DEX (option label MEAD_1) is presented in Table 39. In each table, the alternative numbers used for scenario analysis is presented alongside. Those cycles with a non-zero rate are not shown.

In the base case, the 6-year ratio of DEX to FAc implant count is 4.40. This ratio can be varied in the model by selection of alternative competing rates through a range of 4.32 to 7.48.

Table 38. Number of FAc implants per eye per cycle

FAc strategy		Implantations per eye per 3-month cycle				
Cycle*	Years	Basecase FAME_1	FAME_2	RWE_1	RWE_2	RWE_3
0	0.00	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	0.25					
2	0.50					
3	0.75					
4	1.00	[redacted]	[redacted]			
5	1.25	[redacted]	[redacted]			
6	1.50	[redacted]	[redacted]			
7	1.75	[redacted]	[redacted]			
8	2.00	[redacted]	[redacted]			
9	2.25	[redacted]	[redacted]			
10	2.50	[redacted]	[redacted]			[redacted]
11	2.75	[redacted]	[redacted]			
12	3.00			[redacted]	[redacted]	
13	3.25					
14	3.50					
15	3.75					
16	4.00					
17	4.25					
18	4.50					
19	4.75					
20	5.00					
21	5.25					
22	5.50					
23	5.75					
24	6.00					
	Total=	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Dex, dexamethasone 0.7 mg intravitreal implant; FAc, fluocinolone 0.19 mg intravitreal implant; RWE, real-world evidence. *Cycles during which there is no retreatment are not shown.

Table 39. Number of DEX implants per eye per cycle

DEX strategy		Implantations per eye per 3-month cycle			
Cycle*	**Years**	**Basecase MEAD_1**	**MEAD_2**	**RWE_1**	**RWE_2**
0	0.00	1.00	1.00	1.00	1.00
1	0.25		0.87		
2	0.50	0.87	0.72	1.00	
3	0.75		0.61		1.00
4	1.00	0.72	0.48		
5	1.25		0.34	1.00	
6	1.50	0.61	0.09		1.00
7	1.75			1.00	
8	2.00	0.48			
9	2.25			1.00	
10	2.50	0.34			1.00
11	2.75			1.00	
12	3.00	0.09			
13	3.25	1.00	1.00	1.00	1.00
14	3.50				
15	3.75				
16	4.00				
17	4.25	1.00	1.00	1.00	1.00
18	4.50				
19	4.75				
20	5.00				
21	5.25				
22	5.50				
23	5.75				
24	6.00				
	Total=	6.11	6.11	8.00	6.00

Abbreviations: Dex, dexamethasone 0.7 mg intravitreal implant; FAc, fluocinolone 0.19 mg intravitreal implant; RWE, real-world evidence. *Cycles during which there is no retreatment are not shown.

B.4.2.8 Adverse events

The ITC included three safety outcomes. Proportion of patients reporting serious ocular AEs; proportion of patients reporting IOP-related AEs (any AE related to increased intraocular pressure or glaucoma); and proportion of patients reporting cataract-related AEs (assessed only in patients with a phakic lens at baseline). It found that no statistically significant differences were observed between FAc and DEX in the proportion of patients reporting serious ocular AEs, IOP-related AEs, or cataract-related AEs. In a review of these outcomes, including the method, a clinical expert confirmed that no statistical difference was synonymous with no clinical difference, and that the findings were aligned with expectation based on clinical experience. However, the four types of drug-related adverse events included in the NICE evaluation of DEX for the same population (TA824) were also included in this cost-comparison: endophthalmitis, vitreous haemorrhage, and retinal detachment; with raised IOP included separately under the cost category of 'complication of disease'. A panel of three UK clinical experts were asked if the rates accepted for DEX in TA824 were still applicable, whether these rates would be observed for the FAc intravitreal implant, and if not, what should the rate be? All three experts agreed that the TA824 annual proportions would apply, and equally across steroid strategies for endophthalmitis and retinal detachment. However, one participant expected a higher proportion experiencing vitrectomy (due to adverse reaction to steroid) for the FAc intravitreal implant versus the proportion included for DEX in TA824. Although this was a minority finding, twice the proportion for the FAc intravitreal implant was applied in the model. This was an arbitrary inflation in the absence of any offered estimate. As mentioned, the ITC found no statistical difference in the occurrence of IOP-related adverse events based on the two included RCTs. Expert clinical advice was consistent with this result (see section B.4.2.11). The adverse event rates used in the model are presented in Table 40.

Table 40. Adverse event rates used in the model

Resource	Steroid implant	Affected proportion (%)		
		Year 1	Year 2	Year 3+
Raised IOP	FAc	26%	13%	9%
	DEX	26%	13%	9%
Cataract extraction	FAc	12%	49%	17%
	DEX	12%	49%	17%
Vitrectomy	FAc	2%	2%	4%
	DEX	1%	1%	2%

Abbreviations: Dex, dexamethasone 0.7 mg intravitreal implant; FAc, fluocinolone 0.19 mg intravitreal implant.

B.4.2.9 Intervention and comparator acquisition costs

One implant of FAc or DEX is a single dose and also one unit. The respective unit costs are detailed in Table 41. List prices were sourced from the British National Formulary.(101) The PAS discount for FAc is previously agreed and included in the model. No discount is included for DEX.

Table 41. Acquisition costs of alternative steroid intravitreal implants

	Fluocinolone acetonide (ILUVIEN®)	**Dexamethasone (Ozurdex®)**
Short name	FAc	DEX
Manufacturer/Supplier	Alimera Sciences Ltd	AbbVie Ltd
Description	Fluocinolone acetonide intravitreal implant	Dexamethasone intravitreal implant
Legal category	POM (hospital only)	POM (hospital only)
Dose	190 micrograms	700 micrograms
Unit size	190 micrograms	700 micrograms
PRN. frequency (months)	Up to 36	Up to 6
NHS list price	£5,500	£870
Unit price after PAS	[redacted]	£870.00
Source	BNF 27.6.23 (101)	BNF 27.6.23 (101)

Abbreviations: BNF, British National Formulary; PAS, Patient Access Scheme; POM, prescription only medicine; PRN, *pro re nata* (as the need arises)

B.4.2.10 Healthcare resource use and costs

Resource categories outside drug acquisition, are drug administration, routine disease management, complications of disease, and drug-related adverse events. These cost categories and sources of unit costs take the approach and use the same sources as NICE TA824 (for the same population). Unit costs are updated from the NHS schedule of reference costs 2019/20 to 2021/22.(102) Resource utilisation rates are in some cases adjusted from those used in TA824 and TA613, based on a validation exercise using a survey of three expert clinicians.(3, 4)

Cost of administering treatment

The unit costs for the administration of intravitreal implants in both the outpatient and day-case settings are presented in Table 42. The assumption in TA824 that all IVI administration procedures are conducted in the outpatient setting was adjusted to 95% based on expert clinical opinion that co-morbidity in a small minority of patients requires the day unit setting.

Table 42. Unit costs of intravitreal injection of steroid implants

Item	Setting	£ / unit	Precedent	Source (102)
Intravitreal injection	Day unit	£1,364.27	TA824, DEX*	NHS reference costs 2021/22: Day Case (DC) - BZ87A - Minor Vitreous Retinal Procedures, 19 years and over
Intravitreal injection	Outpatient clinic	£165.16	TA824, DEX*	NHS reference costs 2019/20: Outpatient procedure - service code 130 Ophthalmology - BZ87A - Minor vitreous retinal procedures
*Unit cost presented in NICE TA824 have been updated from 2019/20 to 2021/22.				

Cost of routine disease management

As reference, TA824 used the following annual counts of resource use for routine disease management (Table 43). The annual counts used in the model are presented in Table 44, these are the mean of three sets of estimates elicited from

structured interviews with three clinical experts. Respective unit costs are presented in Table 45, these were sourced from the National Schedule of Costs 2021/22.(102)

Table 43. Annual resource count for routine management of DMO used in NICE TA824 (DEX)

Resource		Occurrences per year				
		Year 1	Year 2	Year 3	Year 4	Year 5+
Routine outpatient visit (includes IOP check) *	DEX	3	2	2	2	2
Optical coherence tomography	DEX	3	2	2	2	2
Fluorescein angiography	DEX	1	0	0	0	0
Abbreviations: FAc, fluocinolone 0.19 mg intravitreal implant; Dex, dexamethasone 0.7 mg intravitreal implant. *Based on EAG preferred assumptions in NICE TA349.						

Table 44. Annual number of routine management resources used in the model

Resource		Occurrences per year					
		Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Routine outpatient visit (includes IOP check)	FAc	3.67	3.17	3.17	3.67	3.17	3.17
	DEX	4.73	4.73	4.73	4.73	4.73	4.73
Optical coherence tomography	FAc	2.83	4.17	3.17	3.17	3.17	3.17
	DEX	3.40	3.73	3.73	3.73	3.73	3.73
Fluorescein angiography	FAc	0.67	0.00	0.00	0.33	0.00	0.00
	DEX	0.67	0.00	0.00	0.33	0.00	0.00
Abbreviations: FAc, fluocinolone 0.19 mg intravitreal implant; Dex, dexamethasone 0.7 mg intravitreal implant.							

Table 45. Unit cost of resource for routine disease management

Item	Setting	£ / unit	Source (102)*
Routine monitoring visit	Outpatient clinic	£101.95	NHS reference costs 2019/20 - WF01A code 130 Ophthalmology; consultant led non-admitted, face to face attendance, follow-up
Optical coherence tomography	Weighted direct access	£52.47	NHS reference costs 2019/20 - RD40Z, diagnostic imaging - direct access:

			ultrasound scan less than 20 minutes (without contrast). Without contrast (n=1,934,917), direct access, £52.42. With contrast (n=14,618), direct access, £59.07
Fluorescein angiography	Outpatient clinic	£137.53	NHS reference costs 2019/20: Outpatient procedure - service code 130 Ophthalmology - BZ87A - Minor vitreous retinal procedures
*Unit cost presented in NICE TA824 have been updated from 2019/20 to 2021/22.			

Cost of complications of disease

Table 46 presents the proportion of patients affected by three DMO management complications. These are categorised as complications of disease although occurrence may be aggravated by treatment. In this case, proportions do not differ across the steroid treatment strategies for raised IOP and cataract extraction. This position is supported by the result of the ITC and outcomes from a survey of clinical experts with experience of both steroid implants in the NHS setting. However, based on feedback from one of three UK clinicians, the frequency of vitrectomy was increased. The increased was arbitrarily assumed to be a factor of two. Otherwise, proportions are all based on those used in NICE TA613, the evaluation of FAc in the same modelled population. Table 47 details the respective unit costs used in them model for the three types of complication. Unit costs were sourced from the National Schedule of Costs 2021/22.(102)

Table 46. Proportion of people with DMO being treated with intravitreal steroids affected by complications of disease

Item		**Affected proportion**			**Assumptions in model**
		Year 1	**Year 2**	**Year 3+**	
Raised IOP	FAc	25.8%	13.2%	9.2%	No different to TA824 and no difference between steroid strategies
	DEX	25.8%	13.2%	9.2%	
Cataract extraction	FAc	12.3%	49.5%	17.4%	This is relevant only to the phakic eye so the TA613 estimate is adjusted to account for an all phakic population (235/375 phakic in FAME 200ug/day arm;
	DEX	12.3%	49.5%	17.4%	

					factor of 1.596). No difference between steroid strategies
Vitrectomy	FAc	2.0%	2.0%	4.4%	Higher rate of vitrectomy for FAc. Clinical advice suggested a potentially higher rate. Assumption is double
	DEX	1.0%	1.0%	2.2%	
Abbreviations: FAc, fluocinolone 0.19 mg intravitreal implant; Dex, dexamethasone 0.7 mg intravitreal implant.					

Table 47. Unit cost of resource for complications of disease

Event	Procedure	£ / unit	Source (102)*
Raised IOP - surgical	Trabeculectomy (major)	£1,128.66	NHS reference costs 2021/22 - BZ93B - Major, Glaucoma or Iris Procedures, with CC Score 0-1 (day case)
	Trabeculectomy (intermediate)	£423.99	NHS reference costs 2021/22 - BZ94B - Intermediate, Glaucoma or Iris Procedures, with CC Score 0 (day case)
	6 extra IOP visits	£611.69	6 extra IOP visits were assumed for patients with DMO who were treated for raised IOP (as per NICE TA349)
	Total	£1,388.01	Weighted average. Assumed that intermediate and major trabeculectomies are equally frequent
Raised IOP - medical	Beta-blockers	£1.53	eMIT, last updated 22Mar2023 (Accessed Sept 2023); Timolol 0.25% eye drops 5 ml
	Prostaglandins	£1.00	eMIT, last updated 22Mar2023 (Accessed Sept 2023); Latanoprost 50micrograms/ml eye drops 2.5 ml
	CA inhibitors	£1.53	eMIT, last updated 22Mar2023 (Accessed Sept 2023); Brinzolamide 10mg/ml eye drops 5 ml
	Combination	£2.41	eMIT, last updated 22Mar2023 (Accessed Sept 2023); Dorzolamide 20mg/ml / Timolol 5mg/ml eye drops 5 ml (2%/0.5% e.g. Cosopt, tidomat)
	Brimonidine	£2.19	eMIT, last updated 22Mar2023 (Accessed Sept 2023); Brimonidine 0.2% eye drops 5 ml
	6 extra IOP visits	£611.69	6 extra IOP visits were assumed for patients with DMO who were treated for raised IOP (as per NICE TA349)
	Total	£661.07	Weighted average of drugs plus 6 IOP visits
Cataract extraction	Cataract extraction procedure	£1,269.47	NHS reference costs 2021/22 - BZ34C - Phacoemulsification cataract extraction and lens implant, with CC score 0-1 (day case)

Vitrectomy	Vitreous Retinal Procedures	£4,977.36	NHS reference costs 2021/22 - BZ86B - Intermediate Vitreous Retinal Procedures, 19 years and over, with CC Score 0-1 (Non-elective long stay)
		£779.07	NHS reference costs 2021/22 - BZ86B - Intermediate Vitreous Retinal Procedures, 19 years and over, with CC Score 0-1 (Non-elective short stay)
	Total	£1,068.31	Weighted average based on 33 FCE non-elective long stay and 446 FCE non-elective short stay
Abbreviations: IOP, Intraocular pressure. *Unit cost presented in NICE TA824 have been updated from 2019/20 to 2021/22.			

Cost of adverse events

Table 48 presents the frequency per administration of adverse events linked to steroid implantation. These estimates are those used for DEX in TA824 for the same population. This position is supported by the result of the ITC and outcomes from a survey of clinical experts with experience of both steroid implants in the NHS setting.

Table ***49*** details the unit costs for each of the three included adverse event types.

Unit costs were sourced from the National Schedule of Costs 2021/22.(102)

Table 48. Proportion of people with DMO, being treated with intravitreal steroids, affected by adverse events

Item		**Proportion per administration**	**Assumptions in model**
Endophthalmitis	FAc	0.4%	No different to TA824 and no difference between steroid strategies
	DEX	0.4%	
Vitreous haemorrhage	FAc	0.4%	
	DEX	0.4%	
Retinal detachment	FAc	0.2%	
	DEX	0.2%	
Abbreviations: FAc, fluocinolone acetonide 0.19 mg intravitreal implant; Dex, dexamethasone 0.7 mg intravitreal implant.			

Table 49. Unit cost of resource for adverse events

Event	Procedure	£ / unit	Source (102)
Endophthalmitis	Vitreous biopsy	£2,187.96	NHS reference costs 2021/22 - BZ87A - Minor Vitreous Retinal Procedures, 19 years and over (Elective inpatient)
		£753.53	NHS reference costs 2021/22 - BZ87A - Minor Vitreous Retinal Procedures, 19 years and over (Non-elective short stay)
		£1,118.66	Weighted average of non-elective short stay and elective inpatient
Vitreous haemorrhage	Vitreous biopsy	£4,977.36	NHS reference costs 2021/22 - BZ86B - Intermediate Vitreous Retinal Procedures, 19 years and over, with CC Score 0–1 (Non-elective long stay)
		£779.07	NHS reference costs 2021/22 - BZ86B - Intermediate Vitreous Retinal Procedures, 19 years and over, with CC Score 0–1 (Non-elective short stay)
		£1,068.31	Weighted average of non-elective short stay and non-elective long stay
Retinal detachment	Retinal attachment procedure	£4,977.36	NHS reference costs 2021/22 - BZ86B - Intermediate Vitreous Retinal Procedures, 19 years and over, with CC Score 0-1 (Non-elective long stay)
		£779.07	NHS reference costs 2021/22 - BZ86B - Intermediate Vitreous Retinal Procedures, 19 years and over, with CC Score 0-1 (Non-elective short stay)
		£3,730.61	NHS reference costs 2021/22 – BZ84B - Major Vitreous Retinal Procedures, 19 years and over, with CC Score 0-1 (Non-elective long stay)
		£1,348.25	NHS reference costs 2021/22 – BZ84B - Major Vitreous Retinal Procedures, 19 years and over, with CC Score 0-1 (Non-elective short stay)
		£1,170.91	Weighted average. The management of retinal detachment was estimated to be an intermediate/major vitreous day case procedure in 80% and 20% of cases, as per ERG preferred assumptions in TA349
Abbreviations: - *Unit cost presented in NICE TA824 have been updated from 2019/20 to 2021/22.			

B.4.2.11 Clinical validation

Input parameters

Three practising NHS clinicians with experience managing DMO patients administered the steroid implants, and experience of health technology appraisal in DMO, were consulted for opinion. Validation, including any adjustment, was sought on the applicability of prior resource consumption estimates, specifically those used in TA824 (DEX) and TA613 (FAc).(3, 4) Feedback from structured interviews was used for the determination of NHS resources in routine clinical management, complications of DMO, and treatment-related adverse events.

Modelling approach

One practicing NHS clinician with experience managing DMO patients administered the steroid implants, and experience of health technology appraisal in DMO, was consulted for opinion. Validation was sought on the plausibility of ITC outcomes, the premise supporting a cost-comparison, and the approaches and assumptions used in the cost-comparison itself.

In the opinion of the clinical expert, the ITC approach was sound, and outcomes were plausible. They also reflected her experience of real-world results. The modelling approach was considered appropriate, but the exclusion of other-treatments remains an uncertainty since the use of additional treatments and subsequent treatments may differ in some patients.

B.4.2.12 Uncertainty in the inputs and assumptions

The accuracy of model outcomes is subject to structural and parameter uncertainty. A series of analyses were conducted to characterise and quantify the leading contributors. Comprehensive one-way sensitivity analysis (OWSA) tested the sensitivity of cost-effectiveness to 20% bi-directional variation in each parameter point estimate, except for drug acquisition unit costs. Probabilistic sensitivity analysis (PSA) was used to test multivariate parameter uncertainty in the relationship

between FAc costs and DEX costs. The PSA also defined 95% credible intervals for total strategy costs. Appropriate distributions were assigned to each parameter and 5,000 value sets were produced, with each input point estimate varied simultaneously. Standard deviation was 10% of the point estimate in most cases. Structural uncertainty was explored in a set of seven scenario analyses which explored alternative assumptions in known areas of uncertainty, in particular the respective re-treatment rates of the two steroid implants.

B.4.3 Base-case results

Through a six-year time horizon, the expected mean number of steroid implants per person and per eye are shown in Table 50. The ratio of DEX to FAc implants is 4.41, and 5.32 fewer FAc implantations are needed compared to DEX over a 6-year horizon.

Table 50. Mean number of implants through 6 years

Steroid strategy	Per person	Per eye
FAc	[redacted]	[redacted]
DEX	6.88	6.11
Increment	[redacted]	[redacted]
Ratio DEX to FAc	[redacted]	[redacted]

Abbreviations: Dex, dexamethasone strategy; FAc, fluocinolone strategy

Base case *per person* costs include discounting of future costs through the 6-year horizon and the PAS discount for fluocinolone acetonide. Results from the deterministic analysis are presented in Table 51 by treatment for each cost category and in total. Over six years a strategy of DEX is expected to cost £14,302, compared to a strategy of FAc, which is expected to cost £[redacted]. Representing a per person saving of [redacted]. [redacted] of the saving comes from administration costs, [redacted] from reduced costs associated with routine clinical management and [redacted] of the saving from reduced drug acquisition costs.

Results of the PSA are presented in Table 57.

Table 51. Deterministic base case summary results. *Per person*, discounted, with PAS

Corticosteroid strategy	Acquisition costs	Administration costs	Routine clinical management costs	Complications of disease costs	Adverse event costs	TOTAL COSTS
FAc	[redacted]	[redacted]	[redacted]	£2,844	£17	[redacted]
DEX	£5,613	£1,452	£4,442	£2,723	£72	£14,302
Increment	[redacted]	[redacted]	[redacted]	£121	-£54	[redacted]
Abbreviations: DEX, dexamethasone strategy; FAc, fluocinolone strategy						

Base case per *eye* costs include discounting of future costs through the 6-year horizon and the PAS discount for FAc (Table 52).

Table 52. Deterministic base case summary results. *Per eye*, discounted, with PAS

Steroid strategy	Acquisition costs	Administration costs	Routine clinical management costs	Complications of disease costs	Adverse event costs	TOTAL COSTS
FAc	[redacted]	[redacted]	[redacted]	£2,527	£15	[redacted]
DEX	£4,987	£1,290	£3,946	£2,419	£64	£12,705
Increment	[redacted]	[redacted]	[redacted]	£108	-£48	[redacted]
Abbreviations: DEX, dexamethasone strategy; FAc, fluocinolone strategy						

Routine clinical management

A breakdown of resource costs for the main components of routine clinical management are presented in Table 53. The cost of routine clinical management

was higher in the DEX strategy, with the majority of saving coming from reduced routine outpatient visits for monitoring disease.

Table 53. Breakdown of costs comprising routine clinical management, per person

Steroid strategy	Routing monitoring cost (incl. IOP check)	Optical coherence tomography cost	Fluorescein angiography cost	Total
FAc	[redacted]	[redacted]	[redacted]	[redacted]
DEX	£3,068	£1,226	£148	£4,442
Increment	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: DEX, dexamethasone strategy; FAc, fluocinolone strategy

Complications of disease

A breakdown of resource costs for complications of disease are presented in Table 54. The cost of complications of disease represents only a small fraction of total costs.

Table 54. Breakdown of costs comprising complications of disease, per person

Steroid strategy	Routing monitoring cost (incl. IOP check)	Optical coherence tomography cost	Fluorescein angiography cost	Total
FAc	[redacted]	[redacted]	[redacted]	[redacted]
DEX	£832	£1,769	£121	£2,723
Increment	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: DEX, dexamethasone strategy; FAc, fluocinolone strategy

Adverse events

A breakdown of resource costs for the included drug-related adverse events are presented in Table 55. The cost of drug-related adverse events is only a small fraction of total costs.

Table 55. Breakdown of costs comprising drug-related adverse events, per person

Steroid strategy	Routing monitoring cost (incl. IOP check)	Optical coherence tomography cost	Fluorescein angiography cost	Total
FAc	£7	£7	£4	£17
DEX	£29	£28	£15	£72
Increment	-£22	-£21	-£12	-£54
Abbreviations: DEX, dexamethasone strategy; FAc, fluocinolone strategy				

B.4.4 Sensitivity and scenario analyses

B.4.4.1 Deterministic sensitivity analysis

Results of the OWSA are presented in Table 56 and Figure 14.

The input with the biggest impact on the total incremental cost was the proportion of DEX procedures in the outpatient versus day case setting. The frequency of DEX reimplantation is next most influential. Third is the commonality of a second phakic DMO eye given treatment, then the proportion of FAc procedures administered in the outpatient setting.

Table 56. Top 12 inputs with greatest impact on per person total incremental costs, with PAS

Rank	Input parameter	Decrease by 20%	Increase by 20%	Range	Impact, %
1	Proportion of DEX procedures in outpatient setting, remainder day unit	[redacted]	[redacted]	[redacted]	[redacted]
2	DEX re-implant frequency modifier	[redacted]	[redacted]	[redacted]	[redacted]
3	Number of phakic eyes per person	[redacted]	[redacted]	[redacted]	[redacted]
4	Proportion of FAc procedures in outpatient setting, remainder day unit	[redacted]	[redacted]	[redacted]	[redacted]
5	Cataract extractions with FAc in year 3+	[redacted]	[redacted]	[redacted]	[redacted]
6	Cataract extractions with DEX in year 3+	[redacted]	[redacted]	[redacted]	[redacted]
7	Unit cost of routine monitoring visit	[redacted]	[redacted]	[redacted]	[redacted]
8	Cost of one implant administration in the hospital outpatient unit	[redacted]	[redacted]	[redacted]	[redacted]
9	Cataract extractions with FAc in year 2	[redacted]	[redacted]	[redacted]	[redacted]
10	Cataract extractions with DEX in year 2	[redacted]	[redacted]	[redacted]	[redacted]
11	Outpatient review visits for DEX in year 6	[redacted]	[redacted]	[redacted]	[redacted]
12	Outpatient review visits for DEX in year 1	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: DEX, dexamethasone strategy; DMO; Diabetic macular oedema; FAc, fluocinolone strategy					

Figure 14. Tornado diagram of input sensitivity

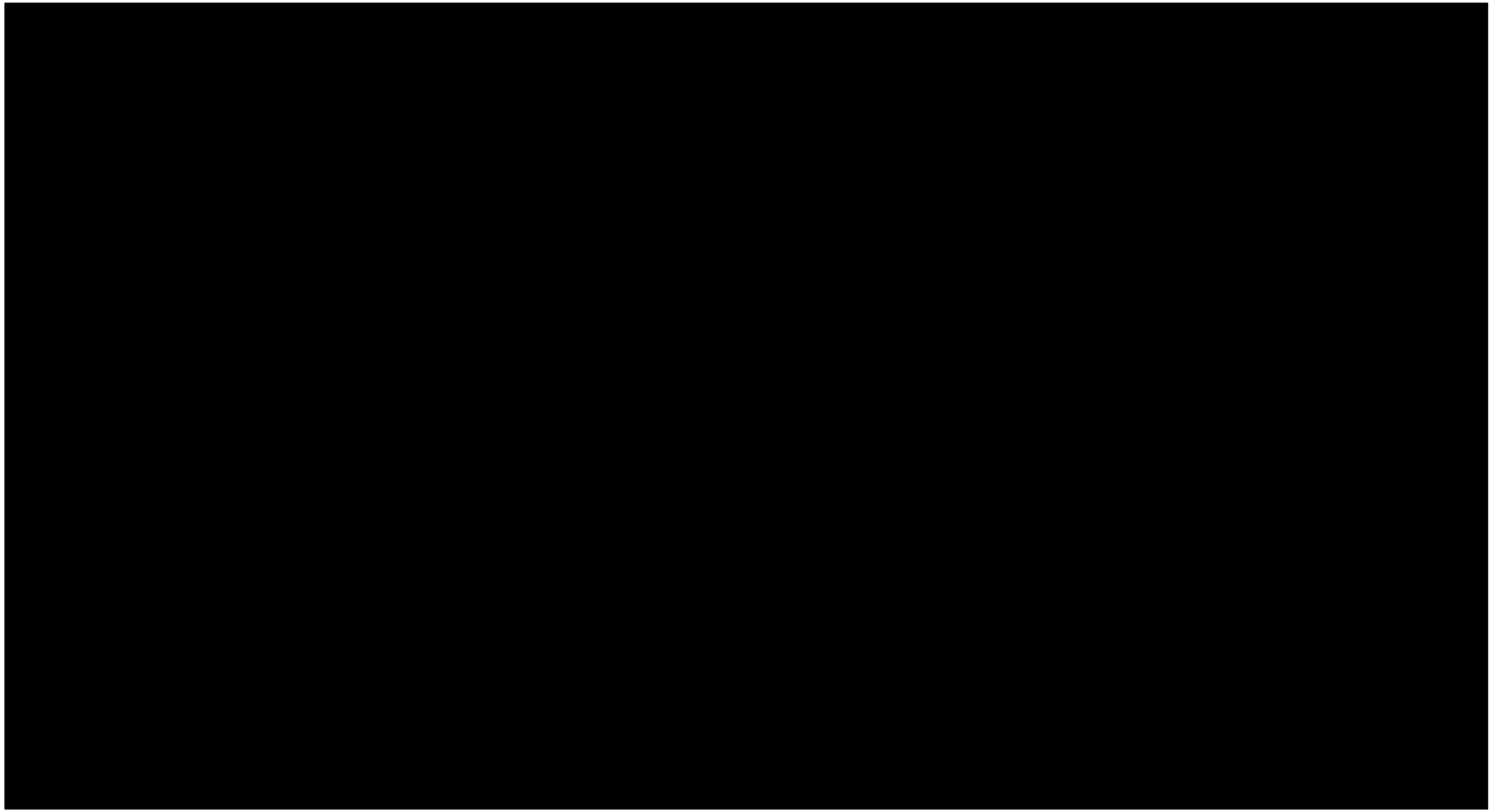


Figure 15. Scatterplot of FAc strategy costs plotted against Dex strategy costs

B.4.4.2 Probabilistic sensitivity analysis

The PSA explored uncertainty in the per person total incremental costs, based on a standard deviation equal to 10% of the mean. A scatterplot of total FAc strategy costs versus total DEX strategy costs is presented in Figure 15. All 100% of the 5,000 PSA results returned a cost-saving outcome.

The probabilistic result for the base case was a mean cost saving of [redacted], [redacted], compared to deterministic [redacted], with a credible interval of [redacted] to [redacted]. The DEX total strategy cost was £14,575 compared to deterministic £14,302, with a credible interval of £11,491 to £18,014 (Table 57). Probabilistic and deterministic outcomes slighted different in their determination of the DEX total strategy cost, which was higher in the probabilistic analysis.

Table 57. Probabilistic base case summary results. Per person, discounted, with PAS

Steroid strategy	Acquisition costs	TOTAL COSTS [95% CrI]
FAc	[redacted]	[redacted]
DEX	£5,608	£14,575 [£11,491, £18,014]
Increment	[redacted]	[redacted]

Abbreviations: DEX, dexamethasone strategy; FAc, fluocinolone strategy

B.4.4.3 Scenario analysis

The primary areas of interest for alternative approaches were the respective frequencies of re-implantation. The base case used the ITT population of MEAD and the adjusted population of FAME that was the basis of the ITC. However, the full ITT population of FAME and multiple real-world sources for this outcome, for both strategies, were of interest and tested in this analysis. The matrix below (Table 58)

shows the results of comparisons between each FAc source versus each DEX source.

Table 58. Per person total incremental costs using alternative sources of re-treatment frequency, with PAS

			DEX			
			RCT - MEAD - ITT. Soonest permitted re-injection – BASECASE	RCT - MEAD - ITT. Evenly spread re-injection intervals	RWE - CHROME (Canada) (Lam 2015) - True PRN attainable	RWE - Moorfields Eye Hospital UK (Faes 2023) - Inc. NHS capacity pressures
		TOTAL implants in horizon	6.11	6.11	8.00	6.00
FAC	RCT - FAME - Adjusted ITC FAc 0.2 ug/day cohort - BASECASE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	RCT - FAME - Unadjusted ITT FAc 0.2 ug/day cohort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	RWE - Medisoft (Bailey 2022) - All NHS eyes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	RWE - Birmingham & Midlands Eye Centre (Dobler 2023) - All NHS eyes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	RWE - IRISS (Khoramnia 2022) - Majority NHS eyes (31/47 centres)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: IRiSS, ILUVIEN Registry Safety Study; ITT, Intent to treat; NHS, Nation health service; PRN, *pro re nata* (as needed); RCT, randomised controlled trial; RWE, real-world evidence. The base case estimate is shown in **bold** font.

This matrix of alternative sources for the number of retreatments per cycle shows a picture of consistent cost-saving when a strategy of FAc displaces a strategy of DEX.

Other aspects of the modelling approach were also tested. Table 59 presents seven further alternative scenarios.

Table 59. Scenario analyses exploring time horizon, and medical resource utilisation

Number	Scenario	Base case approach	Per person Incremental total costs, with PAS (FAc vs. Dex)	Impact (% change from base case)
0	Base case		[redacted]	
1	Time horizon to match RCT follow-up. 3 years.	6 years, effectively full two implant cycles of FAc	[redacted]	[redacted]
2	50% DEX re-treatment rate in years 4 and 5 (from 100%)	Follow TA824, all remaining patients alive are retreated once in year 4 and again in year 5	[redacted]	[redacted]
3	No difference in routine clinical management	Routine management with FAc therapy can be less intensive	[redacted]	[redacted]
4	No difference in complications of disease	The frequency of vitrectomy is double with FAc therapy versus DEX therapy	[redacted]	[redacted]
5	All steroid administrations are day cases	All steroid administrations are in the outpatient setting	[redacted]	[redacted]
6	Add mortality beyond 3 years (RCT follow-up)	Mortality is included for years after trial follow-up	[redacted]	[redacted]
7	Additional 3 cycles of FAc retreatment in 3% from 3 years	No retreatments after FAME	[redacted]	[redacted]

Time horizon (Scenario 1)

Steroid implant use after three years, the extent of trial follow-up, is limited to few patients. With uncertainty about the extent of both steroid implant and other DMO therapy after three years, this time horizon is potentially mitigating but it is also a

highly conservative alternative to the base case. Retreatment in FAME was much earlier than seen in real-world studies, so limiting the time horizon to 3 years includes a second FAc implant for 39% using the base case rates. Simultaneously, the full benefit of these second DEX implants would likely be excluded given the extended sustained release of FAc compared to DEX.

Long-term use of steroid treatment (Scenarios 2 and 7)

In TA824 it was assumed that in years 4 and 5 the use of DEX could be approximated to 1 implant per year (no DEX is applied in the sixth year). In a scenario (#2) where this long-term use of DEX is reduced by half, the cost difference between strategies is significantly reduced given that few patients are implanted with FAc after year 3. Long-term uptake of FAc is tested in a scenario (#7) where the proportion of patients receiving FAc is increased through the fourth year, by extending uptake observed through year 3. As expected, the cost difference between strategies is reduced.

Routine clinical management (Scenario 3)

In a scenario where FAc does not reduce the frequency of routine outpatient monitoring visits and optical coherence tomography, the cost difference between strategies is significantly reduced. This is an illustrative scenario demonstrating the anticipated benefit of the extended sustained-release mechanism of FAc, it is not presented as an expectation of clinical reality.

B.4.5 Subgroup analysis

No subgroup analyses were conducted.

B.4.6 Interpretation and conclusions of economic evidence

This cost-comparison found that over 6-years a strategy of FAc is expected to be cost-saving in the displacement of DEX when the company PAS discount is included. Confidence in this result can be taken from the scenario testing of re-

implantation frequency and uptake, which showed a cost-saving across the full range of RCT and real-world sources for re-implantation. The OWSA identified that variation in the mean number of DEX implants over 6 years to be an important input parameter in the model (the unit costs of the steroid implants is fixed). Furthermore, the result of the probabilistic analysis, in which all parameters were varied, was consistent with the deterministic result. In all 5,000 probabilistic tests the DEX strategy was more costly than the FAc strategy, this includes allowance for a 10% swing in re-treatment proportions, so up to a maximum difference of 20% across the two estimates.

Under a premise of equivalent health outcomes and duration of treatment, the finding is generalisable to general practice in England because of consistency in the finding when using alternative settings from real-world NHS evidence. Real-world evidence is particularly relevant because NHS ophthalmology services have been and remain strained by a high demand for intravitreal implantation for the treatment of DMO. The analysis projects a per person reduction in intravitreal implantations over a 6-year period from [redacted] for every DEX candidate instead treated with a FAc implant strategy. This is a reduction of [redacted] implantations per patient, which amounts to [redacted] fewer and a per person saving of [redacted].

A strength of the cost-comparison is the consistency with the TA824 in costing methods, an appraisal which evaluated the comparator in the same population. Perhaps another strength is the breadth of parameter testing, in which variations and alternatives are explored for the important inputs.

That the ITC was unable to compare phakic only eyes is a limitation, but the bias introduced by including pseudophakic eyes is expected to be small, as supported by the subgroup analysis of section B.3.7.1, and less than the bias expected using other methods which attempt to prioritise lens status. A second limitation, relating to the cost analysis, is the exclusion subsequent treatment costs for those patients who are not retreated with FAc, or those who have no or few re-treatments of DEX. However, the impact of this exclusion is likely to be neutral or favour dexamethasone since a)

the rate of uptake of subsequent treatment would be broadly equivalent or higher for DEX though up to five years given its shorter drug-eluting time (Section 4.2.5); and b) subsequent management is commonly re-challenge with anti-VEGF treatment, but in a population of prior-failure where value is demonstrated to be low and use is without recommendation.(18, 95, 103) Linked to the issue of subsequent treatment is uncertainty in the number and need for retreatment prior to discontinuation, notwithstanding the mitigating sensitivity analysis already mentioned as a strength. Further analysis which could reduce overall uncertainty would focus on the timing, type, and extent of subsequent therapy. Whilst use of a three-year horizon would mitigate this aspect of uncertainty, the use of FAME for FAc retreatment rates in the base case becomes highly conservative. Retreatment in FAME was much earlier than is observed in real-world practice because full information was not available about pharmacokinetics and drug-eluting time when FAME recruited. This means that a higher proportion of second implants were administered in the second and third years, the benefit of which would carry beyond the third year.

In summary, the risk-benefit of these competing steroid treatments are equivalent and FAc is a less costly treatment strategy that DEX when the FAc PAS discounted price is included. Displacement of DEX with FAc for treating chronic DMO in phakic eyes after an inadequate response to previous therapy is cost-saving using base case settings and represents a low-risk decision for the NHS payer.

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B.6 Appendices

The following appendices are provided as a separate document to the company submission, Document B.

Appendix C: Summary of product characteristics (SmPC) and UK public assessment report

Appendix D: Identification, selection and synthesis of clinical evidence

Appendix E: Subgroup analysis

Appendix F: Adverse reactions

Appendix G: Cost and healthcare resource identification, measurement and valuation

Appendix H: Price details of treatments included in the submission

Appendix I: Checklist of confidential information

Appendix J: Supplementary information for the indirect treatment comparison

Appendix K: Clinical effectiveness evidence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Cost-comparison appraisal

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

Summary of Information for Patients (SIP)

September 2023

File name	Version	Contains confidential information	Date
ID6307 fluocinolone acetonide_ SIP [noCON]	v1.1	No	6 October 2023

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Fluocinolone acetonide intravitreal implant 0.19 mg (ILUVIEN®)

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

ILUVIEN is approved for use in the National Health Service to treat vision impairment associated with chronic diabetic macular oedema in patients when other available therapies have failed to help.[1] ILUVIEN is already recommended by NICE as a treatment option for diabetic macular oedema patients who have a pseudophakic (artificial or replacement) eye lens, for example people who have had an operation to remove their cataracts. In this appraisal, NICE will determine whether ILUVIEN can also be recommended as a treatment for patients who still have their own original natural eye lens (known as a phakic lens).[2,3]

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

Alimera Sciences Limited was granted a UK marketing authorisation for ILUVIEN from the Medicines and Healthcare products Regulatory Agency for the treatment of vision impairment associated with chronic diabetic macular oedema on 4 May 2012. This approval was granted irrespective of whether a patient had their own original eye lens (phakic) or an artificial or replacement eye lens (pseudophakic) as the clinical studies submitted for this marketing authorisation included patients with both original and replacement eye lenses.

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

Because ILUVIEN has been available to treat NHS patients since 2013 the company, Alimera Sciences Limited, has long-term relationships and frequent contacts with patient organisations who have an interest in preventing blindness. Typically, these contacts have been responding to requests for clinical and patient information about ILUVIEN.

Recently, following the publication of NICE Technology Appraisal 824, Alimera has had several discussions with the Macular Society regarding its involvement providing the patient perspective in the TA824 project. However, it should be noted that no financial support has been provided to any patient organisations by Alimera in the last 3 years (see our Association of the British Pharmaceutical Industry disclosures at https://search.disclosureuk.org.uk/).

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

Diabetic macular oedema (or DMO as it is often shortened to) is a complication of diabetes. It is a major cause of visual loss in people who have diabetes and is considered one of the leading causes of severe visual impairment and preventable blindness in the adult and working age populations around the world[4,5,6,7] and a leading cause of blindness in adult populations around the world. The central portion of the eye is called the retina inside this part of the eye is the macular (the centre of the retina that provides sharp vision). Vision loss caused by diabetic macular oedema occurs when the fluid reaches the macula and builds up, causing swelling. At first, a person may not notice changes to their vision. Over time, diabetic macular oedema can cause the central vision to become blurred. A healthy macular is essential for good vision. Over time, and if not treated optimally, recurrent or repeat episodes of swelling in the macular can cause retinal damage and irreversible sight loss.

The global prevalence of diabetic macular oedema (the total number of individuals in the world who have this disease) is estimated to be 4.6%.[8] There is insufficient published information about the prevalence in the UK, but the most recent estimates would suggest that this is between 5.2% and 7%.

You are at greater risk of diabetic macular oedema if you:[9]

- Have had diabetes for a long time–about one in three people living with diabetes for 20 years or more will develop diabetic macular oedema
- Have poorly controlled blood sugars
- Have high blood pressure
- Have high cholesterol level
- Are a smoker
- Are pregnant

Large studies have shown that people who have well-controlled blood sugar, blood pressure and cholesterol levels, and do not smoke are less likely to develop diabetic macular oedema.[9] If patients are diagnosed with diabetic macular oedema it is very important they get treatment for it. The aim of treatment is to try to stop the fluid building up in the macular. This in turn stops the swelling or thickening to the retina and reduces the chance of this damaging vision.[10, 11] Treatments for diabetic macular oedema are usually laser therapy, or most commonly, injection therapy.

Injection therapy involves injection of either a medicine, or an implant containing a medicine, into the eye. These injections can be a source of fear, stress, and anxiety for patients with diseases that effect their sight, and they usually mean very frequent clinic visits for the actual injections, and also the monitoring of the eye to make sure the treatment is working in the long-term. Patients with diabetic macular oedema have a high burden of treatment and this often also affects their caregivers, who may have to transport them to many injection and monitoring visits.[12] Patients with DMO were found to have a mean of 19.1 appointments over a 6-month period with healthcare professionals, including diabetologists, retina specialists, ophthalmologists, and their GP. For patients with additional comorbidities additional appointments with specialists including neurologists, cardiologists, nephrologists, and podiatrists greatly increase the clinical contact burden for patients.[13] The burden of the disease can be significant for patients with diabetic macular oedema.

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

Diabetic macular oedema may be detected during annual eye screening visits, which are offered to all patients with diabetes in the NHS. Digital photographs of your eye that zoom in on your retina may show signs of early diabetic macular oedema. Patients may not notice any changes in their vision at this stage, but if diabetic macular oedema is not investigated further by eye experts, it may gradually damage the eye. It is important for patients to attend their appointments and make sure they follow the advice of their doctor and eye specialists to make sure they get the right treatment if it is required.

If diabetic macular oedema is detected, patients will usually be referred to a specialist led "medical retina clinic" in the local NHS hospital outpatient department for more detailed assessment of their eyes.[9]

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
    - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
    - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

From the mid-1980s until approximately 2005, the standard therapy for diabetic macular oedema was laser treatment to the eye. A laser is used to produce small burns on areas of leaking blood vessels in the macula. Usually, laser burns are applied over several sessions. The goal of laser therapy is to reduce the amount of fluid in the macula. Several sessions may be required to achieve this. The full effects of laser therapy only occur after several months and patients may be asked to return to clinic three or four months after laser therapy. Whilst laser treatment is effective in reducing vision loss, it has fallen out of vogue with specialists since the arrival or newer eye injections that are also proven to be effective. It can also be uncomfortable for patients as during therapy, they experience bright flashes of light, and often a stinging sensation, which can be uncomfortable. Also, after laser therapy, a patient's vision will often be little blurred for the rest of the day, and they may need to wear may sunglasses their eyes can be sensitive to bright lights for a few hours after treatment.[9]

Approximately 15 years ago, however, a new type of treatment was introduced – the anti-VEGF eye injection. Like ILUVIEN, anti-VEGF medicines are injected directly into the eye. Anti-VEGFs have mostly replaced laser treatment now and are considered the first-choice option for treating diabetic macular oedema. NICE has recommended the use of four anti-VEGF therapies to date called ranibizumab, aflibercept, faricimab and brolucizumab. A fifth anti-VEGF option, bevacizumab, is also sometimes used by eye specialists in clinical practice to treat diabetic macular oedema, although this use has not been approved by the regulatory authorities.

Unfortunately, anti-VEGF treatments do not work for everyone and patients might not get improvement in their diabetic macular oedema.[14] The underlying causes of macular oedema are not fully understood, but it is thought that VEGF and inflammation play an important role in disease progression.[10,11,15] The anti-VEGF treatment can help in part, but the more inflammation that is involved, the less responsive the macular oedema becomes to the anti-VEGF therapy. For some patients, their macular oedema becomes resistant to anti-VEGF therapy. And, because of a lack of other available options, some patients with macular oedema may continue to receive anti-VEGF injections even though they are not getting much benefit from treatment.[10,11,12,16] These patients will, unfortunately, continue to experience loss of vision and damage to the retina, even despite treatment. Also, as the anti-VEGFs require frequent injections (estimated to be 16-18 over a 3-year period)[17] to work, if patients do not get these injections as frequently as proven in the research studies during their development, they can also be less effective.[18]

In these circumstances, one option is to switch from using an anti-VEGF to a corticosteroid injection instead. Corticosteroids treat inflammation and corticosteroid injections into the eye have been shown to help protect the retina from further damage, thus preserving vision.[11,19,20,21]

There are two different corticosteroid options currently available in the UK: dexamethasone implant (OZURDEX®) and fluocinolone acetonide implant (ILUVIEN). Changing treatment to an intravitreal corticosteroid at the appropriate time, especially if a patient is not getting improvements from their treatment, can help improve patient outcomes, preserve vision, and reduce the frequency of injection, so reducing the burden of treatment on both patients and caregivers.

Dexamethasone implant is a shorter-acting corticosteroid implant. It is an implant that gradually releases a steroid into the eye for up to 6 months. A second injection is usually given up to 6 months if patients who have experienced an initial improvement following the first injection of the implant and who, in the physician's opinion, may benefit from further treatment without being exposed to significant risk.[22] The dexamethasone implant is currently recommended by NICE where patients have had a poor response to anti-VEGF therapy or where the patient is not

suitable for an anti-VEGF. Dexamethasone can be used in patients who have a natural eye lens (phakic) or an artificial eye lens (pseudophakic).[23]

ILUVIEN is another corticosteroid implant that is also injected into the eye and is an alternative option to the dexamethasone implant for those patients whose macular oedema has not responded well to other available treatments, such as the anti-VEGF therapies. However, there are two main differences between ILUVIEN and dexamethasone. ILUVIEN is a longer-acting corticosteroid implant: a single injected implant can last up to 3 years, gradually and slowly releasing a micro dose of a steroid called fluocinolone acetonide, into the eye. Secondly, unlike the dexamethasone implant, ILUVIEN is currently only recommended by NICE in patients who have an artificial lens[3] even though the published evidence and NHS eye specialists all confirm that ILUVIEN is an effective, safe, long-acting treatment option for all patients with chronic diabetic macular oedema, whether they have a natural lens or an artificial lens.[24,25] ILUVIEN, if successful, could typically could require patients having at least 5 less injections over a 3 year period compared to dexamethasone implant,[1,23] or 15-17 fewer injections than that recommended for anti-VEGF treatments over a 3 year period.

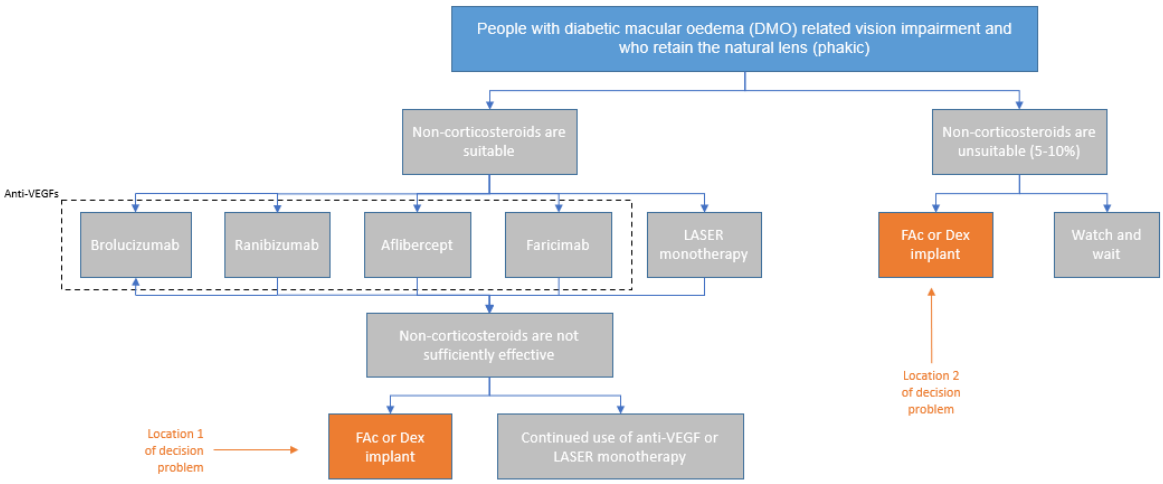


Figure 1 - treatments for diabetic macular oedema that are currently used in the NHS and where ILUVIEN fits into the treatment pathway (see orange boxes). FAc = ILUVIEN implant. Dex = Dexamethasone implant.

As noted above, eye injections can be a source of fear, stress, and anxiety for patients with retinal diseases; the frequent clinic visits, injections, and patient monitoring required to achieve optimal long-term results can lead to a high burden of treatment for patients and their caregivers.[12] With its 36-month duration of action, a single ILUVIEN injection can provide a long-acting protective effect to the retina, allowing the patient to maintain the same level of vision as other treatment options, but with fewer injections.[23]

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for

collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

The visual impairment from diabetic macular oedema is proven to negatively impacts patients' physical and emotional functioning. A number of studies report on the damaging effect of DMO on vision: limiting a patient's ability to perform everyday activities such as driving (UK licences require visual acuity ≥ 6/12), shopping, housework, meal preparation and using the telephone, which can challenge independent living and negatively impact patients' mental well-being.[29,30,31] In addition, the fear of losing sight or independence causes emotional distress for many patients, particularly those with depressive disorder symptoms, which are often linked to diabetes.[32] Health-related quality of life appears to systematically decline as vision impairment and severity of diabetic macular oedema worsen.[32,33] Specifically, progression from mild/moderate diabetic macular oedema to vision-threatening stages are important milestones in the reduction of patient HRQL.[32,33] Furthermore, limitations in physical and mental functioning due to visual impairment associated with diabetic macular oedema can compromise the patient's ability to successfully manage their diabetes and additional comorbidities. Patients with diabetic macular oedema report difficulties with reading nutrition and medication labels, testing blood sugar, self-administering medication and checking for wounds and sores.[34]

Patient compliance and participation in their own disease management is really important in diabetic macular oedema. If compliance to treatment is poor it can increase the likelihood of developing other diabetic complications, and therefore reduce overall life expectancy. In a German study of 207 patients with diabetic retinopathy and diabetic macular oedema, patients stated that without eye problems, their diabetes care would be better.[35] Even in patients with a well-monitored and treated eye condition, the patient still experienced feelings of uncertainty and fear about how one's life will be affected by it in the future.[35]

The treatment and clinical management of diabetic macular oedema can also negatively impact quality of life. In a 5-year study of 30,514 diabetic macular oedema patients, they reported that injections caused stress and anxiety, and the most desired outcome from the perspective of patients was to achieve the same visual outcomes with fewer injections.[36] Patients also reported practical issues such as regular travelling and having to take leave from work to attend appointments.[36] The study estimated that over half of patients had an average of 19.1 appointments with healthcare professionals, accounting for around 20 hours per patient over a 6-month period and that each injection appointment (including travel time) lasted on average 4.5 hours.[36]

During the NICE TA824 committee discussion for dexamethasone implant before it was approved for use in diabetic macular oedema for people with their own natural lens (phakic),[37] it was explained that there was an unmet need for an effective treatment that could be given less frequently. During the NICE process, a patient expert with phakic (natural lens) explained the nature of their experience with anti-VEGF treatment and that the loss of vision had a significant impact on a person's independence and mental health. The patient expert highlighted that having frequent eye injections causes fear and, before the dexamethasone treatment was approved by NICE, there was no alternative because laser therapy had not been very effective for them. They emphasised that reducing the number of times they need treatment, especially for an eye injection, would be of huge benefit for their quality of life.[37] They emphasised that the impact of dexamethasone intravitreal implant would mean less frequent hospital visits and injections compared with anti-VEGF treatments. The NICE committee also stated they were aware that some people with diabetic macular oedema may require help from a carer to travel to appointments. The committee concluded that there was an unmet need for another treatment option for diabetic macular oedema in people who have a phakic lens. It added that people with

diabetic macular oedema and clinicians would welcome an effective new treatment option that is used less frequently.[37]

The NICE committee also identified that having a longer time between treatments will improve outcomes for people with diabetic macular oedema.[37] The clinical experts emphasised that having a longer time between treatments could benefit both people with diabetic macular oedema and clinicians. They highlighted that people with diabetes often have multiple hospital appointments in different departments. The clinical experts consulted in this NICE process also explained that a longer time between treatments will free up the capacity in the NHS as well as improve quality of life for people with diabetic macular oedema.[37] The committee concluded that having a longer time between treatments will improve outcomes for people with diabetic macular oedema who have a natural (phakic) lens.[37]

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

ILUVIEN is a tiny tube that is inserted into the eye and releases very small amounts of the active ingredient, fluocinolone acetonide, over a long period of time for up to 3 years. Fluocinolone acetonide belongs to a group of medicines called corticosteroids. Corticosteroids work to reduce inflammation in the body.

ILUVIEN is used to treat vision loss associated with diabetic macular oedema when other available treatments have failed to help. Diabetic macular oedema is a condition that affects some people with diabetes and causes damage to the light-sensitive layer at the back of the eye responsible for central vision, the macula. The active ingredient (the drug fluocinolone acetonide) helps to reduce the inflammation and the swelling that builds up in the macula in this condition. ILUVIEN can therefore help to improve the damaged vision or stop it from getting worse.

ILUVIEN is used to prevent relapses of inflammation of the back of the eye. This inflammation can cause floaters which are black dots or wispy lines that move across what you can see ('field of vision') or can cause loss of vision by damaging the part of the eye responsible for good vision, called the 'macula'. The loss of vision may not improve unless the inflammation is treated. ILUVIEN helps to reduce the inflammation and the swelling that it can cause in the back of the eye. It can help improve patient's sight or stop it from getting worse. It may stop future attacks of inflammation.

ILUVIEN Package leaflet information for the user.
https://www.medicines.org.uk/emc/files/pil.3061.pdf

ILUVIEN UK website, information for members of the public.
https://staging.patient.iluvien.co.uk

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines? • Yes / No If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together. If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects. **If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.**
ILUVIEN is not intended to be used in combination with any other medicine.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for. How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?
ILUVIEN is given as a single injection into the eye. The injection is administered by a doctor specialising in eye conditions. The ILUVIEN implant contains 190 micrograms of the active ingredient, fluocinolone acetonide, and this is released into the eye in very small micro doses of approximately 0.2 micrograms per day for up to 3 years. As described above, injections into the eye can be a source of fear, stress, and anxiety for patients with retinal diseases, and the frequent clinic visits, injections, and patient monitoring required to achieve optimal long-term outcomes for patients with DMO results in a high burden of treatment for patients and their caregivers.[12] Because a single injection of ILUVIEN can remain effective for up to 36 months, ILUVIEN can reduce the psychological burden and stress on patients and caregivers, allowing the patient to maintain the same level of vision as other treatment options, but with far fewer injections[23] and clinic visits.

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.
The FAME A and FAME B clinical trials were randomised, double-masked, sham injection-controlled, parallel-group, studies conducted over a 36-month period. The first, FAME A, was conducted at 49 sites in the United States, Canada, 4 countries in the European Union, and India; FAME B was conducted at 52 sites in the United States, India, and 3 countries in the European Union. Both studies were identical by design and were conducted in parallel. The studies were completed in 2011. It is important to note that the FAME A and FAME B studies were conducted before the time that anti-VEGF treatments became available. Brief details of the clinical trials are given below.

Population: Patients who still had persistent diabetic macular oedema despite at least one previous laser treatment.

Patient group size: A total of 956 patients were included in the FAME studies. 393 were randomised to receive the higher-dose fluocinolone acetonide implant (released at a dose of 0.5µg/day), 375 were randomised to receive the low-dose fluocinolone acetonide implant (0.2µg/day), and 185 were randomised to receive the dummy or sham injection.

Treatment: The FAME trials evaluated the efficacy and safety of two different doses of fluocinolone acetonide: a high-dose of 0.5µg/day and a low-dose of 0.2µg/day.

Comparator: A dummy, or sham, injection. The sham injection consisted of the needle hub being pressed against the globe of the eye to simulate the injection of an implant.

Key inclusion criteria: Patients could be enrolled in the FAME studies if they met the following key criteria: Males and non-pregnant females at least 18 years of age; a best-corrected visual acuity score of ≥19 and ≤68 letters (20/50 or worse but at least 20/400) in the study eye according to an Early Treatment Diabetic Retinopathy Study chart; diagnosis of diabetes mellitus (type 1 or type 2); had to have received at least 1 macular laser treatment more than 12 weeks before the initial screening visit; and mean foveal thickness of the retina of at least 250µm in the study eye.

Key exclusion criteria: Patients were not permitted to enrol in the study if they: were pregnant, lactating or pf childbearing potential (unless using reliable contraception); had received laser treatment for diabetic macular oedema or any eye surgery in the study eye within 12 weeks of screening; had had a YAG capsulotomy (a type of cataract operation) within 15 days of screening; had glaucoma, ocular hypertension or intraocular pressure >21 mmHg or were receiving treatment with medicines to lower intra-ocular pressure at screening.

Primary outcome measured: The primary efficacy outcome was the proportion of trial participants who had an improvement in their visual acuity of at least 15 letters according to an Early Treatment Diabetic Retinopathy Study chart from the start of the trial to the end of Month 24.

Secondary outcomes measured: Secondary outcomes included other parameters of visual function and foveal thickness, and health-related quality of life.

Key publications relating to the FAME A and B clinical trials are as follows:

- Campochiaro PA, Brown DM, Pearson A, Ciulla T, Boyer D, Holz FG, et al. Long-term benefit of sustained-delivery fluocinolone acetonide vitreous inserts for diabetic macular edema. Ophthalmology. 2011;118(4):626-35.e2.[24]
- 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.[25]
- 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.[26]
- 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.[27]

- Chakravarthy U, Yang Y, Lotery A, Ghanchi F, Bailey C, Holz FG, et al. Clinical Evidence of the Multifactorial Nature of Diabetic Macular Edema. Retina. 2018;38(2):343-51.[28]

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

Section B.3.6 of the company submission presents a full overview of the relevant clinical trial evidence of the efficacy of ILUVIEN.

At the end of 3 years, the percentage of patients in the FAME studies who gained at least 15 in letter score was 28.7% (low dose) and 27.8% (high dose) in the fluocinolone treatment groups compared with 18.9% (*P*=0.018) in the sham injection group. When considering only those patients still in the trial at the end of 3 years, it was 33.0% (low dose) and 31.9% (high dose) compared with 21.4% in the sham group (*P* = 0.030). Preplanned subgroup analysis demonstrated a doubling of benefit compared with sham injections in patients who reported duration of diabetic macular oedema of 3 years or longer at baseline; the percentage who gained at least a 15 letter improvement at month 36 was 34.0% (low dose; *P*<0.001) or 28.8% (high dose; *P*= 0.002) compared with 13.4% (sham). An improvement of at least 2 steps in the Early Treatment Diabetic Retinopathy Study retinopathy scale occurred in 13.7% (low dose) and 10.1% (high dose) compared with 8.9% in the sham group. Almost all patients with a natural lens who received fluocinolone developed cataract, but their visual benefit after cataract surgery was similar to that in the patients with an artificial lens.

Further information about the efficacy and safety for ILUVIEN can be found in the publications listed in 3d) above.

There is no clinical trial that compares the efficacy and safety of the ILUVIEN and dexamethasone intravitreal implants directly. As a result, an indirect treatment comparison was conducted, based on the results of the clinical trials for both treatments, to demonstrate that the two corticosteroid treatment options are similar or comparable in the clinical benefits (efficacy and safety) they offer to patients with diabetic macular oedema.

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

Health-Related Quality of Life was assessed in the main FAME studies using a questionnaire about vision outcomes. The questionnaire contained 25 or 39 items, depending upon the location of the clinical trial site. Improving or maintaining vision is hugely important to patients. In the context of this submission, it is well documented that maintaining or improving vision through effective treatment of diabetic macular oedema is of huge importance to patients. The main impact on the

quality of life over and above that of preserving vision for the patient, is the improvement in the frequency of injections. This is described extensively in section 2d above.

ILUVIEN, if successful in this NICE appraisal, could mean that phakic diabetic macular oedema patients may need at least 5 fewer injections over a 3-year period compared to dexamethasone implant,[1,23] or 15-17 fewer injections than that recommended for anti-VEGF treatments over a 3 year period.[37]

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

The ILUVIEN implant is generally considered safe and well-tolerated. The most frequently reported adverse drug reactions reported in the FAME studies included cataract operation, cataract and increased intraocular pressure. These adverse events are commonly observed with intravitreal corticosteroid therapies; it is well-documented and well understood that the long-term use of corticosteroids may cause cataracts and increased intraocular pressure. These side effects can therefore be considered a class effect of intravitreal corticosteroid therapies in general, including ILUVIEN and dexamethasone. This class side effect profile is well understood by clinicians and easily-managed in clinical practice.

The indirect treatment comparison showed equivalence across three key safety outcomes, supporting equivalent risk-benefit. Expert clinical advice provided to the company confirmed plausibility in the clinical setting.

The ILUVIEN Summary of Product Characteristics can be found here (See section 4.8 for undesirable effects of treatment).
https://www.medicines.org.uk/emc/product/3061/smpc#gref

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration
-

The key benefits for patients with diabetic macular oedema who have natural phakic lenses is another treatment will be available to them if anti-VEGF injections have not worked for them. The comparative data in the company submission has shown that in indirect comparison ILUVIEN is as effective and well tolerated to dexamethasone implant, which is the only other treatment available for them if they do not benefit or can not have appropriate anti-VEGF injections.

However, the major benefit for patient of ILUVIEN is it meets the unmet need for an effective treatment given less frequently. It reduces the number of times they need an injection and other monitoring visits, which are a big burden on patients and their carers.

ILUVIEN, if successful in this NICE appraisal, could mean that phakic diabetic macular oedema patients may need at least 5 fewer injections over a 3-year period compared to dexamethasone implant,[1,23] or 15-17 fewer injections than that recommended for anti-VEGF treatments over a 3 year period.[37]

Around 1/3 of diabetic macular oedema patients are pseudophakic, and currently able to benefit from ILUVIEN. Patients who retain their original natural eye lens are not currently able to benefit from ILUVIEN.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

Like the dexamethasone implant for diabetic macular oedema, steroid implant injections do carry some risks, most notably a patient may develop a cataract faster than they do if they do not have steroid implant treatment. It's important that patients do understand that drying the excess of fluid in the eye caused by diabetic macular oedema is a critical objective in the therapeutic management of this disease. The importance of preserving retina function in patients who have not responded to prior treatment is key. Lens replacement is among the safest and lowest cost surgical procedures worldwide,[38] whereas the retina cannot easily be replaced. However, cataract surgery is one of the safest routine surgical procedures in the NHS, and while the lens of the eye can be replaced, once the retina and macular of the eye are damaged, it is not possible to replace or repair them.

Around 1/3 of diabetic macular oedema patients are already pseudophakic (have had their cataracts removed).

3i) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by

patients; were any improvements that would be important to you missed out, not tested or not proven?)

- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

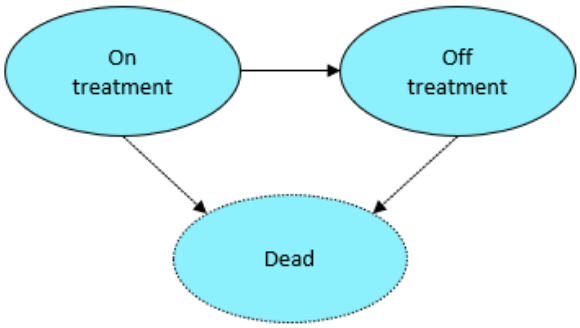
A QALY calculation has not been made for this NICE evaluation. Because the two corticosteroid treatment options (dexamethasone and ILUVIEN) are assumed to provide similar or comparable clinical benefits, the company has simply conducted a comparison of the costs associated with each of the two treatments.

A summary of the key features of the cost comparison model is provided below.

Model structure

- The objective of the cost comparison model is to quantify and cost the resource use associated with the two corticosteroid treatments (ILUVIEN and dexamethasone) to inform a cost-comparison between the two.
- The analysis adopts a three-state cohort transition structure (Figure 1). This facilitates transition off-treatment and introduces mortality - if it is not implicit from retreatment estimates. Retreatment estimates from trials and real world-studies account for discontinuation including death, however, mortality is applied in an alternative scenario in the model to long-term retreatment estimates (those after year 3) brought forward from the published NICE appraisal of dexamethasone implant. Transitions are allowed every three months, to retain consistency with other economic models for diabetic macular oedema previously evaluated by NICE.

Figure 1. Model diagram



Key: Ovals are representative of states which simplify DMO status into two dimensions; treatment status (on/off) and mortality (dead/alive). Arrows represent permitted transitions between states. Dead is an absorbing state but is not used in the base case, denoted by the dashed boarder, and dashed arrows.

- The decision problem specifies the population as people with chronic diabetic macular oedema that is insufficiently responsive to available therapies who have a natural lens. This is the population for the cost comparison.

Modelling inputs

- ILUVIEN does not extend life, so mortality is not included in the model.

- Although treatment with ILUVIEN can have an impact on patient quality of life, this has not been included in the model, as the model is a simple comparison of costs.
- Because the two treatments are assumed to offer comparable clinical benefits, the effect of treatment on visual outcomes, or any difference in effect between treatments, is not considered in the cost-comparison. The model does not directly consider changes in vision, patient utility or estimate quality-adjusted life-years. Treatment effect is considered indirectly in respect to the need and timing of retreatment, this is a function of loss of vision and discontinuation, which may be independent.
- Three safety outcomes are included in the model: raised intraocular pressure, cataract extraction and vitreous haemorrhage.

Modelling how the costs of treatment differ between treatments

- The main outcome of the model is the incremental total cost to the NHS and Personal Social Services payer in England per patient between ILUVIEN and dexamethasone treatment.
- Five aspects of resource and cost are included in the model: the steroid implant acquisition cost, steroid implantation administration, treatment and procedures for adverse events and complications of disease, and the routine management of disease.
- The cost of additional and subsequent treatments is not included.

Uncertainty

- The accuracy of model outcomes is subject to structural and parameter uncertainty. A series of analyses were conducted to characterise and quantify the leading contributors. Comprehensive one-way sensitivity analysis tested the sensitivity of cost-effectiveness to 20% bi-directional variation in each parameter point estimate, except for drug acquisition unit costs.
- Probabilistic sensitivity analysis was used to test multivariate parameter uncertainty in the relationship between ILUVIEN costs and dexamethasone costs.
- Structural uncertainty was explored in a scenario analysis which explored alternative assumptions in known areas of uncertainty, in particular the respective re-treatment rates of the two corticosteroid implants.

Cost effectiveness results

- This findings of the companies model will be assessed by NICE in this technology appraisal. NICE will decide if the information submitted by the company is expected to be cost-saving in the displacement of the dexamethasone implant. It will also look at the cost savings when the company patient access scheme discount is included. NICE will then decide if the finding is generalisable to general medical practice in England.

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations. If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)
ILUVIEN has been approved for NHS use since 2012 and so it is not a new treatment. A QALY calculation has not been made for this NICE evaluation. Because the two corticosteroid treatment options (dexamethasone and ILUVIEN) are assumed to provide similar or comparable clinical benefits, the company has provided an analysis to assess these comparable benefits, then

simply conducted a comparison of the costs associated with a patient receiving each of the two treatments.

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.
Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme
Find more general information about the Equality Act and equalities issues here

If a person is registered as blind or partially-sighted they are considered disabled, as stated in the Equality Act 2010. Therefore, the patient population addressed in this submission is a protected group under this Act**.**

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc.
Where possible, please provide open access materials or provide copies that patients can access.

Further information about ILUVIEN:

- ILUVIEN Package leaflet information for the user. https://www.medicines.org.uk/emc/files/pil.3061.pdf
- ILUVIEN Summary of Product Characteristics https://www.medicines.org.uk/emc/product/3061/smpc#gref
- ILUVIEN UK website, information for members of the public. https://staging.patient.iluvien.co.uk

Further information on NICE and the role of patients**:**

- Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE
- NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE
- EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/
- EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/
- INAHTA: http://www.inahta.org/
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe:

http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

Diabetic macular oedema: Diabetic macular oedema (or edema, DME) is the accumulation of excess fluid in the extracellular space within the retina in the macular area. It is a complication of diabetic retinopathy, which is in turn a complication of diabetes mellitus.

Glaucoma: Glaucoma is a group of eye conditions that damage the optic nerve. Glaucomas are characterised by an increase of pressure within the eyeball, causing gradual loss of sight.

Intraocular pressure: Intraocular pressure is the medical terms for the pressure of the fluid inside the eyes.

Intravitreal: Intravitreal means 'inside the eye'. If a corticosteroid medicine is administered intravitreally, it is injected directly into the eye.

Ocular: connected or related to eyes or vision.

Phakic: a natural lens of the eye.

Pseudophakic: an artificial or fake lens, also known as an intraocular lens.

Visual acuity: a measure of the ability of the eye to distinguish shapes and the details of objects at a given distance. Visual acuity measures c*larity and sharpness of* vision at a distance. It is usually tested by reading an eye chart.

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Cost Comparison Appraisal

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

Company response to clarification questions

November 2023

File name	Version	Contains confidential information	Date
ID6307 fluocinolone acetonide_Company response to clarification questions[Redacted]	1.0	No	8 November 2023

List of abbreviations

AE	Adverse Event
BCVA	Best-corrected visual acuity
CI	Confidence interval
CRT	Central Retinal Thickness
CS	Company Submission
DEX	Dexamethasone intravitreal implant
DMO	Diabetic Macular Oedema
EAG	NICE External Assessment Group
EMs	Effect modifiers
EOT	End of Treatment
ESS	Effective Sample Size
ETD	Estimated Treatment Difference
FAc	Fluocinolone Acetonide
FAP	Full Analysis Population
FAS	Full Analysis Set
IOP	Intraocular Pressure
ITC	Indirect Treatment Comparison
ITT	Intention To Treat
MAIC	Matching-Adjusted Indirect Comparison
NICE	National Institute for Health and Care Excellence
PP	Per Protocol
RCT	Randomised Controlled Trial
RWE	Real-World Evidence
SD	Standard Deviation
SE	Standard Error
TE	Treatment Experienced

Section A: Clarification on effectiveness data

A1. Please present Document B Table 8 for the phakic subset ITT.

Please see below for an updated version of Document B Table 8 including baseline characteristics for the overall pooled FAME patient population, as well as disaggregated by lens status. Patients with phakic lens eyes are typically younger, more often male, and with a shorter duration of diabetes and diabetic macular oedema at baseline than pseudophakic counterparts. Otherwise, baseline characteristics are generally well aligned between the two patient groups.

Table A1.1. Patient demographics and baseline characteristics in the pooled FAME studies by lens type

	FAME studies (FAME A and FAME B populations pooled)								
	All			Phakic			Pseudophakic		
	FAc 0.2 µg/day	FAc 0.5 µg/day	Sham	FAc 0.2 µg/day	FAc 0.5 µg/day	Sham	FAc 0.2 µg/day	FAc 0.5 µg/day	Sham
N	375	393	185	235	265	121	140	128	64
Demographics									
Mean age (SD), yrs	63.0 (9.3)	62.2 (9.3)	61.9 (9.6)	60.2 (9.2)	60.8 (9.1)	59.7 (8.9)	67.7 (7.6)	65.3 (9.0)	66.2 (9.5)
Male, n (%)	215 (57.3)	243 (61.8)	108 (58.4)	145 (61.7)	176 (66.4)	74 (61.2)	70 (50.0)	67 (52.3)	34 (53.1)
Race, n (%)									
Asian	85 (22.7)	87 (22.1)	40 (21.6)	58 (24.7)	67 (25.3)	25 (20.7)	27 (19.3)	20 (15.6)	15 (23.4)
Black	22 (5.9)	32 (8.1)	11 (5.9)	13 (5.5)	21 (7.9)	9 (7.4)	9 (6.4)	11 (85.9)	2 (3.1)
Caucasian	264 (70.4)	269 (68.4)	132 (71.4)	160 (68.1)	174 (65.6)	86 (71.1)	104 (74.3)	95 (74.2)	46 (71.9)
Other	3 (1.1)	5 (1.3)	2 (1.1)	3 (1.3)	3 (1.1)	1 (0.8)	0	2 (1.6)	1 (1.6)
Diabetes characteristics									
Diabetes Type, n (%)									
Type 1	29 (7.7)	21 (5.3)	13 (7.0)	17 (7.2)	9 (3.4)	10 (8.3)	12 (8.6)	12 (9.4)	3 (4.7)
Type 2	340 (91.0)	366 (93.1)	170 (91.9)	214 (91.1)	252 (95.1)	109 (90.1)	126 (90.0)	115 (90.0)	61 (95.3)
Not recorded	6	5	2	4	4	2	2	1	0

	(1.6)	(1.3)	(1.1)	(1.7)	(1.5)	(1.7)	(1.4)	(0.8)	
Mean duration of diabetes, yrs (SD)	17.0 (9.4)	16.2 (8.7)	16.4 (8.5)	16.1 (8.2)	15.3 (7.8)	16.0 (7.5)	18.7 (9.5)	19.0 (9.3)	17.3 (9.3)
Mean Hba1c % (SD)	7.8 (1.6)	7.7 (1.6)	7.8 (1.7)	7.9 (1.7)	7.8 (1.6)	8.0 (1.9)	7.7 (1.4)	7.6 (1.5)	7.5 (1.0)
DMO characteristics									
Mean duration of DMO, yrs (SD)	3.6 (2.92)	3.5 (2.60)	3.9 (3.78)	3.4 (2.86)	3.2 (2.35)	3.6 (2.73)	4.0 (2.97)	4.1 (2.93)	4.6 (5.15)
Mean BCVA letter score	53.3 (12.7)	52.9 (12.2)	54.7 (11.3)	53.6 (12.2)	52.8 (12.0)	55.4 (11.3)	52.9 (13.5)	53.0 (12.7)	53.4 (11.2)
Mean central retinal thickness, µm (SD)	461 (160)	485 (174)	451 (152)	461 (159)	475 (173)	441 (142)	462 (163)	508 (175)	471 (169)
Lens status, n (%)									
Phakic	235 (62.7)	265 (67.4)	121 (65.4)	235 (100)	265 (100)	121 (100)	-	-	-
Pseudophakic	140 (37.3)	128 (32.6)	64 (34.6)	-	-	-	140 (100)	128 (100)	64 (100)
Prior DMO treatment, n (%)									
Laser	375 (100)	393 (100)	185 (100)	235 (100)	265 (100)	121 (100)	140 (100)	128 (100)	64 (100)
Intravitreal corticosteroid	63 (16.8)	61 (15.5)	28 (15.1)	29 (12.3)	22 (8.3)	14 (11.6)	34 (24.3)	39 (30.5)	14 (21.9)
No prior DMO treatment, n (%)	0	0	0	0	0	0	0	0	0
Abbreviations: BCVA, best-corrected visual acuity, DMO, diabetic macular oedema, FAc, Fluocinolone Acetonide SD, standard deviation.									

A2. Please augment Document B tables 9 and 10 with the reasons for discontinuation to parallel Figure 4, also augmenting this with 12 month and 24-month data.

a. If it is also possible to present this for the phakic subset this would be much appreciated.

Please see below for augmented versions of Document B Table 9 and 10, including study completion rates at 6, 12, 24, and 36 months from baseline, consistent with Figure 4 of the CS.

Table A2.1. FAME A - Summary of Patient Disposition (Randomised Patients)

Category	Treatment Group			
	Sham	0.2µg/day FAc	0.5µg/day FAc	Total
Total subjects randomised (N)	95	190	196	481
Randomised and not treated (n, %)	0	0	1(0.5)	1(0.2)
Randomised and treated (n, %)	95 (100.0)	190 (100.0)	195 (99.5)	480 (99.8)
Total completed (n, %)	67 (70.5)	141 (74.2)	132 (67.3)	340 (70.7)
Total discontinued (n, %)	28 (29.5)	49 (25.8)	64 (32.7)	141 (29.3)
Adverse event	3 (3.2)	2 (1.1)	14 (7.1)	19 (4.0)
Unsatisfactory therapeutic effect	2 (2.1)	0	1 (0.5)	3 (0.6)
Protocol violation	2 (2.1)	2 (1.1)	3 (1.5)	3 (0.6)
Subject withdrew consent	6 (6.3)	19 (10.0)	13 (6.6)	38 (7.9)
Lost to follow-up	9 (9.5)	14 (7.4)	14 (7.1)	37 (7.7)
Death[1]	6 (6.3)	11 (5.8)	19 (9.7)	36 (7.5)
Unknown	0	1 (0.5)	0	1 (0.2)
Study completion rate				
Month 6	91 (95.8)	184 (96.8)	184 (93.9)	459 (95.4)
Month 12	81 (85.3)	168 (88.4)	175 (89.3)	424 (88.1)
Month 24	70 (73.7)	149 (78.4)	146 (74.5)	365 (75.9)
Month 36	67 (70.5)	141 (74.2)	132 (67.3)	340 (70.7)

[1]A total of 37 subjects died during the study. Reason for study discontinuation was not reported as “death” for 1 subject.

Abbreviations: FAc, Fluocinolone Acetonide

Table A2.2. FAME B - Summary of Patient Disposition (Randomised Patients)

Category	Treatment Group			
	Sham	0.2µg/day FAc	0.5µg/day FAc	Total
Total subjects randomised (N)	90	186	199	475

Randomised and not treated (n, %)	0	1(0.5)	1(0.5)	2(0.4)
Randomised and treated (n, %)	90 (100)	185 (99.5)	198 (99.5)	473 (99.6)
Total completed (n, %)	59 (65.5)	133 (71.5)	147 (73.9)	339 (71.4)
Total discontinued (n, %)	31 (34.4)	53 (28.5)	52 (26.1)	136 (28.6)
Adverse event	2 (2.2)	2 (1.1)	1 (0.5)	5 (1.1)
Unsatisfactory therapeutic effect	1 (1.1)	0	0	1 (0.2)
Protocol violation	0	0	2 (0.1)	2 (0.4)
Subject withdrew consent	8 (8.9)	12 (6.5)	14 (7.0)	34 (7.2)
Lost to follow-up	15 (16.7)	23 (12.4)	23 (11.6)	61 (12.8)
Death	5 (5.6)	16 (8.6)	12 (6.0)	33 (6.9)
Study completion rate				
Month 6	83 (92.9)	174 (93.5)	190 (95.5)	447 (94.1)
Month 12	77 (85.6)	162 (87.1)	178 (89.4)	417 (87.8)
Month 24	64(71.1)	140 (75.3)	157 (78.9)	361 (76.0)
Month 36	59 (65.5)	133 (71.5)	147 (73.9)	339 (71.4)
Abbreviations: FAc, Fluocinolone Acetonide				

The following tables show 6, 12, 24, and 36 month completion rates for the phakic subgroup of FAME A and FAME B. Completion rates were consistent between the overall trial populations of FAME A and B and the phakic subgroup, with 71.4% and 71.2% of phakic patients completing FAME A and B, respectively.

Table A2.3. FAME A - phakic lens study completion rates

Time-point	**Treatment Group**			
	Sham	**0.2µg/day FAc**	**0.5µg/day FAc**	**Total**
Total subjects randomised (N)	61	124	130	315
Month 6 (n, %)	59 (96.7)	120 (96.8)	124 (95.4)	303 (96.2)
Month 12 (n, %)	57 (93.4)	112 (90.3)	122 (93.8)	291 (92.4)
Month 24 (n, %)	50 (82.0)	102 (82.3)	101 (77.7)	253 (80.3)
Month 36 (n, %)	44 (72.2)	91 (73.4)	90 (69.2)	225 (71.4)

Table A2.4. FAME B - phakic lens study completion rates

Time-point	Treatment Group			
	Sham	0.2µg/day FAc	0.5µg/day FAc	Total
Total subjects randomised (N)	60	111	135	306
Month 6 (n, %)	54 (90.0)	107 (96.4)	135 (100.0)	296 (96.7)
Month 12 (n, %)	51 (85.0)	103 (92.8)	126 (93.3)	280 (91.5)
Month 24 (n, %)	41 (68.3)	86 (77.5)	113 (83.7)	240 (78.4)
Month 36 (n, %)	34 (56.7)	81 (73.0)	103 (76.3)	218 (71.2)

A3. PRIORITY QUESTION: Please disaggregate Document B Table 32 into the separate SAEs experienced and present this for (1) all patients, (2) the phakic subgroup and (3) the ITC phakic subgroup.

This can be presented on a FAS or ITT basis, whichever is simplest to present.

Please see the table below for a breakdown of serious ocular adverse events occurring in at least 2% of patients in any treatment group. Results have been further disaggregated by study arm, and by phakic subgroups of the FAME A and B pooled FAS, and of the ITC analysis cohort. Adverse events experienced were consistent across the three subgroups, with the exception of cataract operations which necessarily occur in a higher proportion of patients in the phakic subgroups.

Table A3.1. Serious Ocular Adverse Events in the Study Eye with an Incidence of at Least 2% in Any Treatment Group

Population, SAE preferred term	Treatment Group		
	Sham n (%)	FAc 0.2 µg/day n (%)	All n (%)
FAS (FAME A+B pooled)			
N	185	375	560
Cataract Operation	33 (17.8)	188 (50.1)	221 (39.5)
Glaucoma	2 (1.1)	12 (3.2)	14 (2.5)
Intraocular pressure increased	0	12 (3.2)	12 (2.1)

Population, SAE preferred term	Treatment Group		
	Sham n (%)	FAc 0.2 µg/day n (%)	All n (%)
Trabeculectomy	0	10 (2.7)	10 (1.8)
Trabeculoplasty	0	3 (0.8)	3 (0.5)
Vitrectomy	16 (8.6)	19 (5.1)	35 (6.3)
Vitreous Haemorrhage	6 (3.2)	10 (2.7)	16 (2.9)
FAS (FAME A+B pooled) – Phakic only			
N	121	235	356
Cataract Operation	33 (27.3)	188 (80.0)	221 (62.1)
Glaucoma	0	6 (2.6)	6 (1.7)
Intraocular pressure increased	0	9 (3.8)	9 (2.5)
Trabeculectomy	0	7 (3.0)	7 (2.0)
Trabeculoplasty	0	1 (0.4)	1 (0.3)
Vitrectomy	10 (8.3)	13 (5.5)	23 (6.5)
Vitreous Haemorrhage	4 (3.1)	8 (3.4)	12 (3.4)
ITC Cohort – Phakic only			
N	75	138	213
Cataract Operation	19 (25.3)	107 (77.5)	126 (59.2)
Glaucoma	0	3 (2.2)	3 (1.4)
Intraocular pressure increased	0	4 (2.9)	4 (1.9)
Trabeculectomy	0	3	3

Population, SAE preferred term	Treatment Group		
	Sham n (%)	FAc 0.2 µg/day n (%)	All n (%)
		(2.2)	(1.4)
Trabeculoplasty	0	0	0
Vitrectomy	7 (9.3)	6 (4.3)	13 (6.1)
Vitreous Haemorrhage	2 (2.7)	3 (2.2)	5 (2.3)
Abbreviations: FAc, Fluocinolone Acetonide, FAS, full analysis set, SAE, serious adverse event			

FAME / MEAD

A4. Document B Page 73 states that "*Of note, 13% of patients enrolled into FAME received an additional FAc implant during the follow-up period*". This seems to be somewhat less than that within the excel model initial 3-year period. Please provide an account of this.

The value of 13% represents the proportion of trial participants receiving *at least one* re-implantation. The model estimates are based on a count of the *total number* of retreatments, i.e., the difference between the two estimates is due to the fact that some trial participants received more than one re-implant.

The figure of 13% of FAME participants requiring FAc re-implantation (any number) during follow-up was based was based on the full analysis set for the low-dose (0.2 µg/day FAc) group (N=376), as reported by Fallico and colleagues.(1) 13% is calculated as follows: (39+11)/376 = 0.133 (to 3 decimal places).

The model base case uses the proportions given in Table 38 of the CS Document B (page 128, column 'Basecase FAME_1), where a count of retreatments is given for sequential quarter-year periods through 3 years. The counts here are from individual patient data analysis for this technology appraisal. Counts for the base case are found in the model in worksheet 'Retreatment IPD' cell range E11:E23. Calculated proportions are given in F11:F23 and are based on the full analysis set (N=376). Two alternative counts are supplied in the same worksheet, for two alternative populations.

A5. What, if any, rescue medications/procedures were permitted during FAME?

a. **Please tabulate how many patients received each rescue medication/procedure during the pooled FAME data in the 0.2µg arm and the placebo arm.**

b. **If it is also possible to present this for the phakic subset this would be much appreciated.**

a. Please find below a table summarising the number of patients that received each rescue medication/procedure in the pooled FAME data in the FAc 0.2µg/day arm and in the placebo arm. This data shows the pooled data and was taken from the full population.

Table A5.1. Rescue medications used across the pooled FAME trials

	Sham (N=184)		FAc 0.2 ug/day (N=374)	
Rescue medication	**Subjects, N (%)**	**No. events**	**Subjects, N (%)**	**No. events**
Any disallowed treatment	[redacted]	[redacted]	[redacted]	[redacted]
Any Anti-VEGF Treatment	[redacted]	[redacted]	[redacted]	[redacted]
Avastin	[redacted]	[redacted]	[redacted]	[redacted]
Lucentis	[redacted]	[redacted]	[redacted]	[redacted]
Macugen	[redacted]	[redacted]	[redacted]	[redacted]
Unspecified	[redacted]	[redacted]	[redacted]	[redacted]
Any Steroid Treatment	[redacted]	[redacted]	[redacted]	[redacted]
Intravitreal Triamcinolone Acetonide	[redacted]	[redacted]	[redacted]	[redacted]
Posterior Subtenon Steroid	[redacted]	[redacted]	[redacted]	[redacted]
Intravitreal Dexamethasone	[redacted]	[redacted]	[redacted]	[redacted]
Unspecified	[redacted]	[redacted]	[redacted]	[redacted]

Sources: Integrated Summary of Safety [ISS] 36-month tables, 10 September 2012; Alimera Sciences Data on File no. 6.

b. Please find below the same table but for the phakic subset. Please note, the phakic data refers to the chronic DMO population as opposed to the full population. Hence, for consistency, the FAc 0.2µg arm and the placebo arm are included alongside the phakic subset, which includes patients that were phakic throughout, and those that had a phakic lens at baseline and underwent cataract extraction after treatment with the FAc 0.2µg implant.

Table A5.2. Rescue medications used across the pooled FAME trials for the phakic only population

Rescue medication	Sham (N=112)		FAc 0.2 ug/day, Chronic DMO all eyes (N=209)		0.2 ug/day, Chronic/ Phakic-Pseudophakic (N=97)		0.2 ug/day, Chronic/ Phakic-Phakic (N=17)	
	Subjects, N (%)	No. events	Subjects, N (%)	No. events	Subjects, N (%)	No. events	Subjects, N (%)	No. events
Any disallowed treatment	**39 (34.8)**	[redacted]	**28 (13.4)**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any Anti-VEGF Treatment	**17 (15.2)**	[redacted]	**7 (3.3)**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Avastin	[redacted]	[redacted]	[redacted]	[redacted]				
Lucentis	[redacted]	[redacted]	[redacted]	[redacted]				
Macugen	[redacted]	[redacted]	[redacted]	[redacted]				
Unspecified	[redacted]	[redacted]	[redacted]	[redacted]				
Any Steroid Treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Intravitreal Triamcinolone Acetonide	[redacted]	[redacted]	[redacted]	[redacted]				
Posterior Subtenon Steroids	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Intravitreal Dexamethasone	[redacted]	[redacted]	[redacted]	[redacted]				
Unspecified	[redacted]	[redacted]	[redacted]	[redacted]				

Sources: Integrated Summary of Safety [ISS] 36-month tables, 10 September 2012; Alimera Data on File no. 6.

A6. In Table 14 of Document B.3.4, please include the number of people in each set (total and per treatment group) and, if analysis sets have the same N, confirm whether or not these contain the same people and the same timepoints.

Tables A6.1 and A6.2 provide a breakdown of all patients randomised (total per treatment group) as per the defined analysis sets in Table 14 of the CS. They also provide a breakdown of the number of people in each of the analysis sets which are:

- All Randomised
- Intention to Treat Population (ITT)
- Full Analysis Population (FAP)
- Safety Population and
- Per Protocol Population (PP)

All analysis sets contain the same number of patients i.e., patients randomised to a treatment arm and treated with either active IMP or placebo ***with the exception of*** the FAP.

- In FAME A one patient in the 0.5μg/day FAc arm of the study was never treated and in
- FAME B, one patient in the 0.2μg/day FAc arm and one patient in the 0.5μg/day FAc arm were never treated.

The per protocol analysis included the data for all study patients unless they met the criteria for one or more exclusion. The most common reason for exclusion was use of prohibited treatments for DMO, which was more prevalent in FAME A, and much more prevalent in the sham arm of both studies (34.7%, FAME A – Table A6.1; 31.1%, FAME B - Table A6.2).

Table A6.1. FAME A Breakdown of randomised subjects per analysis sets

FAME A				
All Randomised (All patients randomised and treated)				
	Treatment Group			
Category	Sham	0.2μg/day FAc	0.5μg/day FAc	Total
Total subjects randomised. (All randomised and treated)	95	190	195	480

Intention to Treat (ITT) (All patients randomised and treated)				
	Treatment Group			
Category	Sham	0.2μg/day FAc	0.5μg/day FAc	Total
Intention to Treat (ITT)[1] (All randomised[3] and treated) (n, %)	95 (100.0)	190 (100.0)	195 (99.5)	480 (99.8)
Full Analysis				
	Treatment Group			
Category	Sham	0.2μg/day FAc	0.5μg/day FAc	Total
Full Analysis[2] (Includes Randomised and treated patients and patients randomised but not treated) (n, %)	95	190	196	481
	0	0	1 (0.5)* (*Patient randomised but not treated)	1 (0.2)
Safety (All patients randomised and treated)				
Category	Sham	0.2μg/day FAc	0.5μg/day FAc	Total
	Treatment Group			
Safety (All randomised and treated patients) (n, %)	95 (100.0)	190 (100.0)	195 (99.5)	480 (99.8)
Per Protocol				
Category	Sham	0.2μg/day FAc	0.5μg/day FAc	Total
	Treatment Group			
Per Protocol[4] (All randomised and treated patients with no exclusions (i.e., protocol violations) (n, %)	95 (100.0)	190 (100.0)	195 (99.5)	480 (99.8)
At least 1 violation (Over the course of the study) (n, %)	36 (37.9)	49 (25.8)	51 (26.0)	136 (28.3)
Prohibited treatments (Over the course of the study) (n, %)	33 (34.7)	36 (18.9)	42 (21.4)	111 (23.1)

[1] The pre-specified primary efficacy data set.
[2] Data set was added after key findings of the unmasked 24-month FAME data were made available.
[3]The Full Analysis dataset included all randomised patients. The method of last observation carried forward (LOCF) was used to impute for all missing values. This dataset was used on the basis that it most closely follows the intention-to-treat principle. The Full Analysis Set includes data for 3 subjects who were randomised and not treated (1 subject in FAME A and 2 subjects in FAME B). All primary, secondary, and exploratory efficacy variables were analysed using this dataset.
[4]Data for all subjects were included in the Per Protocol Analysis unless one or more of the reasons for exclusion were met. The most common reason for exclusion was use of prohibited treatments for DMO, which was more prevalent in FAME A, and much more prevalent in the sham arm of both studies (34.7%, FAME A; 31.1%, FAME B).

Table A6.2. FAME B Breakdown of randomised subjects per analysis sets

FAME B				
All Randomised				
	Treatment Group			
Category	Sham	0.2μg/day FAc	0.5μg/day FAc	Total
Total subjects randomised. (All randomised and treated)	90	186	199	475
Intention to Treat (ITT)				
	Treatment Group			
Category	Sham	0.2μg/day FAc	0.5μg/day FAc	Total
Intention to Treat (ITT)[1] (All randomised[3] and treated) (n, %)	90 (100)	185 (99.5)	198 (99.5)	473 (99.6)
Full Analysis				
	Treatment Group			
Category	Sham	0.2μg/day FA	0.5μg/day FA	Total
Full Analysis[2] (Includes Randomised and treated patients and patients randomised but not treated) (n, %)	90 (100)	185 (99.5)	198 (99.5)	473 (99.6)
	0 1 (0.5)	1 (0.5) (*Patient randomised but not treated)	1 (0.5) (*Patient randomised but not treated)	2 (0.4)
Safety				
Category	Sham	0.2μg/day FA	0.5μg/day FA	Total
	Treatment Group			
Safety	90 (100)	185 (99.5)	198 (99.5)	473 (99.6)

(All randomised and treated) (n, %)				
Per Protocol (All patients randomised and treated per protocol)				
Category	Sham	0.2μg/day FA	0.5μg/day FA	Total
	Treatment Group			
Per Protocol[4] (All randomised and treated) (n, %)	90 (100)	185 (99.5)	198 (99.5)	473 (99.6)
At least 1 violation (n, %)	34 (37.8)	34 (18.3)	35 (17.6)	103 (21.7)
Prohibited treatments (n, %)	28 (31.1)	21 (11.3)	22 (11.1)	71 (14.9)

[1] The pre-specified primary efficacy data set.
[2] Data set was added after key findings of the unmasked 24-month FAME data were made available.
[3]The Full Analysis dataset included all randomised patients. The method of last observation carried forward (LOCF) was used to impute for all missing values. This dataset was used on the basis that it most closely follows the intention-to-treat principle. The Full Analysis Set includes data for 3 subjects who were randomised and not treated (1 subject in FAME A and 2 subjects in FAME B). All primary, secondary, and exploratory efficacy variables were analysed using this dataset.
[4]Data for all subjects were included in the Per Protocol Analysis unless one or more of the reasons for exclusion were met. The most common reason for exclusion was use of prohibited treatments for DMO, which was more prevalent in FAME A, and much more prevalent in the sham arm of both studies (34.7%, FAME A; 31.1%, FAME B).

In response to the second part of question A6, matching an N number is normal in study analysis and thus provided as per the FAME A and FAME B CSR. Given the very short turnaround time for these clarification responses, it is not possible to provide a per patient match per study visit today that would allow us to confirm that the analysis sets contain the same patients at the same timepoints. We contend that provided aggregated matching per visit is sufficient. Please refer Tables A6.3 and A6.4 which delineate patient disposition for the Safety and Per Protocol populations per study visit (from Screening Visit to Month 36).

Table A6.3. FAME A Number of Subjects Included in the Study Populations through Month 36 by Study Visit (Randomised Patients).

FAME A				
Full Analysis (LOCF) (All patients randomised)				
	Treatment Group			
Category	Sham (N=95) n (%)	0.2μg/day FA (N=190) n (%)	0.5μg/day FA (N=196) n (%)	Total (N=481) n (%)

Screening through Month 36(n, %)	95 (100.0)	190 (100.0)	196 (100.0)	481 (100.0)
Intention to Treat (ITT) (All randomised[3] and treated)				
	Treatment Group			
Category	Sham	0.2μg/day FA	0.5μg/day FA	Total
Intention to Treat (ITT)[1] (All randomised[3] and treated) (n, %) (LOCF)	95 (100.0)	190 (100.0)	195 (99.5)	480 (99.8)
All Randomised				
	Treatment Group			
Category	Sham	0.2μg/day FA	0.5μg/day FA	Total
Full Analysis[2] (Randomised and treated) (LOCF) (n, %)	95 (100.0)	190 (100.0)	195 (99.5)	480 (99.8)
Per Protocol				
	Treatment Group			
Category	Sham	0.2μg/day FA	0.5μg/day FA	Total
Screening (n, %)	91 (95.8)	175 (92.1)	183 (93.4)	449 (93.3)
Month 6 (n, %)	75 (78.9)	161 (84.7)	168 (85.7)	404 (84.0)
Month 12 (n, %)	59 (62.1)	138 (72.6)	150 (76.5)	347 (72.1)
Month 18 (n, %)	51 (53.7)	125 (65.8)	125 (63.8)	301 (62.6)
Month 24 (n, %)	46 (48.4)	112 (58.9)	113 (57.7)	271 (56.3)
Month 30 (n, %)	42 (44.2)	106 (55.8)	105 (53.6)	253 (52.6)
Month 36 (n, %)	39 (41.1)	103 (54.2)	98 (50.0)	240 (49.9)
Safety				
	Treatment Group			
Category	Sham	0.2μg/day FA	0.5μg/day FA	Total
Screening (n, %)	95 (100.0)	190 (100.0)	195 (99.5)	480 (99.8)
Baseline (n, %)	95 (100.0)	190 (100.0)	195 (99.5)	480 (99.8)
Month 6 (n, %)	91 (95.8)	184 (96.8)	184 (93.9)	459 (95.4)
Month 12 (n, %)	81 (85.3)	168 (88.4)	175 (89.3)	424 (88.1)
Month 18 (n, %)	77 (81.1)	153 (80.5)	155 (79.1)	385 (80.0)
Month 24 (n, %)	70 (73.7)	149 (78.4)	146 (74.5)	365 (75.9)
Month 30 (n, %)	67 (70.5)	143 (75.3)	139 (70.9)	349 (72.6)
Month 36 (n, %)	67 (70.5)	140 (73.7)	133 (67.9)	340 (70.7)
LOCF = Last observation carried forward.				

Table A6.4. FAME B Number of Subjects Included in the Study Populations through Month 36 by Study Visit (Randomised Patients)

FAME B				
Full Analysis (LOCF)				
	Treatment Group			
Category	Sham (N=95) n (%)	0.2μg/day FA (N=190) n (%)	0.5μg/day FA	Total (N=481) n (%)

			(N=196) n (%)	
Screening through Month 36 (all patients randomised) (n, %)	90 (100)	186 (100)	199 (100)	475 (100)
Intention to Treat (ITT)				
	Treatment Group			
Category	Sham	0.2μg/day FA	0.5μg/day FA	Total
Intention to Treat (ITT)[1] (All randomised[3] and treated) (n, %) (LOCF)	90 (100)	185 (99.5)	198 (99.5)	473 (99.6)
All Randomised				
	Treatment Group			
Category	Sham	0.2μg/day FA	0.5μg/day FA	Total
Full Analysis[2] (Randomised and treated) (LOCF) (n, %)	90 (100)	185 (99.5)	198 (99.5)	473 (99.6)
Per Protocol				
	Treatment Group			
Category	Sham	0.2μg/day FA	0.5μg/day FA	Total
Screening (n, %)	81 (90.0)	169 (90.9)	183 (92.0)	433 (91.2)
Month 6 (n, %)	69 (76.7)	156 (83.9)	176 (88.4)	401 (84.4)
Month 12 (n, %)	58 (64.4)	141 (75.8)	162 (81.4)	361 (76.0)
Month 18 (n, %)	50 (55.6)	130 (69.9)	139 (69.8)	319 (67.2)
Month 24 (n, %)	39 (43.3)	124 (66.7)	138 (69.3)	301 (63.4)
Month 30 (n, %)	35 (38.9)	117 (62.9)	131 (65.8)	283 (59.6)
Month 36 (n, %)	31 (34.4)	110 (59.1)	119 (59.8)	260 (54.7)
Safety				
	Treatment Group			
Category	Sham	0.2μg/day FA	0.5μg/day FA	Total
Screening (n, %)	90 (100)	185 (99.5)	198 (99.5))	473 (99.6)
Baseline (n, %)	90 (100)	185 (99.5)	198 (99.5)	473 (99.6)
Month 6 (n, %)	83 (92.2)	174 (93.5)	190 (95.5)	447 (94.1)
Month 12 (n, %)	77 (85.6)	162 (87.1)	178 (89.4)	417 (87.8)
Month 18 (n, %)	73 (81.1)	148 (79.6)	158 (79.4)	379 (79.8)
Month 24 (n, %)	64 (71.1)	140 (75.3)	157 (78.9)	361 (76.0)
Month 30 (n, %)	62 (68.9)	135 (72.6)	151 (75.9)	348 (73.3)
Month 36 (n, %)	59 (65.6)	130 (69.9)	144 (72.4)	333 (70.1)
LOCF = Last observation carried forward.				

A7. Please provide the baseline characteristics of patients with phakic eyes and pseudo-phakic eyes separately in separate tables. Please provide these both overall and by treatment group.

Please refer to the response to clarification question **A1.**

A8. Please tabulate the clinical effectiveness results for FAME and MEAD from section B.3.6 in the form of the following table. For the whole trial population and for the phakic eyes subgroup only:

Please see Table A8.1 below for a tabulated summary of clinical effectiveness results for FAME and MEAD, respectively. Results for FAME have been presented for the FAS and for the phakic subgroup. Phakic lens subgroup results are not publicly available for MEAD and are therefore not presented.

Table A8.1. FAME (pooled A+B) - primary and secondary efficacy endpoints at 36 months

Results at 36 months						
Outcome, population		FAc 0.2 µg		Sham		P-value *
		N	Result	N	Result	
Primary efficacy endpoint						
Proportion of patients who experienced an increase from baseline of ≥15 letters in BCVA in their study eye (%)	FAS	376	28.7%	185	18.9%	0.018
	FAS – phakic only	236	28.4%	121	19.8%	0.114
Secondary efficacy endpoints						
Mean change from baseline in BCVA letter score (SD)	FAS	376	+5.3 (18.7)	185	+2.0 (15.5)	<0.018
	FAS – phakic only	236	+5.0 (18.8)	121	+2.2 (14.4)	0.111
Mean change from baseline	FAS	369	-181.1 (198.6)	182	-142.7 (220.5)	0.022

in foveal thickness as assessed by OCT µm (SD)	FAS – phakic only	236	-166.8 (203.2)	121	-128.4 (216.8)	0.109

* Analysis of the proportion of patients with BCVA improvement of ≥15 letters from baseline used Cochran-Mantel-Haenszel chi-square test stratified by BCVA strata. Analysis of the average change in BCVA from baseline used an analysis of covariance model with treatment group and baseline visual acuity strata as fixed effects. Analysis of the average change in foveal thickness from baseline used an analysis of covariance model with treatment group and baseline visual acuity strata as fixed effects and baseline excess average foveal thickness as the covariate.
Abbreviation: BCVA, best corrected visual acuity, FAS, full analysis set, OCT, optical coherence tomography, SD, standard deviation.

Table A8.2. MEAD - primary and secondary efficacy endpoints at 36 months

Results at 36 months						
		DEX (0.7mg)		Sham		P-value*
Outcome, population		**N**	**Result**	**N**	**Result**	
Primary efficacy endpoint						
Proportion of patients who experienced an increase from baseline of ≥15 letters in BCVA in their study eye (%)	FAS[1]	351	22.2%	350	12.0%	<0.001
	Treatment experienced[2]	247	21.5%	261	11.1%	0.002
Secondary efficacy endpoints						
Mean change from baseline in BCVA letter score (SD)	FAS[1]	351	+ 3.5 (8.4)	350	+2.0 (8.0)	0.023
	Treatment experienced[2]	247	+3.2 (8.7)	261	+1.5 (7.5)	0.024
Mean change from baseline in central retinal thickness as assessed by OCT µm, (SD)	FAS[1]	351	-111.6 (134.1)	350	-41.9 (116.0)	<0.001
	Treatment experienced[2]	247	−126 (131)	261	−39 (121)	<0.001

[1]Boyer et al – 2014
[2]Augustin et al - 2015
* Analysis of the proportion of patients with BCVA improvement of ≥15 letters from baseline used the Cochran Mantel-Haenszel general association test stratified by study. Analysis of the average change in BCVA or CRT from baseline during the study (AUC approach) used an

analysis of covariance model with treatment and study as fixed effects and baseline BCVA or CRT as the covariate.
Abbreviations: AUC, area under the curve, BCVA, best corrected visual acuity, CRT, central retinal thickness, FAS, full analysis set, OCT, optical coherence tomography, SD, standard deviation.

ITC

A9. PRIORITY QUESTION: Please provide the EAG codes and anonymised data (IPD and estimates for naïve analysis) to enable replication of all the ITC methods used in this submission.

- **Please present the estimate and standard errors clearly stating the outcome and the analysis set used.**

Alimera Sciences are currently preparing a fully anonymised individual patient dataset, along with target patient characteristics for matching, and outcomes for dexamethasone intravitreal implant including central estimates and standard errors. This will be provided to the EAG alongside R scripts for reproducing all ITC analysis as soon as possible. Alimera Sciences will work with the EAG to enable secure transfer of these materials following submission of these clarifications.

A10. PRIORITY QUESTION: Please re-run the ITC analyses in patients with <u>phakic eyes only</u>, including the following effect modifiers in addition to the five already included: changes in glycaemic control over the 3 years, severity of cataract at baseline, and changes in blood pressure control.

a. Please provide information on the feasibility of this analysis, treatment effect modifiers, data inputs, results, and forest plots.

b. Please provide baseline characteristics (as per CS Table 28) for the ITC-phakic eyes only population.

The ITC analyses presented in the submission are based on a comparison of a combined phakic and pseudophakic lens patient population. This approach was taken as there is currently limited available published evidence for DEX intravitreal implant in a phakic lens only patient population, and none in treatment experienced patients. Additionally, the presence of the cataract was identified by clinicians interviewed as part of the ITC process as a treatment effect modifying factor, with the

potential to bias ITC results. As the presence of cataract is clearly linked to a patient's lens status, and there was a statistically significant imbalance in lens status between the treatment experienced subgroups of FAME and MEAD, this factor was included in the MAIC analysis presented in the submission to mitigate the potential bias introduced by between study heterogeneity. In this context, the requested analysis of an ITC based on the phakic subgroup of FAME and a combined phakic and pseudophakic population from MEAD is guaranteed to present a biased estimate of comparative efficacy between FAc and DEX intravitreal implants.
Regarding the additional treatment effect modifiers, data regarding the severity of cataract, changes in glycaemic control, and changes in blood pressure control over the three-year trial period have not been identified for MEAD. This means that the requested analysis is not possible to conduct. However, baseline characteristics between trials were consistent with respect to HbA1c (7.4% [SD 1.1] vs. 7.5% [1.0], in the ITC cohort of FAME and the treatment experienced cohort of MEAD, respectively). Furthermore, only hypertension was identified as a potential treatment effect modifying factor by clinicians interviewed as part of the ITC, and as other patient disease characteristics were otherwise well matched between the two trials, the inability to match on these variables is not anticipated to bias results in the presented ITC which is anchored by the sham arm of each trial.
These caveats notwithstanding, an additional set of ITC analyses have been produced based on the requested comparison between a phakic population treated with FAc intravitreal implant, and a combined phakic and pseudophakic population treated with DEX intravitreal implant has been undertaken, with results as follows. Alimera Sciences reiterate that this analysis should not be preferred to the ITC analysis presented in the submission, where between study heterogeneity has been mitigated, rather than artificially exacerbated.

Baseline characteristics

A total of 214 patients were included within the phakic only ITC cohort of FAME (FAc 0.2 mg; n=139; Sham: n=75), and 508 patients were included in the TE cohort of MEAD (DEX 0.7mg: n=247; Sham n=261). Demographic and baseline data for the two cohorts are summarised in the table below. In general, patient characteristics were well aligned between the trials; however, differences were observed in mean age at baseline, mean duration of diabetes, and mean central retinal thickness.

Table A10.1. Demographic and baseline data for the phakic only ITC cohort of FAME and MEAD

	FAME (phakic ITC cohort)			MEAD (TE cohort)			p-value[1]
	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)	**<0.001**
Gender - Male, n (%)	92 (66.2)	48 (64.0)	140 (65.4)	150 (60.7)	168 (64.4)	318 (62.6)	0.526
Race-Caucasian, n (%)	101 (72.7)	56 (74.7)	157 (73.4)	188 (76.1)	192 (73.6)	380 (74.8)	0.756
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)	0.508
Type 2	124 (89.2)	70 (93.3)	194 (90.7)	220 (89.1)	238 (91.2)	458 (90.2)	0.946
Not recorded	3 (2.2)	-	3 (1.4)	-	-		-
Mean duration of diabetes, yrs (SD)	14.8 (9.4)	13.8 (8.0)	14.4 (8.9)	16.4 (8.7)	16.2 (9.7)	16.3 (9.2)	**0.003**
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)	0.177
DMO characteristics							
Mean duration of DMO[2], yrs (SD)	2.4 (2.8)	2.9 (4.6)	2.6 (3.6)	2.3 (2.2)	2.7 (2.4)	2.5 (2.3)	0.888
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)	0.874
Mean CRT, µm (SD)	491 (125)	490 (119)	491 (123)	478 (153)	472 (131)	474 (142)	**0.047**
Lens status, n (%)							
Phakic	139 (100)	75 (100)	214 (100)	182 (73.7)	179 (68.6)	361 (71.1)	-
Pseudophakic	-	-	-	65 (26.3)	82 (31.4)	147 (28.9)	
Prior DMO treatment, n (%)							

	FAME (phakic ITC cohort)			MEAD (TE cohort)			p-value[1]
	FAc 0.19 mg	Treated sham	All	DEX 0.7 mg	Treated sham	All	
Laser	139 (100)	75 (100)	214 (100)	231 (93.5)	243 (93.1)	474 (93.3)	**<0.001**
Intravitreal steroid	21 (15.1)	10 (13.3)	31 (14.5)	58 (23.5)	61 (23.4)	119 (23.4)	**0.009**
Intravitreal anti-VEGF	NE*	NE*	NE*	25 (10.1)	26 (10.0)	51 (10.0)	-

[1]P-values were based on one-sample t-tests for continuous variables and chi-square tests for categorical variable, comparing values for the “All” cohort of both trails.

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

Abbreviations: anti-VEGF, anti-vascular endothelial growth factor, 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.

Population weighting and ESS

Matching on imbalanced baseline treatment effect modifiers did not substantially reduce the ESS of the FAME phakic only ITC cohort (n=173; ~ 14% reduction). Neither did matching on all potential treatment effect modifiers (N=173, ~19% reduction). Demographic and baseline characteristics for the re-weighted ITC cohorts are shown in Table A10.2 below.

Table A10.2. Reweighted demographic and baseline characteristics for FAME (ITC cohort – phakic only) following population matching on levels of effect modifying variables in MEAD (treatment experienced cohort)

	FAME – FAC 0.2 mg (ITC cohort – phakic only)			FAME – Treated sham (ITC cohort – phakic only)			FAME – ALL (ITC cohort – phakic only)			MEAD (TE) – All
	Pre-weighting	Weighting based on imbalanced EMs*	Weighting based all EMs*	Pre-weighting	Weighting based on imbalanced EMs*	Weighting based all EMs*	Pre-weighting	Weighting based on imbalanced EMs*	Weighting based all EMs*	Target values
n (ESS)	139	119	111	75	64	62	214	183	173	508
Demographic characteristics										
Mean age (SD), yrs	60.7 (9.1)	60.4 (9.3)	60.3 (8.0)	60.2 (8.5)	60.1 (8.1)	60.8 (9.3)	60.6 (8.9)	60.3 (8.9)	60.6 (8.9)	62.8 (8.9_
Gender - Male %	66.2	65.1	67.0	64.0	65.7	34.6	65.4	65.3	65.4	62.6
Race-Caucasian %	72.7	70.3	76.1	74.7	76.1	70.9	73.4	72.3	72.7	74.8
Diabetes characteristics										
Diabetes - Typ1 %	8.6	7.9	6.3	6.7	6.0	8.4	7.9	7.3	7.6	9.9
Mean duration of diabetes, yrs (SD)	14.8 (9.4)	14.7 (9.6)	13.7 (7.1)	13.8 (8.0)	13.6 (7.4)	14.8 (9.3)	14.4 (8.9)	14.3 (8.9)	14.4 (8.6)	16.3 (9.2)
Mean Hba1c % (SD)	7.5 (1.2)	7.5 (1.2)	7.3 (0.9)	7.3 (0.9)	7.3 (0.9)	7.5 (1.2)	7.4 (1.1)	7.4 (1.1)	7.4 (1.1)	4.5 (1.0)
DMO characteristics										

	FAME – FAC 0.2 mg (ITC cohort – phakic only)			FAME – Treated sham (ITC cohort – phakic only)			FAME – ALL (ITC cohort – phakic only)			MEAD (TE) – All
	Pre-weighting	Weighting based on imbalanced EMs*	Weighting based all EMs*	Pre-weighting	Weighting based on imbalanced EMs*	Weighting based all EMs*	Pre-weighting	Weighting based on imbalanced EMs*	Weighting based all EMs*	Target values
Mean BCVA letter score (SD)	55.6 (9.5)	56.3 (9.44)	55.6 (9.6)	56.2 (9.7)	56.1 (9.1)	55.7 (9.1)	55.8 (9.6)	56.2 (9.6)	55.7 (9.3)	55.7 (9.3)
Mean CRT, µm (SD)	491 (125)	475 (144)	468 (135)	490 (119)	471 (138)	477 (146)	491 (123)	474 (142)	474 (142)	474 (142)
Mean duration of DMO[2], yrs (SD)	2.4 (2.8)	2.4 (3.0)	2.7 (2.5)	2.9 (4.6)	2.5 (2.6)	2.4 (2.2)	2.6 (3.6)	2.4 (2.9)	2.5 (2.3)	2.5 (2.3)
Lens status, Phakic %	100	100	100	100	100	100	100	100	100	71.1

Notes: MAIC uses the approach proposed by Signorovitch et al., assigning weights to patients in the FAME ITC cohort based on aggregate levels of EMs in the MEAD TE cohort. Imbalanced EMs include baseline CRT. All EMs include baseline CRT, baseline BCVA, and duration of DMO.
Abbreviations: anti-VEGF, anti-vascular endothelial growth factor, 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.

Direct estimates of treatment efficacy and safety

Direct estimates of treatment efficacy and safety for FAc 0.19 mg versus sham, as calculated using patient-level data from FAME, are shown in the tables below. Estimates for the overall phakic ITC cohort, the adjusted ITC cohort after application of MEAD inclusion and exclusion criteria, and matched analysis cohorts are presented. Reported efficacy and safety estimands for DEX 0.7 mg versus sham for the MEAD trial (treatment experienced cohort) are also included for reference.(2) All analysis methods are otherwise consistent with those presented in the submission dossier.

Table A10.3. Efficacy estimands for FAME (phakic ITC cohort) and MEAD (treatment experienced cohort) used in ITC analyses

Trial	Population	Treatment group	BCVA						CRT		
			n	Proportion of patients 15-point letter scores at month 36 (%)	ETD vs Sham (SE)	n	Mean change from baseline in BCVA at month 36 (SD)	ETD vs Sham (SE)	n	Mean change from baseline in CRT at month 36 (SD)	ETD vs Sham (SE)
MEAD	Treatment experienced	DEX 0.7 mg	247	21.5	10.3 (3.26)	247 (167)	+3.2 (8.7)	1.6 (0.97)	247 (167)	−126 (131)	−85 (15.2)
		Treated sham	261	11.1	-	261 (114)	+1.5 (7.5)	-	261 (114)	−39 (121)	-
FAME	FAS - phakic	FAc 0.19 mg	236	28.4	8.6 (4.66)	236	+4.97 (18.8)	2.74 (1.96)	236	-167 (203)	-26 (20.3)_
		Treated sham	121	19.8	-	121	+2.23 (14.4)	-	121	-128 (217)	-
	ITC cohort (without censoring)	FAc 0.19 mg	139	30.2	11.5 (5.95)	139 (97)	+6.3 (10.7)	4.1 (1.72)	139 (95)	-173 (151)	-58 (21.6)
		Treated sham	75	18.7	-	75 (48)	+1.8 (8.2)	-	75 (44)	-110 (128)	-
	ITC cohort (with censoring)	FAc 0.19 mg	139	25.9	17.9 (4.86)	139 (60)	+7.8 (10.9)	5.4 (2.61)	139 (58)	-188 (140)	-94 (45.8)
		Treated sham	75	8.0	-	75 (12)	+2.1 (8.1)	-	75 (11)	-96 (143)	-
	MAIC – adjusting for	FAc 0.19 mg	119*	30.3	10.2 (6.67)	82*	+6.2 (10.3)	4.04 (1.68)	82*	-170 (164)	-72.8 (26.0)

Trial	Population	Treatment group	BCVA						CRT		
			n	Proportion of patients 15-point letter scores at month 36 (%)	ETD vs Sham (SE)	n	Mean change from baseline in BCVA at month 36 (SD)	ETD vs Sham (SE)	n	Mean change from baseline in CRT at month 36 (SD)	ETD vs Sham (SE)
	imbalanced EMs (without censoring)	Treated sham	64*	20.1	-	40*	+2.0 (7.9)	-	37*	-88 (126)	-
	MAIC – adjusting for imbalanced EMs (with censoring)	FAc 0.19 mg	119*	25.0	14.3 (5.83)	52*	+7.4 (10.4)	4.9 (2.88)	50*	-168 (143)	-97 (50.2)
		Treated sham	64*	10.6	-	11*	+2.5 (7.7)		10*	-78 (136)	-
	MAIC – adjusting for all EMs (without censoring)	FAc 0.19 mg	111*	31.9	11.2 (7.00)	76*	+6.5 (9.9)	-4.3 (1.64)	74*	-174 (167)	-76 (23.4)
		Treated sham	62*	20.7	-	39*	+2.2 (8.1)	-	35*	-86 (127)	-
	MAIC – adjusting for all EMs (with censoring)	FAc 0.19 mg	111*	26.1	15.5 (6.08)	46*	+7.6 (10.1)	-5.6 (2.77)	45*	-171 (146)	-109 (54.4)
		Treated sham	62*	10.6	-	10*	+2.0 (7.8)	-	10*	-68.0 (134)	-

Imbalanced EMs include baseline CRT. All EMs include baseline CRT, baseline BCVA, and duration of DMO.
Abbreviations: BCVA, best-corrected visual acuity, CRT, central retinal thickness, DEX 0.7 mg, dexamethasone intravitreal implant 0.7 mg, EM, effect modifier, ETD, estimated treatment difference, FAc 0.19 mg, fluocinolone acetonide intravitreal implant 0.19 mg, ITC, indirect treatment comparison, MAIC, matched adjusted indirect comparison, SD, standard deviation, SE, standard error.

Table A10.4. Safety estimands for FAME (Phakic ITC cohort) and MEAD (TE cohort) used in ITC analyses

Trial	Population	Treatment group	Proportion of patients reporting ocular AEs (%)								
			N (ESS)	Serious ocular AE[a]	RD vs Sham (SE)	N (ESS)	IOP-related AE[a]	RD vs Sham (SE)	N (ESS)	Cataract-related AE (in phakic eyes)	RD vs Sham (SE)
MEAD	Treatment experienced	DEX 0.7 mg	247	6.9	6.1 (1.70)	247	38.1	33.5 (3.35)	182	70.3	50.2 (4.52)
		Treated sham	261	0.8	-	261	4.6	-	179	20.1	-
FAME	FAS - phakic	FAc 0.19 mg	236	10.6	4.8 (2.92)	236	35.2	23.6 (4.26)	236	81.4	30.9 (5.20)
		Treated sham	121	5.8	-	121	11.6	-	121	50.4	-
	ITC cohort – phakic (without censoring)	FAc 0.19 mg	139	9.4	2.7 (3.79)	139	36.0	22.6 (5.65)	139	82.0	34.0 (6.63)
		Treated sham	75	6.7	-	75	13.3	-	75	48.0	-
	ITC cohort– phakic (with censoring)	FAc 0.19 mg	139	7.2	5.9 (2.56)	139	27.3	23.3 (4.41)	139	62.6	41.3 (6.26)
		Treated sham	75	1.3	-	75	4.0	-	75	21.3	-
	MAIC – phakic adjusting for imbalanced EMs[b] (without censoring)	FAc 0.19 mg	(119)	9.0	2.0 (4.14)	(119)	40.2	28.3 (6.06)	(119)	82.5	33.8 (7.10)
		Treated sham	(64)	7.0	-	(64)	11.8		(64)	48.7	-
	MAIC – phakic adjusting for imbalanced	FAc 0.19 mg	(119)	6.9	6.0 (2.47)	(119)	30.8	26.0 (5.33)	(119)	62.7	38.4 (7.15)
		Treated sham	(64)	0.9	-	(64)	4.7	-	(64)	24.3	-

Trial	Population	Treatment group	Proportion of patients reporting ocular AEs (%)								
			N (ESS)	Serious ocular AE[a]	RD vs Sham (SE)	N (ESS)	IOP-related AE[a]	RD vs Sham (SE)	N (ESS)	Cataract-related AE (in phakic eyes)	RD vs Sham (SE)
	EMs[b] (with censoring)										
	MAIC – phakic adjusting for all EMs[c] (without censoring)	FAc 0.19 mg	(111)	9.0	1.6 (4.45)	(111)	40.0	28.4 (6.12)	(111)	82.9	34.2 (6.95)
		Treated sham	(62)	7.4	-	(62)	11.6	-	(62)	48.7	-
	MAIC – phakic adjusting for all EMs[c] (with censoring)	FAc 0.19 mg	(111)	7.2	6.4 (2.77)	(111)	30.6	26.8 (5.22)	(111)	84.3	34.8 (7.11)
		Treated sham	(62)	0.8	-	(62)	2.8	-	(62)	49.5	-

[a] Any AE related to increased intraocular pressure or glaucoma.
[b] Imbalanced EMs includes mean CRT at baseline.
[c] All EMs include mean CRT at baseline, mean BCVA at baseline, and mean duration of DMO at baseline.
Abbreviations: AE - adverse events, DEX 0.7 mg - dexamethasone intravitreal implant 0.7 mg, EM - effect modifier, ESS – effective sample size, FAc 0.19 mg - fluocinolone acetonide intravitreal implant 0.19 mg, IOP - intraocular pressure, ITC - indirect treatment comparison, MAIC - matching adjusted indirect comparison, RD - risk difference, SD - standard deviation, SE - standard error.

Comparative efficacy

In the base-case MAIC analysis (adjusting for imbalanced treatment effect modifiers and censoring patients at the point of additional therapy) no significant differences were observed in the proportion of patients who gained ≥15 letters between the FAc 0.19 mg and DEX 0.7 mg groups. While directionality of the point estimate tended slightly towards FAc, the confidence intervals were wide and included the null (estimated treatment difference (ETD): [redacted]% (95% CI: [redacted]; p = [redacted]). Similar results were obtained from analyses employing alternative ITC methods. Similarly, for mean change from baseline in BCVA letter score, results from the base-case MAIC analysis demonstrated numerical but non-statistically significant improvement for FAc 0.19 mg over DEX 0.7 mg, with an ETD of [redacted] letters (95% CI: [redacted]; p = [redacted]). Consistent results were obtained from the non-censored analysis matching for imbalanced treatment effect modifiers (ETD: [redacted] letters [95% CI: [redacted]; p =[redacted]]), as well as from analyses matching for all treatment effect modifiers, the AITC, and the naïve analysis.

With respect to mean change from baseline in CRT, estimates derived from the base-case MAIC demonstrated equivalence of FAc 0.19 mg and DEX 0.7 mg intravitreal implants. While directionality of the point estimate slightly favoured FAc 0.19 mg, it was accompanied by a wide confidence interval (ETD: [redacted] µm ([redacted]; p = [redacted])). Similar results were obtained from analyses employing alternative ITC methods, with no significant differences between FAc and DEX intravitreal implants.

Full comparative efficacy results based on the phakic population of FAME are presented in the table and figures below.

Table A10.5. ITC analyses of FAc 0.19 mg versus DEX.07mg for key efficacy outcomes

Population – FAME	Population – MEAD	Endpoint	ETD FAc 0.19 mg vs DEX 0.7 mg[95%CI]	SE	P-value
	Treatment experienced	Proportion ≥15-letter	[redacted]	[redacted]	[redacted]

Population – FAME	Population – MEAD	Endpoint	ETD FAc 0.19 mg vs DEX 0.7 mg[95%CI]	SE	P-value
Naïve analysis - FAS - phakic only		improvement in BCVA			
		Change from baseline in BCVA	[redacted]	[redacted]	[redacted]
		Change from baseline in CRT	[redacted]	[redacted]	[redacted]
AITC - ITC cohort – phakic only (without censoring)	Treatment experienced	Proportion ≥15-letter improvement in BCVA	[redacted]	[redacted]	[redacted]
		Change from baseline in BCVA	[redacted]	[redacted]	[redacted]
		Change from baseline in CRT	[redacted]	[redacted]	[redacted]
AITC - ITC cohort – phakic only (with censoring)	Treatment experienced	Proportion ≥15-letter improvement in BCVA	[redacted]	[redacted]	[redacted]
		Change from baseline in BCVA	[redacted]	[redacted]	[redacted]
		Change from baseline in CRT	[redacted]	[redacted]	[redacted]
MAIC - phakic only adjusting for imbalanced EMs (without censoring)	Treatment experienced	Proportion ≥15-letter improvement in BCVA	[redacted]	[redacted]	[redacted]
		Change from baseline in BCVA	[redacted]	[redacted]	[redacted]
		Change from baseline in CRT	[redacted]	[redacted]	[redacted]
MAIC – phakic only adjusting for imbalanced EMs (with censoring)	Treatment experienced	Proportion ≥15-letter improvement in BCVA	[redacted]	[redacted]	[redacted]
		Change from baseline in BCVA	[redacted]	[redacted]	[redacted]
		Change from baseline in CRT	[redacted]	[redacted]	[redacted]
MAIC – phakic only adjusting for all EMs	Treatment experienced	Proportion ≥15-letter improvement in BCVA	[redacted]	[redacted]	[redacted]

Population – FAME	Population – MEAD	Endpoint	ETD FAc 0.19 mg vs DEX 0.7 mg[95%CI]	SE	P-value
(without censoring)		Change from baseline in BCVA	[redacted]	[redacted]	[redacted]
		Change from baseline in CRT	[redacted]	[redacted]	[redacted]
MAIC – phakic only adjusting for all EMs (with censoring)	Treatment experienced	Proportion ≥15-letter improvement in BCVA	[redacted]	[redacted]	[redacted]
		Change from baseline in BCVA	[redacted]	[redacted]	[redacted]
		Change from baseline in CRT	[redacted]	[redacted]	[redacted]

Abbreviations: AITC - adjusted indirect treatment comparison, BCVA - best corrected visual acuity, CRT – central retinal thickness, EM – effect modifier, ETD – estimated treatment difference, FAS – full analysis set, IOP - intraocular pressure, ITC - indirect treatment comparison, MAIC – matching adjusted indirect comparison, SE - standard error.

Figure A10.1. ITC analyses of FAc 0.19 mg versus DEX 0.7mg for the proportion of patients achieving ≥15-letter BCVA improvement from baseline to EOT

Abbreviations: AITC - adjusted indirect treatment comparison, BCVA - best-corrected visual acuity, CI - confidence interval, DEX 0.7 mg - dexamethasone intravitreal implant 0.7 mg, EOT - end of treatment, EM - effect modifier, ETD - estimated treatment difference, FAc 0.19 mg - fluocinolone acetonide intravitreal implant 0.19 mg, ITC - indirect treatment comparison, MAIC - matching-adjusted indirect comparison

Figure A10.2. ITC analyses of FAc 0.19 mg versus DEX 0.7mg for the mean change in BCVA letter score from baseline to EOT

Abbreviations: AITC - adjusted indirect treatment comparison, BCVA - best-corrected visual acuity, CI - confidence interval, DEX 0.7 mg - dexamethasone intravitreal implant 0.7 mg, EOT - end of treatment, EM - effect modifier, ETD - estimated treatment difference, FAc 0.19 mg - fluocinolone acetonide intravitreal implant 0.19 mg, ITC - indirect treatment comparison, MAIC - matching-adjusted indirect comparison.

Figure A10.3. ITC analyses of FAc 0.19 mg versus DEX 0.7mg for the mean change in CRT (µm) from baseline to EOT

Abbreviations: AITC - adjusted indirect treatment comparison, CRT - central retinal thickness, CI - confidence interval, DEX 0.7 mg - dexamethasone intravitreal implant 0.7 mg, EOT - end of treatment, EM - effect modifier, ETD - estimated treatment difference, FAc 0.19 mg - fluocinolone acetonide intravitreal implant 0.19 mg, ITC - indirect treatment comparison, MAIC - matching-adjusted indirect comparison

Comparative safety

In general, the proportion of patients experiencing serious ocular AEs, IOP-related AEs, and cataract-related AEs were similar between the FAc 0.19 mg treatment group of FAME and DEX 0.7mg treatment group of MEAD. ITC analyses for the proportion of patients experiencing ocular AEs further demonstrated comparability of FAc 0.19 mg and DEX 0.7 mg. In the base case MAIC analysis, there were no statistically significant differences observed in the proportion of patients reporting serious ocular AEs (ETD: [redacted] % (95% CI: [redacted]; p = [redacted])), IOP-related AEs (ETD: [redacted]% (95% CI: [redacted]; p = [redacted])), or cataract-related AEs (ETD: [redacted] (95% CI: [redacted]; p = [redacted])). Results were consistent across all analysis approaches.

Full comparative safety results based on the phakic population of FAME are presented in the table and figures below.

Table A10.6. ITC analyses of FAc 0.19 mg versus DEX.07mg for key safety outcomes

Population – FAME	Population – MEAD	Endpoint	ETD FAc 0.19 mg vs DEX 0.7 mg [95%CI]	SE	P-value
Naïve analysis - FAS - phakic only	Treatment experienced	Serious ocular AE	[redacted]	[redacted]	[redacted]
		IOP-related AE	[redacted]	[redacted]	[redacted]
		Cataract-related AE (in phakic eyes)	[redacted]	[redacted]	[redacted]
AITC - ITC cohort – phakic only (without censoring)	Treatment experienced	Serious ocular AE	[redacted]	[redacted]	[redacted]
		IOP-related AE	[redacted]	[redacted]	[redacted]
		Cataract-related AE (in phakic eyes)	[redacted]	[redacted]	[redacted]
AITC - ITC cohort – phakic only (with censoring)	Treatment experienced	Serious ocular AE	[redacted]	[redacted]	[redacted]
		IOP-related AE	[redacted]	[redacted]	[redacted]
		Cataract-related AE (in phakic eyes)	[redacted]	[redacted]	[redacted]
MAIC - phakic only adjusting for imbalanced EMs (without censoring)	Treatment experienced	Serious ocular AE	[redacted]	[redacted]	[redacted]
		IOP-related AE	[redacted]	[redacted]	[redacted]
		Cataract-related AE (in phakic eyes)	[redacted]	[redacted]	[redacted]
MAIC – phakic only adjusting for imbalanced EMs (with censoring)	Treatment experienced	Serious ocular AE	[redacted]	[redacted]	[redacted]
		IOP-related AE	[redacted]	[redacted]	[redacted]
		Cataract-related AE (in phakic eyes)	[redacted]	[redacted]	[redacted]
MAIC – phakic only adjusting for all EMs (without censoring)	Treatment experienced	Serious ocular AE	[redacted]	[redacted]	[redacted]
		IOP-related AE	[redacted]	[redacted]	[redacted]
		Cataract-related AE (in phakic eyes)	[redacted]	[redacted]	[redacted]
MAIC – phakic only adjusting for all EMs (with censoring)	Treatment experienced	Serious ocular AE	[redacted]	[redacted]	[redacted]
		IOP-related AE	[redacted]	[redacted]	[redacted]
		Cataract-related AE (in phakic eyes)	[redacted]	[redacted]	[redacted]

Abbreviations: AITC, adjusted indirect treatment comparison, AE - adverse event, ETD – estimated treatment difference, FAS – full analysis set, IOP - intraocular pressure, ITC - indirect treatment comparison, MAIC – matched adjusted indirect comparison.

Figure A10.4. ITC analyses of FAc 0.19 mg versus DEX 0.7mg for the proportion of patients experiencing serious ocular AEs

Abbreviations: AE -adverse event, AITC, - adjusted indirect treatment comparison, CI - confidence interval, DEX 0.7 mg - dexamethasone intravitreal implant 0.7 mg, EM - effect modifier, ETD - estimated treatment difference, FAc 0.19 mg - fluocinolone acetonide intravitreal implant 0.19 mg, ITC - indirect treatment comparison, MAIC - matching-adjusted indirect comparison.

Figure A10.5. ITC analyses of FAc 0.19 mg versus DEX.07mg for the proportion of patients experiencing cataract-related AEs (in phakic eyes)

Abbreviations: AE - adverse event, AITC - adjusted indirect treatment comparison, CI - confidence interval, DEX 0.7 mg - dexamethasone intravitreal implant 0.7 mg, EM - effect modifier, ETD - estimated treatment difference, FAc 0.19 mg - fluocinolone acetonide intravitreal implant 0.19 mg, ITC - indirect treatment comparison, MAIC - matching-adjusted indirect comparison.

Figure A10.6. ITC analyses of FAc 0.19 mg versus DEX.07mg for the proportion of patients experiencing IOP-related AEs (any AE related to increased intraocular pressure or glaucoma)

Abbreviations: AE - adverse event, AITC - adjusted indirect treatment comparison, CI - confidence interval, DEX 0.7 mg - dexamethasone intravitreal implant 0.7 mg, EM - effect modifier, ETD - estimated treatment difference, FAc 0.19 mg - fluocinolone acetonide intravitreal implant 0.19 mg, ITC - indirect treatment comparison, MAIC - matching-adjusted indirect comparison.

A11. Please re-run the overall ITC (phakic + pseudophakic) analysis with the additional treatment effect modifiers: severity of cataract at baseline, changes in glycaemic control over the 3 years and changes in blood pressure control

a. **Please provide information on the feasibility of this analysis, treatment effect modifiers, data inputs, results, and forest plots.**

As stated in the response to clarification question **A10**, data regarding the severity of cataract, changes in glycaemic control, and changes in blood pressure control over the three-year trial period have not been identified for MEAD. This means that the requested analysis is not possible to conduct. However, as previously stated, these factors are not anticipated to bias results in the presented ITC.

A12. PRIORITY QUESTION: Please provide the feasibility assessment for all the ITC methods utilised in the submission.

A full feasibility assessment was not conducted due to time constraints of the submission, however, please find attached to these clarifications a full ITC technical report describing the rationale for the ITC, the comparability of the evidence base, endpoints to be considered, statistical analysis methods and associated limitations.

A13. Please provide a table of which clinicians listed the treatment effect modifiers listed in appendix D.1.2 Table 7, i.e., like below:

Please see the table below for the response from each clinician on whether they believed a particular characteristic was a treatment effect modifier. Additional context has been provided regarding characteristics that they believed would be treatment effect modifiers, but only due to correlations with other factors. For example, race/ethnicity was highlighted as being a potential treatment effect modifier by two clinicians, but because of differences in average retinal thickness across different ethnicities; in these cases, the underlying cause was matched preferentially (i.e., matching on retinal thickness rather than race/ethnicity). One exception to this was lens status; clinicians advised that lens status would impact treatment effect due to correlations with the presence of cataract. As data was not available to match on presence of cataract between the studies, lens status was instead used as the matching variable. Hypertension was volunteered by two clinicians as an additional treatment effect modifier, as such, the opinion of clinician 3 on whether hypertension

is a potential treatment effect modifier has been omitted as they were not explicitly asked for their opinion.

Table A13.1. Outcomes of clinician survey of treatment effect modifiers

Patient characteristics	Clinician 1	Clinician 2	Clinician 3	Independent TEM?
Demographic characteristics				
Age	No	Yes	No	Yes
Sex	No	No	No	No
Race/ethnicity	Correlated with retinal thickness	Correlated with retinal thickness	No	No
Diabetes history				
Diabetes type (type 1 vs. type 2)	No	No	No	No
Duration of diabetes	Duration of diabetes is correlated with duration of DMO	Duration of diabetes is correlated with duration of DMO	No	No
HbA1c	HbA1c is correlated with duration of DMO	HbA1c is correlated with duration of DMO	No	No
Eye characteristics				
Duration of DMO	Yes	Yes	Yes	Yes
Classification of DMO	Correlated with retinal thickness	Correlated with retinal thickness	Correlated with retinal thickness	No
Prior treatment for DMO	Yes	Yes	Yes	Yes
Prior treatment type for DMO	Yes	Yes	Yes	Yes
Lens status (phakic vs. pseudophakic)	Correlated with presence of cataract	Correlated with presence of cataract	No	No
Macular perfusion status (ischaemic vs. non-ischaemic)	No	No	No	No
Presence of cataract	Yes	Yes	No	Yes
Central subfield retinal thickness	Yes	Yes	Yes	Yes
Intraocular pressure	No	No	No	No
Baseline Visual Acuity (EDTRS letter score)	Yes	Yes	Yes	Yes
Volunteered by the clinician				
Hypertension	Yes	Yes	-	Yes

A14. Please tabulate the number of people from FAME and MEAD included in the ITC analyses presented in Figure 9, 10, 11 in B.3.9.3 and Figures 5, 6, 7 in Appendix J in the form.

Please see the completed tables below, showing sample size and effective sample size for efficacy outcomes from FAME, safety outcomes for FAME, and all outcomes for MEAD, respectively.

Table A14.1. FAME - Sample size and effective sample size for ITC analyses – efficacy endpoints

FAME					
ITC Method	**Outcome**	**Source**	**Total N**	**ESS for this analysis**	**% of total**
MAIC - matching on imbalanced EMs - censored	Proportion of patients achieving ≥15-letter BCVA improvement from baseline to EOT	B.3.9.3.4 Figure 9	339	294	86.7
MAIC - matching on imbalanced EMs - uncensored	Proportion of patients achieving ≥15-letter BCVA improvement from baseline to EOT	B.3.9.3.4 Figure 9	339	294	86.7
MAIC- matching on all EMs - censored	Proportion of patients achieving ≥15-letter BCVA improvement from baseline to EOT	B.3.9.3.4 Figure 9	339	287	84.7
MAIC- matching on all EMs - uncensored	Proportion of patients achieving ≥15-letter BCVA improvement from baseline to EOT	B.3.9.3.4 Figure 9	339	287	84.7
AITC - censored	Proportion of patients achieving ≥15-letter BCVA improvement from baseline to EOT	B.3.9.3.4 Figure 9	339	339	100
AITC - uncensored	Proportion of patients achieving ≥15-letter BCVA improvement from baseline to EOT	B.3.9.3.4 Figure 9	339	339	100
Naïve analysis	Proportion of patients achieving ≥15-letter BCVA improvement from baseline to EOT	B.3.9.3.4 Figure 9	561	561	100
MAIC - matching on imbalanced EMs - censored	Mean change from baseline in BCVA at month 36 (SD)	B.3.9.3.4 Figure 9	109	96	88.1
MAIC - matching on imbalanced EMs - uncensored	Mean change from baseline in BCVA at month 36 (SD)	B.3.9.3.5 Figure 10	238	205	86.1
MAIC- matching on all EMs - censored	Mean change from baseline in BCVA at month 36 (SD)	B.3.9.3.5 Figure 10	109	92	84.4

MAIC- matching on all EMs - uncensored	Mean change from baseline in BCVA at month 36 (SD)	B.3.9.3.5 Figure 10	238	199	83.6
AITC - censored	Mean change from baseline in BCVA at month 36 (SD)	B.3.9.3.5 Figure 10	109	109	100
AITC - uncensored	Mean change from baseline in BCVA at month 36 (SD)	B.3.9.3.5 Figure 10	238	238	100
Naïve analysis	Mean change from baseline in BCVA at month 36 (SD)	B.3.9.3.5 Figure 10	561	561	100
MAIC - matching on imbalanced EMs - censored	Mean change from baseline in CRT at month 36 (SD)	B.3.9.3.5 Figure 10	105	92	87.6
MAIC - matching on imbalanced EMs - uncensored	Mean change from baseline in CRT at month 36 (SD)	B.3.9.3.6 Figure 11	230	198	86.1
MAIC- matching on all EMs - censored	Mean change from baseline in CRT at month 36 (SD)	B.3.9.3.6 Figure 11	105	88	83.8
MAIC- matching on all EMs - uncensored	Mean change from baseline in CRT at month 36 (SD)	B.3.9.3.6 Figure 11	230	192	83.5
AITC - censored	Mean change from baseline in CRT at month 36 (SD)	B.3.9.3.6 Figure 11	105	105	100
AITC - uncensored	Mean change from baseline in CRT at month 36 (SD)	B.3.9.3.6 Figure 11	230	230	100
Naïve analysis	Mean change from baseline in CRT at month 36 (SD)	B.3.9.3.6 Figure 11	561	561	100

Imbalanced EMs include lens status (% phakic at baseline) and mean CRT at baseline.
All EMs include lens status (% phakic at baseline), mean CRT at baseline, mean BCVA at baseline, and mean duration of DMO at baseline.
Abbreviations: BCVA - best-corrected visual acuity, CRT - central retinal thickness, EM - effect modifier, ESS - effective sample size, , ITC - indirect treatment comparison, MAIC - matching adjusted indirect comparison, SD - standard deviation.

Table A14.2. FAME - Sample size and effective sample size for ITC analyses – Safety endpoints

FAME					
ITC Method	**Outcome**	**Source**	**Total N**	**ESS for this analysis**	**% of total**
MAIC - matching on imbalanced EMs - censored	Serious ocular AE	Appendix J Figure 5	339	294	86.7
MAIC - matching on imbalanced EMs - uncensored	Serious ocular AE	Appendix J Figure 5	339	294	86.7
MAIC- matching on all EMs - censored	Serious ocular AE	Appendix J Figure 5	339	287	84.7
MAIC- matching on all EMs - uncensored	Serious ocular AE	Appendix J Figure 5	339	287	84.7
AITC - censored	Serious ocular AE	Appendix J Figure 5	339	339	100
AITC - uncensored	Serious ocular AE	Appendix J Figure 5	339	339	100
Naïve analysis	Serious ocular AE	Appendix J Figure 5	561	561	100
MAIC - matching on imbalanced EMs - censored	IOP-related AE	Appendix J Figure 6	339	294	86.7
MAIC - matching on imbalanced EMs - uncensored	IOP-related AE	Appendix J Figure 6	339	294	86.7
MAIC- matching on all EMs - censored	IOP-related AE	Appendix J Figure 6	339	287	84.7
MAIC- matching on all EMs - uncensored	IOP-related AE	Appendix J Figure 6	339	287	84.7
AITC - censored	IOP-related AE	Appendix J Figure 6	339	339	100
AITC - uncensored	IOP-related AE	Appendix J Figure 6	339	339	100
Naïve analysis	IOP-related AE	Appendix J Figure 6	561	561	100

MAIC - matching on imbalanced EMs - censored	Cataract-related AE (in phakic eyes)	Appendix J Figure 7	214	195	91.1
MAIC - matching on imbalanced EMs - uncensored	Cataract-related AE (in phakic eyes)	Appendix J Figure 7	214	195	91.1
MAIC- matching on all EMs - censored	Cataract-related AE (in phakic eyes)	Appendix J Figure 7	214	191	89.3
MAIC- matching on all EMs - uncensored	Cataract-related AE (in phakic eyes)	Appendix J Figure 7	214	191	89.3
AITC - censored	Cataract-related AE (in phakic eyes)	Appendix J Figure 7	214	214	100
AITC - uncensored	Cataract-related AE (in phakic eyes)	Appendix J Figure 7	214	214	100
Naïve analysis	Cataract-related AE (in phakic eyes)	Appendix J Figure 7	357	357	100
Imbalanced EMs include lens status (% phakic at baseline) and mean CRT at baseline. All EMs include lens status (% phakic at baseline), mean CRT at baseline, mean BCVA at baseline, and mean duration of DMO at baseline. Abbreviations: AE, adverse event, EM - effect modifier, ESS - effective sample size, , ITC - indirect treatment comparison, MAIC - matching adjusted indirect comparison, SD - standard deviation.					

Table A14.3. MEAD - Sample size and effective sample size for ITC analyses – Efficacy and safety endpoints

MEAD					
ITC Method	**Outcome**	**Source**	**Total N**	**ESS for this analysis**	**% of total**
All ITC methods	Proportion of patients achieving ≥15-letter BCVA improvement from baseline to EOT	B.3.9.3.4 Figure 9	508	508	100
	Mean change from baseline in BCVA at month 36 (SD)	B.3.9.3.5 Figure 10	Proportion of patients contributing to analysis at month 36 was not reported. Only baseline N was provided.		
	Mean change from baseline in CRT at month 36 (SD)	B.3.9.3.6 Figure 11			
	Serious ocular AE	Appendix J Figure 5	508	508	100
	IOP-related AE	Appendix J Figure 6	508	508	100
	Cataract-related AE (in phakic eyes)	Appendix J Figure 7	361	361	100
Abbreviations: AE, adverse event, BCVA - best-corrected visual acuity, CRT - central retinal thickness, EM - effect modifier, ESS - effective sample size, , ITC - indirect treatment comparison, MAIC - matching adjusted indirect comparison, SD - standard deviation.					

A15. Why does the N of FAc 0.2 mg in Figure 5 (n=376) not match up to the N of this group in Table 8 (n=375)?

One additional patient was enrolled in FAME that met the inclusion criteria of MEAD for eligibility of inclusion in the ITC cohort, however, this patient never received study treatment and had no post-screening measurements. As such, they do not contribute to the analysis of FAME.

Section B: Clarification on cost-effectiveness data

FAME trial

B1. Please confirm that all FAME data in the economics relates to the 0.2µg fluocinolone arm pooled across FAME A and FAME B.

This is correct. The model uses data directly from the pooled FAME trials to parametrise two aspects: the number and timing of re-implantations, and the average number of phakic DMO eyes per person. Each of the supporting analyses, using individual patient data and produced for this evaluation, excluded participants in the high dose 0.5µg FAc treatment arm.

B2. PRIORITY QUESTION: The EAG assumes that Document B Table 35 is a tabulation of Document B Figure 13. If not, please tabulate the data of Figure 13.

a. **Table 35 has columns labelled as ITC. Is this the raw data from the FAME subgroup of the N=221 of Table 28; i.e., no statistical ITC in terms of remaining on treatment and dosing has been performed?**

b. **Please augment Table 35 with the data for the FAS phakic patients, pooled across the FAME trials.**

Yes, Document B Table 35 is a tabulated form of Document B Figure 13. Both are reproduced in the model in the 'Retreatment IPD' worksheet.

a) In Document B Table 36, the column headed 'FAME population: ITC, FAc' uses the whole ITC population (N=221). These are simple counts from this adjusted-to-match population. The data in the column headed 'FAME population: Phakic ITC, FAc' is the phakic subgroup of this ITC population (n=139).

b) Document B Table 35 is updated - below - to include data for the FAS phakic patients of the pooled FAME trials (third column)

Table B2.1. Timing and number of retreatments at 3-monthly intervals (CS Table 35, updated)

Years	FAME population: FAS, FAc		FAME population: Phakic FAS, FAc		FAME population: ITC, FAc		FAME population: Phakic ITC, FAc	
	Remaining in-study (%)	Retreated (uncensored), %	Remaining in-study (%)	Retreated (uncensored), %	Remaining in-study (%)	Retreated (uncensored), %	Remaining in-study (%)	Retreated (uncensored), %
0.00	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.50	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.75	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1.00	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1.25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1.50	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1.75	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2.00	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2.25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2.50	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2.75	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3.00	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

B3. Please clarify if Document B Table 35 implies that among those remaining in the study the proportions being retreated would be calculated as (Retreated (uncensored), %) divided by (Remaining in-study (%)).

The given calculation formula would produce the suggested adjusted proportion. However, Table 35 of Document B is supplied as contextual information; the model uses per cycle retreatment proportions from column F in 'Retreatment IPD'. The proportions here are not adjusted conditional on completing the 36-month follow-up of the FAME trials. This condition, a trial design specification, is not applied in real-world clinical practice.

B4. Please augment Document B Table 36 with FAME pooled (1) ITC all patient data, (2) ITC phakic patient data and (3) FAS phakic patient data.

a. **Please also present the means (s.d.s) and median for fluocinolone.**

Document B Table 36 is reproduced below with the addition of data for the following subpopulations in the final three columns: FAS phakic, ITC all patient, ITC phakic.

Table B4.1 Reported number of eyes administered retreatment with intravitreal steroid implant (CS Table 36, updated)

Number of study treatments	MEAD. All DEX patients (n=347)(3)	FAME. All FAc patients (n=376)(4)	FAME. FAS – Phakic only FAc patients (n=235)	FAME. ITC cohort – All FAc patients (n=221)	FAME. ITC cohort - Phakic only FAc patients (n=139)
1, n (%)	44 (12.7)	- (74.4)	171(72.8)	152 (68.8)	94 (67.6)
2, n (%)	54 (15.6)	- (21.6)	54 (22.9)	58 (26.2)	37 (26.6)
3, n (%)	39 (11.2)	- (4%) *	9 (3.8)	9 (4.1)	7 (5.0)
4, n (%)	42 (12.1)	-	1 (0.4)	2 (0.9)	1 (0.7)
5, n (%)	49 (14.1)	-	-	-	-
6, n (%)	88 (25.4)	-	-	-	-
7, n (%)	31 (8.9)	-	-	-	-
Mean (SD)	4.1 (2.0)	1.3 (0.6)	1.3 (0.6)	1.4 (0.6)	1.4 (0.6)
Median	4	1	1	1	1
* received ≥3 study treatments					

B5. Please clarify if within Document B Table 38 FAME_1 is the ITC FAME phakic data, FAME_2 is the FAME all patient FAS data.

a. **What is the rationale for preferring the all patient FAS data over the all patient ITC data?**

Yes, the FAME_1 data in Document B Table 38 is the ITC phakic population; and the FAME_2 data in the table is the FAS population. Please accept our apologies for the labelling errors; the correct labelling of FAME retreatment populations is given in the table below. Neither FAME_1 or FAME_2 data are adjusted for trial completion.

Table B5.1 Labelling corrections in the model

Label error location	Erroneous label	Correct label
'Retreatment' cell J8 and B63	ITC phakic completer population FAc 0.19 mg - BASECASE	ITC phakic population FAc 0.19 mg - BASECASE
'Retreatment' cell J9 and K63	FAS completer population FAc 0.19 mg	FAS population FAc 0.19 mg

In the company base case, the FAME_1 data is used for per cycle retreatment proportions, and this is based on counts from the ITC phakic population. However, the supplied trial-based alternative to the base case is, as the EAG has identified, based on the all patient/FAS population. This population was used to provide context to the phakic restriction. We expect the model base case finding to be insensitive to a switch from ITC phakic to FAS phakic data.

Treatment

B6. What is the rationale for the fluocinolone RWE retreatment being at 3 years for Medisoft, 3 years for Birmingham and 2.5 years for the NHS majority?

The timing of second implants when these real-world study data were imputed into the model was based on the mean times to implant. These are provided in

Table B6.1 below.

Table B6.1. Determination of maximum duration of treatment in the model

Study name	Reference name in model	Reported mean time to second implant	Implemented time in model, years (given quarter-year model cycles)
RWE - MediSoft (Bailey 2022)(5)	RWE_1	1160.7 days (~3.2 years)	3.0
RWE - Birmingham & Midlands Eye Centre (Dobler 2023)(6)	RWE_2	38±4 months	3.0
RWE - IRiSS (Khoramnia 2022)(7)	RWE_3	986.1±318.0 days	2.5

B7. What is the rationale for the maximum treatment duration with fluocinolone being 5.25 years compared to 5 years for dexamethasone?

The calculation of the maximum treatment duration of FAc (5.25 years) is described in Document B, Figure 13, page 116 as follows: *'In the base case, FAc discontinuation is estimated to be at 5.25 years, that is 9 cycles or 2.75 years after the final implant in cycle 12, 2.75 years after the first implant. DEX discontinuation is estimated to be at 5.0 years, that is 3 cycles or 0.75 years after the final occasion of implant, which is in cycle 17, 4.25 years after the first implant.'* This is represented in the model by cells 'Retreatment' K40:L49.

A period of 2.75 years (9 cycles) was chosen for the duration of effect for the second implant. This is based on the average re-implantation interval across the two RCT sources and three RWE sources (2.7 years, calculated using 'Retreatment' cells H8:H12.

The calculation of the maximum treatment duration of Dex (5.00 years) is described Document B, but in the text above Figure 13, on page 115. 'In TA824 the submitting company argued that DEX would not continue past 5 years'. Indeed, in the modelling of TA824, DEX was resourced through all five years.(8)

Miscellaneous

B8. Please state the source and if applicable subgroup of the 235/375 for the rate of cataract extraction.

With apologies, the original source for the modelled cataract extraction rates cannot at this time be identified. A revised source is provided.

Campochiaro and colleagues report: *Forty-eight patients in the low-dose FAc group who were phakic at baseline (N=375) had not had cataract surgery by month 36.(4)* Annualisation of this one-off event from a three-year count results in an annual risk of 41.1% based on 327 eyes with cataract extraction (see cell range 'MRU and Adverse events' P11:R12). Clinical expert feedback from our survey of medical resource use was that cataract extraction would be equally frequent across the two corticosteroid implant strategies, FAc and DEX. Original and revised estimates are provided below. The net saving output of the model is not changed by these new cataract extraction input estimates.

Table B8.1. Original and revised cataract extraction rates used in the model

Cataract extraction rates used in the model	Strategy	Year 1	Year 2	Year 3+
Rates used in original model v1.0 submitted 6 October 2023	FAc	12.3%	49.5%	17.4%
	Dex	12.3%	49.5%	17.4%
Revised rates	FAc	41.1%	41.1%	41.1%
	Dex	41.1%	41.1%	41.1%

B9. Please clarify the source and calculation of the 1.596 cataract adjustment for the phakic population.

This adjustment was intended to inflate the originally sourced proportion of patients undergoing cataract extraction to reflect a phakic only population. Inflation was not necessary given that cataract extraction is not possible in the pseudophakic eye. In any case, the source is updated and the adjustment is not required.

B10. The cost of cataract extraction does not appear to be conditioned by the annual risk of cataract extraction, *Unit costs* D57. Is this the intention?

a. Please also clarify the source and calculation of the 2.32% annual risk estimate.

This is an annualised probability of cataract extraction from the population-based Blue Mountains Eye Study, in which cataract formation resulted in a cumulative incidence of cataract surgery in DMO patients of 20.9% over 10 years.(9) However, this rate was not used in the model but was artifactually included. The model uses the cataract extraction rates described in question B8, which represent IVI steroid therapy-based risks.

B11. Please clarify why in the excel model, MEAD-1 has a follow up of 3.00 years while MEAD-2 has a follow up of 3.25 years.

The follow-up period for scenarios MEAD_1 and MEAD_2 should in both cases be 3.0 years. In the submitted model the follow-up period for MEAD_2 was given as 3.25 years. When corrected to 3.0 years, and the scenarios analysis macro is re-run, there is a slight improvement in net saving between the corticosteroid strategies.

Whilst investigating this query a coding error relating to pick-up of appropriate scenario data was identified. 'Retreatment' R28:R40 should use the data for MEAD_2 given in cells 'Retreatment' X219:X232. A revised model is not provided, it is considered more practical for the coding for this scenario to be corrected by the EAG.

Table B11.1. Revised scenario outputs for model cells 'Scenarios' G32:36

Scenario	Results before coding correct, using MEAD_2 follow-up period 3.25	Results with coding correction, using MEAD_2 follow-up period 3.00
RCT - FAME - ITC phakic population FAc 0.19 mg - BASECASE	-£2,543	-£2,431
RCT - FAME - FAS population FAc 0.19 mg	-£2,896	-£2,784

RWE - MediSoft (Bailey 2022) - All NHS eyes	-£3,471	-£3,360
RWE - Birmingham & Midlands Eye Centre (Dobler 2023) - All NHS eyes	-£3,458	-£3,346
RWE - IRiSS (Khoramnia 2022) - Majority NHS eyes (31/47 centres)	-£3,785	-£3,674

B12. Please clarify if within the excel model, the adverse events rates are not per patient during follow-up but per implant, and if so, how this is aligned with the adverse event data presented in Document B.3.10.

In the model, medical resource use is divided into categories of Routine disease management, Complications of disease, and Treatment-related adverse events. CS section B.3.10 (ITC) describes treatment-emergent adverse events in the FAME and MEAD trials in three 'bundles': serious ocular adverse events, cataract-related adverse events, and intraocular pressure-related adverse events (these three were grouped and subject to an indirect treatment comparison. Results are presented in section B.3.9.3.7 and given again in the table below). No statistically significant differences were observed between FAc and DEX in the proportion of patients reporting serious ocular AEs, IOP-related AEs, or cataract-related AEs.

Table B12.1. ITC analyses of FAc 0.19 mg versus DEX.07 mg for the proportion of patients reporting ocular AEs (CS, Table 30)

ITC safety outcome	MAIC CENSORED			MAIC UNCENSORED		
	FAc 0.19 mg vs sham (SE)	DEX 0.7 mg vs sham (SE)	FAc 0.19 mg vs DEX 0.7 mg ETD [95%CI; P-value]	FAc 0.19 mg vs sham (SE)	DEX 0.7 mg vs sham (SE)	FAc 0.19 mg vs DEX 0.7 mg ETD [95%CI; P-value]
Serious ocular AE	10.9 (2.49)	6.1 (1.70)	[redacted]	8.6 (3.80)	6.1 (1.70)	[redacted]
IOP-related AE*	25.5 (3.84)	33.5 (3.35)	[redacted]	26.1 (4.54)	33.5 (3.35)	[redacted]

Cataract-related AE (in phakic eyes)	41.5 (6.52)	50.2 (4.52)	[redacted]	38.4 (6.88)	50.2 (4.52)	[redacted]
*Any AE related to increased intraocular pressure or glaucoma Abbreviations: AE, adverse event, DEX 0.7 mg, dexamethasone intravitreal implant 0.7 mg, DMO, diabetic macular oedema, ETD, estimated treatment difference, FAc 0.19 mg, fluocinolone acetonide intravitreal implant 0.19 mg, IOP, intraocular pressure, ITC, indirect treatment comparison, TE, treatment experienced.						

Cataract and intraocular pressure-related adverse events (as discussed in CS section B.3.10) relate to two out of the three the items within the Complications of disease category: Raised IOP and Cataract extraction. The third that is modelled is vitrectomy - a procedure to remove of the vitreous and replace with another solution - which is associated with a variety of eye problems. Whilst these three events are not termed adverse events in the model, they can be considered adverse events since corticosteroid therapy is known to have effect on their frequency (see section B.3.10).

Beyond cataract and intraocular pressure-related adverse events, the model also considers endophthalmitis, vitreous haemorrhage, and retinal detachment, which as serous ocular events were included in previous economic models for DMO because they may require medical or surgical intervention.(8, 10)

Table B12.2. Adverse events described in B.3 implemented in the model

Term used in CS B.3	Method of inclusion in the model	Overall ITC finding (CS B3.9)	ITC adjusted proportion of patients over 3-years	Model input estimate and mode of application
Serious ocular AE	TRAE, endophthalmitis	No statistically significant differences were observed between	FAc 10.9% DEX 6.1%	FAc & DEX Proportion per IVI admin 0.4%
	TRAE, vitreous haemorrhage			FAc & DEX Proportion per IVI admin 0.4%

	TRAE, retinal detachment	FAc and DEX		FAc & DEX Proportion per IVI admin 0.2%
IOP-related AE	Complication of disease, Raised IOP		FAc 25.5% DEX 33.5%	FAc & DEX Proportion per DMO eye Y1: 25.8% Y2: 13.2% Y3+: 9.2%
Cataract-related AE (in phakic eyes)	Complication of disease, Cataract extraction		FAc 41.5% DEX 50.2%	FAc & DEX Proportion/ phakic DMO eye Y1: 12.3% Y2: 49.5% Y3+: 17.4% **Updated model submitted Nov 2023** **Annual rate, FAc and Dex: 41.1%**
Not described	Complication of disease, Vitrectomy		n/a	FAc Proportion/ phakic DMO eye Y1: 2% Y2: 4% Y3+: 4.4% Dex Proportion/ phakic DMO eye Y1: 1% Y2: 1% Y3+: 2.2%

In terms of implementation within the model, the cost analysis applies the cost of resources for Complications of disease on a per eye basis, and the Treatment-related adverse events on a per implant administration basis. The three complications of disease events are included in the model according to a time-dependent risk in cells ‘Cost analysis’ W7:Y31 and W37:Y61 for FAc and DEX strategies respectively. The cost of these complications of disease are applied whether ‘on’ or ‘off’ steroid treatment. The three treatment-related adverse events included in the model are endophthalmitis, vitreous haemorrhage, and retinal

detachment. The rates for these TRAEs are described in the model as the 'proportion per admin' ('MRU and Adverse events' Cells AA8:AC8). To clarify, this is intended as the proportion of eyes experiencing the adverse event per implant administration. The implementation in the model is coded in cells 'Cost analysis' Z7:AB31 for the FAc strategy, and Z37:AB61 for the DEX strategy. In each of these cells, the per implant adjustment is made via the column O, the per cycle proportion administered implant.

Section C: Textual clarification and additional points

SLR of clinical, cost and healthcare resource use

C1. Document B.3.1.1 states that "427 records underwent full text screening, resulting in the exclusion of 402 records." However, Appendix D.1.1, Table 3 only lists 133 excluded studies. Please provide a list of all excluded studies including reasons for exclusion and, author and year information.

The 133 excluded studies highlighted in Appendix D.1.1 are journal articles only, the remaining excluded studies were records identified from clinical trial databases. A full list of excluded records (totalling 402 records) and rationale for exclusion are provided alongside these clarifications

C2. Document B.3.1.1 states that "71 records were set aside for backwards referencing". Please provide more information on this process, in particular what criteria were used to identify these records? Does "backwards referencing" mean manual reference list checking?

That is correct; studies identified that did not meet the inclusion criteria of the clinical SLR but did potentially include references to relevant data were set aside, and their reference lists manually checked to ensure all relevant references were captured within the clinical SLR.

C3. Please provide details of the search strategies and sources used for the targeted searching undertaken to identify further FAc and DEX real-world studies with NHS retreatment information (beyond those included in the

systematic reviews by Fallico et al and Bucolo et al). (Document B.4.2.7 and Appendix G)

A literature search was done to identify real-world studies relevant to the decision problem for this evaluation and to current UK clinical practice. However, no formal structured methods as per NICE or Cochrane manuals for a SLR were implemented. The company considered that a non-systematic literature search would be sufficiently informative to supplement the independent SLRs conducted by Fallico et al. and Bucolo et al. This approach was deemed justified firstly on the basis of Alimera Sciences being very close to the literature in DMO and informed about all real- world studies being performed in the NHS. Secondly, Alimera Sciences readily and frequently leverage advisory and support from NHS key opinion leaders in the DMO space to understand treatment practices and real-world experience, and implications on NHS service delivery and budget for the FAc implant and other treatment modalities (corticosteroid and non-corticosteroid therapies) utilised in the clinical management of DMO. Expert consultation was thus sought as it is considered that clinical experts in the NHS can reliably inform reinjection rates in the real-world setting. NHS based UK key opinion leaders in DMO are readily aware of real-world practices and norms and the body of clinical evidence generation both done and underway in the NHS in this specialist area. The real-world data supporting reinjection rates used to support the cost comparison model in the CS are considered consistent and representative of reinjection trends for both the FAc and DEX implants in daily clinical practice in the NHS. Both subject matter expert feedback and outputs from our literature search outputs align; however, we acknowledge that this non-systematic approach does not allow for replication.
The company considers that the real-world data identified and presented in the CS enables representative extrapolation of re-injection rates relevant to patient care and unmet need within the NHS.

C4. Please correct the value of the AITC Censored analysis in Figure 6 in Appendix J. The value says 3.9 but this is incorrect given the accompanying figure.

With apologies for the error, the company has noted that the tables and figures in Appendix J were not taken from the final ITC. Please find attached an updated version of Appendix J with corrected analysis values.

C5. The reference to Yang 2015 (reference 12) is cited as Yang Y, Bailey C, Loewenstein A, Massin P. INTRAVITREAL CORTICOSTEROIDS IN DIABETIC MACULAR EDEMA: PHARMACOKINETIC CONSIDERATIONS. Retina. 2015;35(12):2440-9. We believe the correct reference should be: Yang Y, Bailey C, Holz FG, et al. Long-term outcomes of phakic patients with diabetic macular oedema treated with intravitreal fluocinolone acetonide (FAc) implants. Eye (London, England) 2015;29(9):1173-80. Could the company confirm if this is correct?

Yes, this correct. We apologise for this error.

In terms of the Yang et al paper reference number 12 (Yang Y, Bailey C, Loewenstein A, Massin P. INTRAVITREAL CORTICOSTEROIDS IN DIABETIC MACULAR EDEMA: PHARMACOKINETIC CONSIDERATIONS. Retina. 2015;35(12):2440-9),. Please note that this reference applies only to page 16 of the CS whereby the pharmacokinetic properties of intravitreal corticosteroids are discussed. All other annotated references to the Yang et al manuscript should reference “Long-term outcomes of phakic patients with diabetic macular oedema treated with intravitreal fluocinolone acetonide (FAc) implants. Eye (London, England) 2015;29(9):1173-80.” A PDF of this second Yang et al. publication is attached.

C6. Please provide information for footnote 2 in CS Table 28.

The superscript 2 in Table 28 is a legacy footnote and should have been deleted. We apologise for this error.

REFERENCES

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NICE National Institute for Health and Care Excellence

Cost Comparison Appraisal

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

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

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- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	Diabetes UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Diabetes UK is the country's leading diabetes charity representing the 4.9 million people living with diabetes in the UK. We help people manage their diabetes effectively by providing information, advice and support. We campaign with people with diabetes and healthcare professionals to improve the quality of diabetes care across the UK's health services. We fund pioneering research into care, cure and prevention for all types of diabetes. The majority of Diabetes UK's income is from legacies and donations. We also earn income from activities which support our charitable mission, such as our Diabetes UK Professional Conference. A small percentage of our income is from support for specific programmes of work from or sponsorship of events by the pharmaceutical industry. We are a growing community with more than 300,000 supporters nationwide – including people with diabetes, their friends and families – and more than 100,000 lay and healthcare professional members.

4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	No
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	Conversations with diabetes specialist healthcare professionals

Current treatment of the condition in the NHS

6. Do people using the technology feel that it works in the same way as the comparator(s)?	
7. Are there any key differences?	
8. Will this technology be easier, the same, or more difficult to take than the comparator(s)? If so, please explain why	

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	We welcome another treatment option to help prevent sight loss due to DMO in phakic eyes. DMO is the main cause of visual impairment in people living with diabetes and negatively impacts on people's living with diabetes, and their carers, quality of life. Visual impairment also negatively impacts the ability of people living with diabetes to manage their diabetes so presents the risk of further complications The reduced frequency of injections outlined within this appraisal would mean people living with diabetes need fewer visits to their clinics. We know from recent insight work the cost of transport to clinics, parking costs and time off work is particularly challenging for people living with diabetes and their carers so a treatment option to reduce this burden is welcomed. In addition, people typically live with other comorbidities which also require long term treatment and monitoring by healthcare professionals, further adding to the burden of clinic visits and the associated inconvenience and cost.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	

Key messages

13. In up to 5 bullet points, please summarise the key messages of your submission.	• Additional treatment option for treating chronic diabetic macular oedema in phakic eyes is welcomed • Diabetes is a relentless condition to live with, and a treatment option which reduces the number of clinic visits and therfore impact on people's day to day lives is to be welcomed. • We know people living with diabetes are experiencing delays in appropriate monitoring and treatment, and this includes eye care. A treatment option that has the potential to reduce the number of clinic visits by people living with diabetes may help to reduce the pressure on NHS services, which we welcome. https://diabetes-resources-production.s3.eu-west-1.amazonaws.com/resources-s3/public/2023-05/DUK_Diabetes%20is%20Serious%20Report%202023.pd • • •

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Cost Comparison Appraisal

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

Patient Organisation Submission

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You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	MACULAR SOCIETY
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	The Macular Society is the leading national charity fighting to end sight loss caused by macular disease. Every day over 300 people in the UK face the shock of a diagnosis of macular disease. This sight loss can rob people of their independence, leaving them unable to drive, read or recognise their family. Our members tell us what a profoundly isolating condition it is. People with macular disease are seven times more likely to feel distressed or depressed. We help people adapt to life with sight loss, regain their confidence and independence and take back control of their lives. We are one of the few sight loss charities that actively fund and support medical research into macular disease. With the exception of the details in the answer to 4b, all our income is fundraised from legacies, grants, donations from individuals and fundraising activities such as our lottery, raffle, appeals and community and challenge events. We have 15,000 members who we communicate with on a regular basis, an e-newsletter that is sent monthly to 70,000 people, 370,000 website visitors a year and our Helpline responds to over 16,000 queries a year.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in	Allergan £150 for consultancy work

the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	**DMO patient survey** We carried out a survey and published a report highlighting patient experience of DMO in June 2021. A total of 41 patients with DMO were surveyed about their experiences and their perceptions of the management and support they have received for their diabetes and DMO. This work aimed to understand how the information and support for diabetes compares to that for DMO. **Wet AMD survey** A survey was conducted by the Macular Society in early 2020 to understand the burden that frequent anti-VEGF injections and ophthalmology appointments has on wet AMD patients and their carers or family. A total of 449 responses were received from across the UK. A full report was published August 2020. **Service users** Users of the charity's services, such as our Befriending service and Helpline are surveyed every other year. We also survey our volunteers every other year, most of our volunteers are also affected by macular disease.

	Local peer support groups Our Regional Managers who manage our network of around 400 local groups across the UK feedback regularly. They are our 'frontline', having face to face (or phone to phone) interaction every day with people affected by macular disease. We gather case studies which record the experiences of individuals living with macular disease and the impact on their families and carers. We use our social media channels to interact with people with macular disease and provide information and advice. It is also an important way for people to find others with the same condition where they have a rare form of macular disease and to share experiences.

Current treatment of the condition in the NHS

6. Do people using the technology feel that it works in the same way as the comparator(s)?	Patients understand that both are steroid treatments which slowly release drug into the eye to treat their diabetic macular oedema.
7. Are there any key differences?	Dexamethasone needs to be administered more frequently than fluocinolone acetonide.
8. Will this technology be easier, the same, or more difficult to take than the comparator(s)? If so, please explain why	Both are intravitreal injections but dexamethasone needs to be administered more frequently than fluocinolone acetonide. Each intravtreal injection carries an associated risk of complications, such as raised intraocular pressure. The most serious being endophthalmitis.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	**Treatments** Information from a survey of patients: Two-thirds of responders (65 per cent) were receiving anti-VEGF injections to treat their DMO. Another 7.5 per cent (those who responded "other") had stable DMO and were under observation, receiving injections when needed. One in ten (10 per cent) were receiving steroid injection as treatment and one in eight (12.5 per cent) had laser treatment. One responder was not receiving any treatment due to their sight loss being 'too bad to treat'. Anti-vascular endothelial growth factor (anti-VEGF) injections are the first line of treatment for DMO, and involve injecting these drugs into the eye at repeated intervals. These drugs work to stop the growth and leaking of blood vessels which leads to the damage and vision loss seen in DMO. Some patients do not respond well to these anti-VEGF drugs, or respond better to steroid injections. However, currently there are more restrictions on the use of steroids for DMO due to the increased risk of developing cataracts after steroid use in the eye. Almost four in five participants (78 per cent) feel anxious at least sometimes about their DMO treatment. Often this anxiety is due to having injections, which can be painful. Planning their life around injections can also be stressful, including taking time off work or finding someone to take them to the clinic. **"Regular trips to the hospital for check-ups, having to arrange holidays etc around treatment. Painful treatment."** The remaining 22 per cent do not feel anxious about their treatment, and see injections as a positive step to maintaining their vision. **"Only positively. It has given me reassurance that my sight is being preserved as well as it can be for as long as possible."** **Care** There is significant pressure on NHS eye care services. Patients regularly feedback personal experiences of cancelled appointments, frustration over communication with clinics, and many hours

	spent waiting around in clinic. Injections are not available in local health care settings, meaning many patients travel a good distance to attend injection clinics and need a driver to accompany them. There is also a challenge between the management of diabetes and eye condition. Around one in five (22 per cent) responded that they feel like they weren't managing their eye health well, compared to only one in 20 (5 per cent) who felt they weren't managing their diabetes well.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	The main disadvantage is that it will be an intravitreal injection which may need to be given regularly. Appointments at an eye clinic, with all the attendant difficulties of travelling, needing someone to accompany them, costs of transport and hours at the hospital, will still be required, if at a reduced rate. Intravitreal injections carry a very small but serious risk of sight loss due to complications, such as endophthalmitis. There is an increased risk factor for cataracts (diabetes and having injections in the eye are also risk factors). Some patients can also experience significant pain for a short time afterwards due to corneal abrasion or drying of the cornea, which can be alleviated with lubricating gel.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Those who already struggle to attend all their eye clinic appointments, for the reasons given above, will benefit if they have to attend less often. Many patients also suffer from other health conditions associated with diabetes and advancing age, which can leave them unable to maintain their treatment regime. For some just leaving home can be extremely difficult. Only patients who are well enough, have the right transport means and the ability to make arrangements to attend can benefit.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Yes, age and disability are issues that need to be considered. As the drugs currently available are not a cure and do not work effectively in everyone. A proportion of patients will still experience significant sight loss such that they will be registered as sight impaired or severely sight impaired. There are also specific groups that may need to be taken into consideration: Pregnancy is a major risk factor for the progression of retinopathy and DMO and is associated with increased prevalence and severity of retinopathy compared to non-pregnant diabetic women. Women with type I diabetes are particularly vulnerable to ocular changes during pregnancy. People with learning disabilities - Type 1 and Type 2 diabetes are more common in people with learning disabilities, this group is likely to have more difficulty managing their diabetes. Reports suggest they are 10 times more likely to experience serious sight loss than other people in the general population. There are possible barriers that may affect those with learning disabilities such as a general lack of awareness of the importance of eye screening, problems understanding and processing instructions, fear that the procedures will hurt, memory of previous poor experiences and needing to interact with strangers. Ethnicity is considered a complex risk factor of diabetes. Type 2 diabetes is estimated to be three to four times more common in people of Asian and African–Caribbean origin compared to white Europeans. A UK study found that minority ethnic groups (both South Asians and African/Afro-Caribbeans) had increased odds of having retinopathy compared to their white counterparts. People from lower socio-economic backgrounds tend to have worse DMO outcomes. There is also wider evidence that outcomes are worse in white males who are socio-economically deprived.

Key messages

13. In up to 5 bullet points, please summarise the key messages of your submission.	• The numbers of people with DMO is increasing and over burdening hospital eye clinics • The treatment burden on patients and carers is significant and longer acting drugs can alleviate the problem. • Any measures that reduce the need or frequency of travelling to eye clinics for an invasive, distressing and sometimes painful treatment is a step in the right direction.

Thank you for your time.

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Cost Comparison Appraisal

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

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 13 pages.

1. Your name	[redacted]
2. Name of organisation	The Royal College of Ophthalmologists
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	• An employee or representative of a healthcare professional organisation that represents clinicians? No • A specialist in the treatment of people with this condition? Yes • A specialist in the clinical evidence base for this condition or technology? No • Other (please specify):
5. Brief description of the organisation (including who funds it).	The RCOphth is the professional body for ophthalmologists in the UK. It sets standards and assures the excellence in the science and practice of ophthalmology, achieved by working with national health system organisations in both primary and secondary care, and in collaboration with the UK NHS and government. The RCOphth is funded through membership subscriptions. Ad hoc contributions are received from industry towards particular projects, and in support of the RCOphth Annual Congress through Optic UK.
6. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal stakeholder list.] If so, please state the name of manufacturer, amount, and purpose of funding.	Yes: In 2023 No payments from Alimera In 2022 £1080.00 was received from Alimera as a fee for services for event evaluation for CPD approval https://www.rcophth.ac.uk/events-courses/rcophth-education/professional-development/cpd/cpd-approval-of-events/

7. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

8. Is the technology clinically similar to the comparator(s)? Does it have the same mechanism of action, or a completely different mechanism-of-action? Or in what way is it different to the comparator(s)?	The technology is comparable to dexamethasone implants in the treatment of DMO. The mechanisms of action (of fluocinolone implants) are similar to that of dexamethasone implant. There is, however, a difference in duration of action, with fluocinolone implant having a longer duration (based on it pharmacokinetics/pharmacodynamics in the eye).
9. If there are differences in effectiveness between the technology and its comparator(s) are these clinically meaningful?	The clinical effectiveness is similar, although as indicated above the duration of action is different. This difference in duration translates into less frequent delivery or fluocinolone implant compared to dexamethasone implant. Fluocinolone implant would last 2-3 years compared to the dexamethasone implant that requires re-treatment in 4-6 months.
10. What impact would the technology have on the current pathway of care?	Currently, NICE TA613 recommends fluocinolone implant as an option for treating DMO in eyes that are insufficiently responsive to non-corticosteroid therapy in pseudophakic eyes. The planned revision to the technology will allow treatment of DMO in eyes that have the (phakic) lens intact, i.e. eyes that are not pseudophakic. It will allow treatment of all eyes with DMO that are non-responsive to, or unsuitable for non-corticosteroid therapy, similar to treatment recommendations with the dexamethasone implant (as per NICE TA824).
11. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care. The technology should be used by retinal specialists with expertise in the treatment of patients with diabetic retinopathy, including DMO.

12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Fluocinolone implant is already used in the treatment of DMO in eyes that are pseudophakic. The extension of use to eyes that phakic will allow the technology to be used in the same way (in all eyes, irrespective of lens status).
13. Have there been substantial changes to the treatment pathway since the comparator appraisal that might impact the relevance of the comparator's appraisal?	Dexamethasone implant is now recommended in the treatment of eyes with DMO that are insufficiently responsive to non-corticosteroid therapies. There are no substantial changes to the treatment pathway since the comparator appraisal last year (NICE TA824).
14. Overall, is the treatment likely to offer similar or improved health benefits compared with the NICE-recommended comparator?	Yes, the treatment is likely to offer similar or improved health benefits compared to dexamethasone implants in DMO. The extended treatment (to eyes that are not pseudophakic) will lead to better resolution of DMO in such eyes, better visual acuity improvements, less frequent hospital visits, and increased patient satisfaction compared current care. The existing data (registration RCT) on efficacy of fluocinolone implant in DMO includes eyes that are phakic as well as pseudophakic, and demonstrate clinical similarity in the whole population (similar to dexamethasone). This review will allow for parity with the dexamethasone intravitreal implant, and will be consistent with the approved label for fluocinolone implant (EMA) which covers both the phakic and pseudophakic population.
15. Do the clinical trials on the technology reflect current UK clinical practice?	Yes. The existing data (registration RCT) on efficacy of fluocinolone in DMO includes eyes that are phakic as well as pseudophakic, and demonstrate clinical similarity in the whole DMO population.

16. Is the technology likely to affect the downstream costs of managing the condition (for example, does it affect the subsequent treatments)	It is possible that downstream management costs will be reduced. Phakic eyes that are insufficiently unresponsive to non-corticosteriod intravitreal therapies will benefit meaningfully from this technology. The proposed use will include treatment of eyes that are phakic, and unresponsive, or unsuitable for other (non-corticosteroid) DMO treatments. Access to the technology in phakic DMO will provide physicians with an opportunity at an early stage to switch non/sub-optimal responding patients from anti-VEGF treatment to fluocinolone or dexamethasone implant (subject to choice after discussions between the specialist and the patient). This early switch will likely avoid any irreversible damage to the retina and improve patient outcomes: more cost-effective of the technology. Capacity sparing: The use of intravitreal fluocinolone implant results in a reduced burden of injections when compared to intravitreal anti-VEGF injections and, therefore, capacity sparing. As fluocinolone has a longer duration of action (compared to non-corticosteroid therapies and dexamethasone implant), it is expected that patients treated with the technology will attend fewer appointments due to longer injection intervals resulting in reduction in clinic visits. This is even more important in the post-COVID pandemic era. Adoption of the expanded technology indication can further “free-up” clinic slots and staff resources which can potentially be made available for other conditions and services. Subsequent treatments should not be affected otherwise. No further investment is required in extending this technology to phakic eyes with DMO.
17. Are there any potential equality issues that should be taken into account when considering this treatment? Consider whether these issues are different from issues with current care and why	No. However, this technology will be available to groups did not have access previously, including pregnant diabetic women, and persons with recent cardiovascular events.

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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*
Date completed	*Date completed 27/11/2023*

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Declared competing interests of the authors

None.

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Professor Noemi Lois Clinical Professor of Ophthalmology, Queens University and an Honorary Consultant Ophthalmologist and Vitreoretinal Surgeon at the Belfast Health and Social Care Trust, Belfast, Northern Ireland, UK

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.

This report should be referenced as follows:

Patel M, Cummins E, Waugh N, Brown A, Colquitt J, Loveman E, Grove A: Fluocinolone acetonide intravitreal implant for treating chronic diabetic macular oedema in phakic eyes after an inadequate response to previous treatment (Review of TA613) [ID6307]. A Cost Comparison Technology Appraisal. Warwick Evidence, 2023.

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 3.2). 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 **Error! Reference source not found.**).

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 3.2.1). 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 Section3.2.1.

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 **Error! Reference source not found.** 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 **Error! Reference source not found.** and Table).

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 3.1.4) 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 12.

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 12). 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 3.2.1.1.1 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.

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centre/press-releases/2023/03/21/nhs-patient-backlogs-are-leading-to-life-changing-sight-loss (Accessed 06 November 2023).
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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 32.

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]

Cost Comparison Appraisal

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

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Wednesday 6 December 2023** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as [redacted] should be highlighted in turquoise and all information submitted as [redacted]' in pink.

Issue 1 Mediators of insufficient response

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 9. Clinical Effectiveness Evidence. Bullet point 2b. **Page 116. Clinical effectiveness evidence summary. Bullet point 2b.** "Clinical advisors suggest that insufficient response may mean insufficient treatment due to pressures on the NHS capacity to deliver services to patients." Whilst the company agrees with the statement it does not fully represent the published literature on this topic or comments made later in the EAR on	We propose that this sentence be amended to read: "Clinical advisors suggest that insufficient response may mean insufficient treatment due to pressures on the NHS capacity to deliver services to patients. ***Additionally, insufficient response to treatment is well defined clinically and characterised in the literature whereby up to 40% of patients are considered to have an insufficient response to***	We consider this an avoidable ambiguity; the comment from clinical expert gives one potential reason for insufficient response but does not convey the other reasons why there may be an insufficient response or describe what that may look like in terms of response to treatment (or lack of) in respect of visual acuity (VA, measured in EDTRS letters) and anatomy (optical coherence tomography, OCT; central retinal thickness, CRT). To that extent, the statement, in isolation, is somewhat misleading. Even when treatments are delivered optimally, there may be an insufficient response due to the treatment not being effective. The pathophysiology of Insufficient (suboptimal, inadequate) response, and variability in responses, are well-defined and described in recent NHS England Guidance, the Royal College of Ophthalmologist Consensus Working Group guidelines (Amoaku et al 2020) and by Downey et al (2021) and is also mentioned within much of the text of the EAR. These sources provide guidance in terms of the optimal interval between treatments and suboptimal responses in terms of CST and ETDRS letters.Link:https://pubmed.ncbi.nlm.nih.gov/32504038/	Not a factual error. The caveat for statement 2b on page 9 and page 116 is "Clinical advisors suggest" which is adequate to signify that it is not published literature on this topic. No change made.

insufficient response. Mediators of response are multi-factorial. Insufficient response may be due to insufficient treatment and/or the first line anti-VEGF therapy not being effective. Effective response to anti-VEGF therapy is well characterised in the literature and underpins clinical assessment in practice and should be incorporated into the above statement.	***anti-VEGF therapy*.”**		
Page 17. “The EAG note that a definition of “insufficiently responsive” is not provided in the NICE scope for this appraisal...We have identified variations in the criteria		See comment above. Insufficient response is well-defined, documented and characterised in the product SmPCs, in the literature and in clinical practice.	Not a factual error. No change made. EAG states that “insufficiently responsive” is not provided in the NICE scope.

included in literature and CS.”			Not in the product SmPCs, in the literature and in clinical practice as stated by the company.

Page 18. Bullet 1 "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". Whilst the company agrees with the statement, we feel this does not fully represent published materials on this and also comments made later in the report on insufficient response. Insufficient response may be due to insufficient treatment and/or the first line anti-VEGF therapy not being effective	We propose that this sentence be amended to read: "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 or ***as a consequence of insufficient treatment effect to first line anti-VEFG therapy***. Clinical advisors suggest that patients may be seen only every 6-8 weeks because of pressure in the NHS".	Please see justification provided immediately above.	Not a factual error. The caveat for bullet 1 on page 17 is "Clinical advisors suggest that". Again this is adequate to signify that it is not published literature on this topic. No change made.

and not uniquely a consequence of sub-optimal dosing in real world practice due to resource issues and pressures.			

Page 22. Critique of the decision problem in the company's submission. "An **inadequate response** means a gain of fewer than 5 letters, or any loss of letters, in people with visual loss at baseline. In those without visual loss, gains will be smaller, and maintenance will be the outcome." 'Inadequate response' has been incorrectly defined because it omits the objective measure of CRT. An 'inadequate response' is also assessed clinically by CRT measurement and this should be included to reflect current practice.	We propose that this sentence be amended to read: "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."	CRT is an objective measure of response used both clinically and in RCTs. The literature pertaining to predicting response thus encompasses this marker of response in tandem with VA assessment. Predicting insufficient response: 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. 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.	Change made to page 22. "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."

Page 19. Section 1.2.2 “In summary, in people with no 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.” We consider “no response” does not align with the previous elements of this sub-section and is open to misinterpretation of the real-world clinical experience of this patient cohort. This is not consistent with prior statements on insufficient response and other comments made in the EAR.	We propose that this sentence be amended to read: “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.”	We consider the use of “non-response” is open to misinterpretation as sub-optimal response is characteristic this patient cohort in the literature. In patients with good, sufficient response after loading dose of anti-VEGF, then anti-VEGF therapy should be continued. In patients with less than sufficient response after loading phase (<5 letters <20% CST) reduction by OCT or in patients where clinic capacity or treatment burden is an issue then a switch to corticosteroids may be appropriate. In patients with minimal or no response to after a loading dose of anti-VEGF, improvement is unlikely and an early switch to corticosteroids appears appropriate (Downey et al., 2021; Amoaku et al., 2020; https://www.england.nhs.uk/long-read/operational-note-updated-commissioning-recommendations-for-medical-retinal-vascular-medicines-following-the-national-procurement-for-ranibizumab-biosimilars/ In this summary statement there is no definition on what may be considered a ‘response’ to therapy, or an insufficient response. This risks some patients with a small response to initial therapy being continued on this insufficient therapy when an early switch to steroids may be more appropriate to improve/maintain vision and reduce the DMO.	Change made to page 19. “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.”

Issue 2 IOP risk monitoring

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 21. Section 1.2.4 "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 would be followed up regularly, so not all these visits would be additional." IOP risk monitoring assessment in DMO patients receiving intravitreal corticosteroid therapy is defined in the relevant SmPCs. The above reference to specified 6-monthly monitoring does not align with the SmPCs. We consider it important to add this clarification.	We propose that this sentence be amended to read: "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 is a manageable risk associated with intravitreal corticosteroid therapy which is well characterized in the literature. Both SmPC's for ILUVIEN and the DEX implants detail this risk and provide recommendations on IOP monitoring intervals specific to DMO.	Change made to page 21. 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."

Issue 3 Eyes may in fact be treated bilaterally.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 108. Section 4.21 (Bilateral involvement: timing of concurrent treatment) states in the first sentence: ‘While the SmPCs of fluocinolone and dexamethasone state that treating both eyes concurrently is not recommended…’ The company believes the EAG mean to say ‘’…that *administering treatment* to both eyes concurrently is not recommended.”	We propose that this paragraph be amended to read: ‘’While the SmPCs of fluocinolone and dexamethasone state that *administering treatment* to both eyes concurrently is not recommended.”	SmPC section 4.2 page 108: The recommended dose is one ILUVIEN implant in the affected eye. Administration in both eyes concurrently is not recommended (see Section 4.4) SmPC section 4.2: The safety and efficacy of ILUVIEN administered to both eyes concurrently have not been studied. It is recommended that an implant is not administered to both eyes at the same visit. Concurrent treatment of both eyes is not recommended until the patient's systemic and ocular response to the first implant is known. When response to implantation in the first eye is known then the second eye may be treated. Administration would then be staggered.	Change made on page 108. ’While the SmPCs of fluocinolone and dexamethasone state that *administering treatment* to both eyes concurrently is not recommended.”

Issue 4 Laser treatment

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 120 **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 micro pulse 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] This statement is not relevant to the patient population that is the subject of this TA, i.e., patients who have had sub-optimal response to non-corticosteroid therapy.	The statement is not relevant to the patient population or treatment pathway that are the subject of the decision problem for this TA. We suggest that the paragraph regarding laser and the DIAMONDS trial is deleted.	Laser treatment is not relevant to the patient population or treatment pathway that are the subject of the decision problem for this TA.	Not a factual error. This is additional EAG commentary on service context and additional evidence and does not form part of the EAG appraisal provided in sections 1-7 or EAG estimates provided.

Issue 5 RWE for switching to aVEGF but not for level of subsequent treatment.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 5 Page 111 It is perhaps inconsistent to retain trial-based estimates of rates of subsequent steroid implantation when adopting rates of aVEGF utilisation from real-word sources. One source is available to furnish both estimates.	The company suggests adoption of the Medisoft study implantation rate for FAc for the EAG base case. This is the adoption of company Fac reimplantation scenario 3 (RWE_1, MediSoft, Bailey).	Use of the single source for these two input estimates is methodologically consistent because the impact of aVEGF switching on reimplantation is better accounted for versus the FAME trial – in which use of other medications was discouraged. The company would retain the EAG approach for DEX (I.e., MEAD) as the source of reimplantation for DEX, since the lower completion rates of MEAD indicate probable adjustment for aVEGF switching.	Not a factual error. No revision required. The EAG note that there are questions around what dosing should be assumed during the first three years when allowing for patients reverting to anti-VEGF. But the model structure needs to be borne in mind. It would not be appropriate to apply both the Medisoft dosing and the proportions ceasing treatment due to reverting to anti-VEGF as this will result in the number of administrations being below the Medisoft dosing data. Given the model structure there is no ready means of fully aligning all the dosing data, much of which is poorly aligned with other possible sources. The EAG remains of the opinion that the most reasonable approach when modelling anti-VEGF

			revisions is to apply the FAME and MEAD dosing coupled with the anti-VEGF revision proportions being the proportions of patients ceasing fluocinolone/dexamethasone, and if extending to a 6-year time horizon basing the subsequent three year's dosing upon something aligned with response rates.

Issue 6 Misleading statement regarding the significance of treatment effects for dexamethasone in phakic only patients

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 34, section 3.1.1 the EAG write the following statement: *"In the phakic eyes only subgroup, there were no statistically significant differences between fluocinolone and sham, but there were statistically significant differences between dexamethasone and sham."* This is misleading, as it suggests a statistically significant difference between dexamethasone and sham in phakic patients.	We suggest the following wording: "There were no statistically significant differences between fluocinolone and sham in the phakic eyes only subgroup of FAME. Given a lack of data we cannot draw any conclusions regarding the significance of a treatment effect between dexamethasone and sham in phakic eyes."	Based on the results of a systematic literature review, there is no data in the public domain which suggest a significant difference between dexamethasone and sham in phakic only patients. The data in Table 5 of the technical summary document related to the treatment-experienced subgroup of MEAD, which includes patients with both phakic and pseudophakic lens.	We agree that the statement needs clarifying. However, the intention was to report the results presented in CQ A8, not to draw conclusions regarding dexamethasone in phakic eyes. Sentence changed as follows: "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.”

Issue 7 Misleading statement regarding the decrease in sample size for ITC analyses

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 82, section 3.2.1.1.2 the EAG write the following: *“Table A10.3 from the CQ responses also presents the ESS for each ITC comparison. Some outcomes see large decreases in ESS, such as change in CRT, which has an ESS of 50 (a reduction of 79%). Such large decreases in ESS means the power of the analysis is likely to be compromised, resulting in large confidence intervals due to*	We would like to include some wording to accompany statements regarding the ESS of the ITC analyses. • *On page 9 and 116 the following statement: “The indirect treatment comparison (ITC) analysis which focused on the FAME cohort and phakic-only subgroup, indicates a reduction in estimated treatment effect size (ESS) after adjustments for*	The majority of the reduction in sample size is due to the application of post-treatment censoring consistent with the design of MEAD, rather than the matching process. As such it is misleading to attribute this to the matching adjustment procedure. A more accurate interpretation is that the reduction in the sample is due to missing data points at Month 36.	Not a factual inaccuracy, the company added more detail to the ESS. EAG kept it short for the sake of brevity. For clarity, we have added the detail back in as requested.

lower precision, challenging the interpretability of the results." At multiple points in the document this large reduction in ESS is attributed to "adjustment for imbalanced EMS" (see page 9, 86, 88, 116, 117). This is not correct. The reduction in samples is mainly a result of missing data points at Month 36, and further the application of the censoring algorithm, as the following table demonstrates: **Population** | **Sample size (N)** phakic only ITC cohort FAc arm at baseline | 139 phakic only ITC cohort FAc arm at month 36 | 95 phakic only ITC cohort FAc arm at month 36 with censoring | 58 phakic only ITC cohort FAc arm at month 36 with	*imbalanced effect modifiers" should be changed to "**The indirect treatment comparison (ITC) analysis which focused on the FAME cohort and phakic-only subgroup, indicates a reduction in estimated treatment effect size (ESS) of ~15% after adjustments for imbalanced effect modifiers**."* • *On page 9 and 117 the following statement: "Reduction in ESS in the FAME cohort's phakic-only subgroup, raises concerns about potential bias compared to MEAD-treatment experienced (TE) subgroup." should be changed to "**The loss of sample size when considering only the phakic-only subgroup of FAME, should be considered when making comparisons with the MEAD-treatment experienced (TE) subgroup**."* • On page 82 we suggest: *"Table A10.3 from the CQ*		

censoring and matching				
Here we show that the reduction in ESS due to the adjustment for TEMs is only 14% (50/58). Whereas the reduction due to missing data and censoring is 42% (58/139).		*responses also presents the sample size 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."* • On page 86 we suggest the following wording *"The ESS in analysis for the FAME ITC cohort, particularly in the phakic-only subgroup, indicates some reduction in ESS after adjustments for imbalanced TEMs"* be changed to *"**The ESS in analysis for the FAME***		

	ITC cohort, indicates some reduction in ESS (approximately 15%) after adjustments for imbalanced TEMs*"* • *On page 88 the following statement: "The analysis indicates a reduction in ESS after adjustments for imbalanced effect modifiers" should be changed to: "**The analysis indicates a reduction in ESS of approximately 15% after adjustments for imbalanced effect modifiers**"*		

Issue 8 Typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 3, Acronyms and Glossary There is a typographical error in the definition of DIAMONDS	Correct definition to read: "a pragmatic multicentre allocation…"	Typographical error	Amended
Page 18. Section 1.2.1 "Vila-Gonzale et al (2020) found that only 6% of participants had no reduction in oedema, 22%	The author's name should read: "Vilà González et al." and the	Typographical error	Amended

had full clearance, and 665 has partial clearance."	sentence should read "…and 66.5% had partial clearance".		
Page 21. Section 1.2.4 "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 ***25*** vision is lost first, with central vision being affected later."	Correct the sentence to remove the "25" so the sentence reads: "…in which the nerve fibres are damaged, peripheral vision is lost first..." Alternatively, if "25" is a reference number, make it superscript.	Typographical error	Amended
Page 71. Section 3.1.4.1 "In summary, there 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.	This statement should read: "In summary, there ***is*** a reasonable evidence base to support…"	Typographical error	Amended
Page 83. Table 15. In column 1 of Table 15 the following label is given "FAS - Phakic MAIC*" – however the values presented in the corresponding rows are for the phakic only subgroup of the ITC cohort of FAME.	Change all instances of "FAS - Phakic MAIC*" to "ITC cohort - Phakic MAIC*" to	Typographical error. Incorrect labelling applied.	Amended
Page 85. Table 16, column 5, row 1, the p-value presented is	Change value to 0.266.	Incorrect p-value presented. Typographical error.	

0.181, however we believe this should read 0.266.			
Page 85. Table 16. In the paragraph immediately following Table 16 there is a type where the word “no” erroneously appears in the sentence	Delete the word “no” “The only difference between the two ITCs was that the ITC result of the mean change in CRT from baseline to EOT no favoured fluocinolone instead of dexamethasone (as can be seen in **Error! Reference source not found.**) but this result is not significant”	Typographical error.	
Page 93. Table 22. The drug cost for FLUO in column 2 is given as [redacted]’. The correct entry figure is [redacted]	Change entry to [redacted]	Typographical error	Accepted.

EAG comment

During FAC the EAG spotted an error in the EAG modelling of reversions to anti-VEGF. This has not been highlighted as an issue by the company during FAC.

However, the EAG has updated the EAG report in track changes and provided an EAG revised model for cross checking by the company.