NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Fluocinolone acetonide intravitreal implant for treating chronic diabetic macular oedema (part review of TA301) [ID1421]

The following documents are made available to the consultees and commentators:

1. **Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**

2. **Consultee and commentator comments on the Appraisal Consultation Document** from:
    - Alimera Sciences
    - The Royal College of Ophthalmologists, which has been endorsed by the Royal College of Physicians

3. **Comments on the Appraisal Consultation Document from experts:**
    - Dr Faruque Ghanchi – clinical expert, nominated by Alimera Sciences

4. **Comments on the Appraisal Consultation Document received through the NICE website**

5. **Evidence Review Group critique of company response**

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

Fluocinolone acetonide intravitreal implant for treating chronic diabetic macular oedema in phakic eyes after an inadequate response to previous therapy

Single Technology Appraisal

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and Social Care and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal document (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation.

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health and Social Care, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1	Consultee	Alimera Sciences Limited	The company feel strongly that whenever 'symptomatic cataract' is mentioned it should be made clear to the reader that this refers to the group of patients eligible for cataract surgery according to NICE guidance 77 and deemed cost effective. This is important as it is clear guidance to clinicians on the patient group and surgical options approved by NICE. In the context of referring a patient for cataract surgery, NICE guidance 77 states, "…the decision to refer a person with a cataract for surgery on a discussion with them (and their family members or carers, as appropriate)…" and to "…not restrict access to cataract surgery on the basis of visual acuity."[1] **NICE guidance 77:** In phakic eyes with symptomatic cataract (NICE guidance 77) there is a clear unmet need as vision is declining. Furthermore, NICE guidance 77 can be used as a basis and a means to identify and treat DMO patients that are insufficiently responding to anti-VEGF therapy provided they have a symptomatic cataract. **ICE-UK study[2]:** This study demonstrated that in people with 'phakic eyes and symptomatic cataracts after an insufficient response to anti-VEGF therapy' there was declining vision in spite of on-going treatment.	Comments noted. The committee understood that people with symptomatic cataract should be offered cataract surgery in line with NICE's guideline NG77. The FAD has been amended to reflect this - see FAD section 3.1.
2	Consultee	Alimera Sciences Limited	It is important that NICE is clear that the FAME control arm (active treatment) and treatment arm do not represent the outcome of usual care in the target population. Indeed, at the time of the trial (2005 to 2009) anti-VEGFs were not a standard of care and this is why only very few people had anti-VEGFs before the trial. Alimera Sciences believes that data in ICE-UK in the 12 months prior to ILUVIEN is representative of current clinical practice. ICE-UK collated data from current clinical practices where anti-VEGF was being used as a first-line therapy and prior to the use of ILUVIEN.	Comments noted. The committee considered all the clinical evidence. The committee concluded that FAME does not reflect NHS clinical practice and that evidence was limited (see FAD sections 3.4, 3.5 and 3.6).
3	Consultee	Alimera Sciences Limited	Alimera Sciences would like to clarify that the discussion is about an existing unmet need and that the population in question is an identifiable population from the FAME trial and suitable for cataract surgery according to NICE guidance 77.	Comments noted. The committee understood that there is an unmet need (see

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			Alimera Sciences believes that following cataract surgery the effectiveness of ILUVIEN is no different in VA outcomes in patients with a phakic or pseudophakic lens at baseline as the majority of evidence pertains to the 3 years of therapy rather than the period of time between cataract diagnosis and cataract removal (i.e. 0 and 3 months in the ICE-UK study). Furthermore, having a steroid in the eye has clear advantages at the time of cataract surgery in people at increased risk of cystoid macular oedema (e.g. people with diabetes or uveitis).[1] Alimera Sciences would also like to make it clear that DMO is a progressive disease and detrimental to the retina irrespective of the status of the patient's lens. An untreated or insufficiently responsive DMO eye is at risk of damage and subsequent loss of vision as shown in the 12-months prior to ILUVIEN in the ICE-UK study. Following ILUVIEN administration, the retinal protective effect was demonstrated by the improvement in visual acuity.	section 3.2 in FAD) and considered the clinical evidence for fluocinolone in phakic eyes (the FAD has been amended in section 3.5).
4	Consultee	Alimera Sciences Limited	**The vision outcomes calculated by Alimera Sciences are very conservative** DMO is a progressive disease and detrimental to the retina irrespective of the status of the patient's lens. This is shown in the ICE-UK study where in current UK clinical practice there was a progressive loss in visual acuity during the 12 months preceding the injection of the ILUVIEN implant (*represented by the yellow line in the schematic below*). As a progressive disease, however, visual acuity would be expected to worsen over the long-term if ineffective medicines continued to be given and the small losses in visual acuity observed in the ICE-UK study would quickly become much larger over several years. **Figure. Schematic showing visual acuity outcomes in patients treated with the fluocinolone acetonide (FAc) implant (both model and actual values from the FAME study) and standard of care (models and ICE-UK)**	Comments noted. The committee considered all the evidence submitted, including evidence from clinical trials, patient and clinical experts, the company's submissions and the ERG's critique. It also carefully considered the comments received in response to the ACD. The committee concluded that net gain should be used in both arms (see section 3.9 of FAD).

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			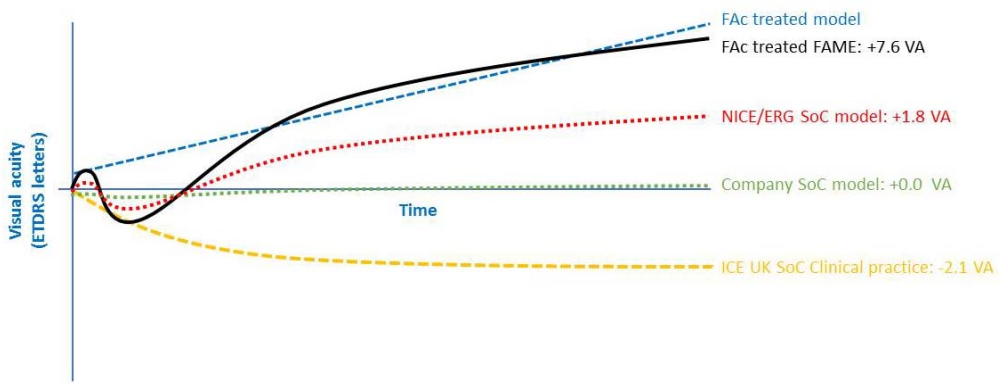 In contrast to Alimera Sciences view, NICE / ERG argue that the sham treated arm in the FAME trial actually reflects usual care (*represented by the red line in the schematic above*). This is incorrect as it does not reflect current clinical practice in the UK (*represented by the yellow line in the schematic above*). In looking at the scenarios, therefore, it was calculated that visual acuity would remain stable (*represented by the green line in the schematic above*), which is unlikely according to ICE-UK data but accounts for possible improvements in visual acuity following cataract surgery. Alimera Sciences believes that this assumption is very conservative considering the progressive nature of DMO. **Alimera Sciences' model is very conservative** The company would like to highlight that the base case ICER from the company was actually £2,187 and was based on a very conservative model of the net treatment effect versus the control arm. Alimera Sciences acknowledges that there is uncertainty around some assumptions and inputs considered in the company base case, we disagree that this scenario should be discarded as "not plausible". We note that the ERG presented a similar scenario with assumption of constant best-corrected visual acuity in the usual care arm, resulting in a cost effective ICER of £18,710. We believe this to be plausible.	

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			Reasons why NICE's position is implausible Firstly, in eyes without prior ILUVIEN treatment and with symptomatic cataract (i.e. eligible for cataract surgery per NICE guidance 77), the extraction of the cataract is clearly unrelated to ILUVIEN treatment and considered cost-effective. Secondly, NICE's position on the mildly improved vision over the long-term is also implausible. Indeed, whilst cataract surgery is expected to provide a transient gain in visual acuity, patients with an insufficient response will continue to be treated with ineffective first-line therapies and thus the retina will remain under-treated and vision will continue to decline. Thirdly, in patients with a pseudophakic eye with chronic DMO insufficiently responsive to available therapies (i.e. predominantly anti-VEGF), ILUVIEN implantation has been shown to be cost-effective in TA301.[3] Yet, NICE has concluded that if a cataract surgery unrelated to ILUVIEN was conducted one day earlier, the therapy would not be cost-effective. This argument seems completely nonsensical as the cataract is unrelated to ILUVIEN and treatment would be equivalent to current guidance outlined in TA301.[3]	
5	Consultee	Alimera Sciences Limited	The "*effect caused by natural recovery and rescue treatments*" does not exist in the target population. Patients selected for treatment with ILUVIEN have an "insufficient response to available treatments" (the label) due to increasing damage to the retina caused by DMO irrespective of lens status. The clinical expert at the NICE committee meeting clearly stated that this proposed "natural" recovery was improbable in this patient group. The ICE-UK clinical data showed a BCVA decreased by 2 letters over 12 months before FAc administration of whom 56 eyes underwent cataract surgery during 12 months prior to implant. In total, 185 (89%) of 208 eyes were pseudophakic before injection of the FAc implant.[4] Alimera Sciences agrees with the Decision Committee that the "net gain" in best-corrected visual acuity in FAME is the best estimate of treatment effect. However, the net gain predicted in the company model is in fact much closer to the net gain estimated in FAME than the gain predicted in the ERG model adaptation, while remaining conservative, as shown below. The Decision Committee did not take note of an essential argument made by the	Comments noted. The FAD has been amended to reflect this - see FAD section 3.9. The committee considered all the evidence submitted, including evidence from clinical trials, patient and clinical experts, the company's submissions and the ERG's critique. It also carefully considered the comments received in response to the ACD. The committee concluded that net gain should be used in both arms (see section 3.9 of FAD).

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			Company to justify the assumption of constant best-corrected visual acuity in the sham arm. Also, we would like to detail this argument here. The company presented in its submission a scenario assuming constant best-corrected visual acuity in the usual care arm of FAME and a scenario where the transition probabilities for usual care were based on the sham arm of FAME. The comparison of the net gain in best-corrected visual acuity in the trial to the model predictions for the phakic population showed that the model predictions were much closer to the trial results in the former scenario. This was a major reason supporting the choice of constant best-corrected visual acuity in usual care arm as base case scenario. The graphs below show: - the mean change in best-corrected visual acuity for the phakic population from the FAME study. - model predictions for the trial phakic population in the scenario with constant best-corrected visual acuity in the usual care arm (scenario considered in Company submission). - model predictions for the trial phakic population in scenario with transition probabilities for usual care based on sham arm of FAME (base case scenario considered by ERG). As shown by these graphs, the base case scenario in Company submission is more consistent with the results of FAME trial, especially in terms of the net gain in best-corrected visual acuity following treatment with the FAc implant. In both the trial results and the company model, there is a net gain in best-corrected visual acuity reaching approximately 8 letters after treatment administration, followed by a decrease in net gain to approximately zero around 20 months, and then a progressive increase in the net gain over time. The curves generated by the company model do not follow very closely those from the trials, but the model actually provides a very conservative prediction of the net gain in best-corrected visual acuity over time. The model with transition probabilities obtained based on sham arm of FAME (ERG scenario) does not reflect the trial results. In particular, this model predicted that best-corrected visual acuity would be worse in the fluocinolone arm than in the sham arm after 10 months, for the phakic trial population.	

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			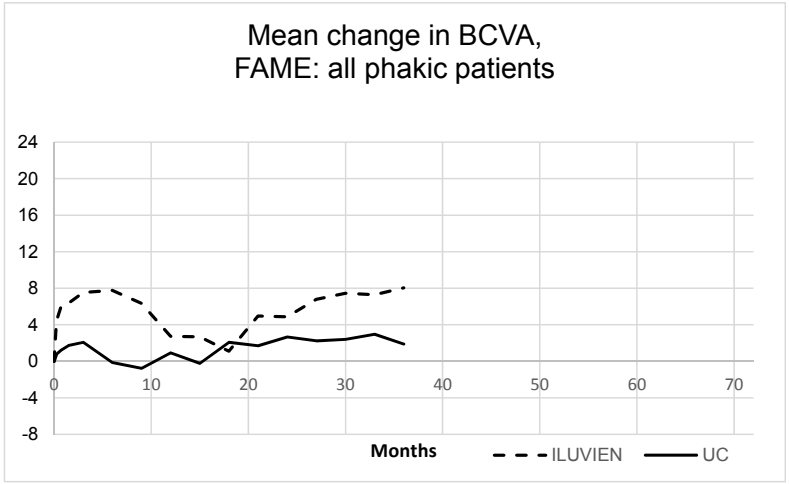 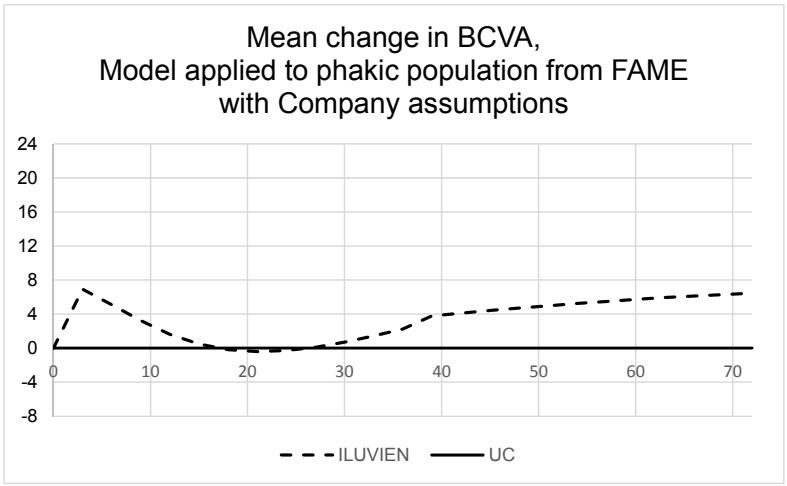	

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			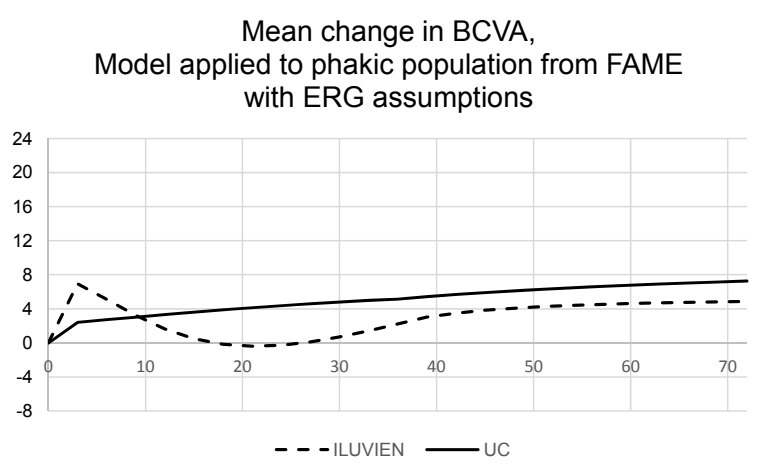 Looking at patients with cataract, the estimates of net gain in best-corrected visual acuity (FAc vs. sham/usual care) are: - in FAME trial, using phakic patients at baseline undergoing surgery cataract during the study as a proxy (95 patients in fluocinolone 0.2 mcg arm, 23 patients in sham arm): +3.2 letters at 12 months and +3.2 letters at 36 months. - in Company base case scenario: +2.6 letters at 12 months and +3.6 letters at 36 months. - in ERG base case scenario: -1.6 letters at 12 months and -2.7 letters at 36 months. While the company provides plausible estimates of the net gain in best-corrected visual acuity, the ERG adaptation of the model clearly does not. As regards “natural recovery and rescue treatments”, it should be noted that: the use of rescue treatments was significantly lower in the FAc arm, so any effect of rescue treatments would also be lower: as reported in Campochiaro *et al*.[5] after 6 weeks in the study, patients were allowed to undergo additional laser treatments, and subsequently treatments were allowed as frequently as every 3 months for persistent or recurrent DME. A significantly higher percentage of patients in the sham group (60.7%) received rescue focal grid laser than in the FAc treatment arm (40.7%) Also, a	

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			greater percentage of patients were given repeated focal/grid laser treatments in the sham group; 11.9% of patients in the sham group received 3 treatments during the trial compared with 6.6% FAc treatment arm.	
6	Consultee	Alimera Sciences Limited	We agree that a very small proportion of people will have a second implant within the first 3 years. The IRISS study estimates a re-injection rate of 1.13 implants but not specific to the UK as this figure is based on usage in the UK, Germany and Portugal. Focusing on only the UK, analyses reveals the most plausible re-injection rate to be a value of 1.06 (n=462 eyes treated with 491 ILUVIEN implants over a mixed follow-up period). This is consistent with the Medisoft study (n=93 eyes treated with 99 ILUVIEN implants over a three year period) and independent of lens status as the majority of patients are pseudophakic due to current UK practice and market restrictions (IRISS safety report published 23rd July 2019).	Comments noted. No change needed (see section 3.10 of FAD).
7	Consultee	Alimera Sciences Limited	This point has been made previously that there are only two therapies that can currently be used in phakic eyes – these are laser and anti-VEGF therapy. However, in the target population (i.e. patients with chronic DMO that are insufficiently responsive and a symptomatic cataract) these therapies would have already been shown to be ineffective. If left untreated or treatment continued with ineffective therapies, the patient risks further retinal damage and long-term vision loss. The above point is reflected in the ICE-UK study where there was a gradual decline in visual acuity with standard of care (i.e. primarily anti-VEGF therapy and the current standard of care) in the 12 months prior to ILUVIEN. Further, the presence of persistent macular oedema could theoretically lead to delays in cataract surgery due to the risk of pseudophakic cystoid macula oedema. In this scenario, an intravitreal steroid prior to cataract surgery would help to dry the oedema and reduce the potential for pseudophakic cystoid macula oedema. As mentioned previously, the majority of the clinical evidence in the UK has been accrued following the approval of TA301 and so the majority of real-world evidence pertains to a 3 year of therapy following ILUVIEN administration. There is less data for the 3 month period (based on ICE-UK) between cataract diagnosis and cataract removal, although the study by Yang *et al*.[6] shows a similar visual acuity outcome being achieved after 3 years of ILUVIEN therapy irrespective of the lens status at baseline.	Comments noted. No change needed. The committee was aware of the unmet need and the target population (see sections 3.1 and 3.2 of FAD). The clinical evidence was considered by committee and is discussed in sections 3.4, 3.5 and 3.6 of the FAD.

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8	Consultee	Alimera Sciences Limited	At the time TA301 was approved it was suggested by NICE that the company collect data from current clinical practices where anti-VEGF is being used before ILUVIEN - acknowledging that anti-VEGF's were not widely used at the time the pivotal trial was conducted. For this reason, Alimera Sciences set-up and conducted the ICE-UK study and from this it is possible to assess the effect of the FAc implant after an insufficient response to anti-VEGF.[2] ICE-UK showed that during the 12 months before ILUVIEN was administered there was a gradual decline in visual acuity with standard of care (i.e. primarily anti-VEGF therapy). Following the injection of the ILUVIEN implant there was an overall improvement of +4.3 letters at 12 months. The company also feels strongly that ICE-UK as ground-breaking non-comparative study should not be dismissed and instead be given more weight as this study was recommended by NICE at the time TA301 was approved and since that time has collected data from current clinical practices where anti-VEGF is being used before ILUVIEN.	Comments noted. No change needed. The clinical evidence was considered by committee and is discussed in sections 3.4, 3.5 and 3.6 of the FAD.
9	Consultee	Alimera Sciences Limited	**NICE guidance 77 is useful for identifying the target population** The discussion here is not about the number of eyes, it's a question of whether the target population is a clear and identifiable cohort of patients. Based on the FAME trial, a small proportion of phakic eyes did have 'symptomatic cataract' and there is NICE guidance (i.e. NG77) on clinical decision making once a diagnosis has been made. Furthermore, the ICE-UK study shows that patients with a phakic lens at the start of ILUVIEN therapy are likely to undergo a cataract operation between 0 and 3 months after the ILUVIEN implant is administered. Hence NICE guidance 77 is useful in identifying the target population and can be used as a basis for commencement of ILUVIEN therapy knowing that cataract surgery is likely to occur relatively soon after the ILUVIEN implant is administered. Speaking from a pragmatic point of view, NICE guidance 77 will help deliver ILUVIEN therapy more efficiently to patients where there is an unmet need. It also means that, as acknowledged in section 3.2 of the ACD, patients do not need "…to wait until after cataract surgery before they are offered intravitreal steroid implants" and that they are treated as effectively as possible thus helping to reduce "…anxiety and stress because	Comments noted. The FAD has been amended to reflect this - see FAD sections 3.1 and 3.2.

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			of the chronic nature of the disease and potential sight loss."	
10	Consultee	Alimera Sciences Limited	**ICE shows an improvement in VA when ILUVIEN is administered at the same time as cataract removal** The submission presented evidence from 14 patients from ICE-UK and 10 patients from retro-IDEAL who had cataract surgery and FAc implant administration at the same time. Results from the ICE-UK study showed a real-world mean gain of 13 letters over a 12-month period following concurrent cataract removal and FAc implant administration.	Comment noted. No change needed. The clinical evidence was considered by committee and is discussed in sections 3.4, 3.5 and 3.6 of the FAD.
11	Consultee	Alimera Sciences Limited	Usual care in patients that are insufficiently responsive to anti-VEGFs is ineffective from a cost and clinical perspective. This is openly stated in section 3.2 of the ACD where it is mentioned that "clinical experts confirmed that in some cases, people continue to have anti-vascular endothelial growth factors (anti-VEGFs), even if they do not work well," an observation supported by the fellow eye arm of the ICE-UK study." By allowing this practice to continue, NICE is condoning this practice and the wasteful use of NHS England and Wales resources. Alimera Sciences would like to reiterate that the ILUVIEN implant is only administered after an insufficient response to prior therapy. The ICE-UK study confirmed this was primarily after anti-VEGF, so by definition the ILUVIEN implant works better than usual care as this reflects continued therapy with an ineffective treatment option. The recommendation being sought by Alimera Sciences relates specifically to patients with 'symptomatic cataract' and eligible for cataract surgery according to NICE guidance 77, which has been deemed cost effective. Further, the presence of persistent macular oedema may delay the decision to perform cataract surgery due to the thickening of the macula. Without cataract surgery, the ILUVIEN implant cannot be used (according to TA 301). Therefore, these patients would have no access to an effective treatment. Of course, the above scenario could be overcome if the patient had been indicated for cataract surgery according to NICE guidance 77. A further benefit to the patient is the macula drying effect of the intravitreal steroid, which helps to reduce oedema before cataract surgery and reduce the risk of cystoid macula oedema after the cataract surgery.	Comments noted. The committee was aware of the unmet need and the target population (see sections 3.1 and 3.2 of FAD).
12	Consultee	Alimera Sciences Limited	Alimera Sciences acknowledges that laser and anti-VEGF may be suitable comparators provided it is clear that the model accounts for these being ineffective therapies as they are being used in patients with chronic DMO that are insufficiently responsive.	Comments noted. No change needed. Comparators are discussed in section 3.3 of the FAD.

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			This fact has been confirmed in the ICE-UK study where it was shown that during the 12 months before ILUVIEN was administered there was a gradual decline in visual acuity with standard of care (i.e. primarily anti-VEGF therapy and the current standard of care). Following the injection of the ILUVIEN implant there was an overall improvement of +4.3 letters at 12 months. This point was made in the consultation meeting but is not properly reflected in the ACD. Whilst the choice of comparator is not under debate, the outcomes associated with it are, and have a large influence on the cost-effectiveness. Modelling any gain or maintenance in vision whilst patients receive 'standard care', in this case continuing ineffective anti-VEGF and laser treatment, is contrary to the observations in ICE-UK of a decline in VA in the study eye in the period before ILUVIEN treatment, and a continuing decline in VA in the fellow eye when continuing on 'standard care'.[7]	
13	Consultee	The Royal College of Ophthalmologists	We feel that the data analysis has lost sight of how the drug is used clinically. The clinical opinion (and what is being requested) is to use Iluvien in patients who have cataracts before they come to have cataract surgery, not in patients who have no cataract. These patients would come to need cataract surgery whether Iluvien was used or not. The issue is whether Iluvien is given pre or post cataract surgery. Currently we have to operate on patients before using Iluvien so the cost of cataract surgery is not included in the model for pseudophakic patients. In the situation of giving Iluvien pre cataract surgery we assume that the cost of this surgery has been included in the model. However, these are all patients who have cataracts and will be having surgery in the near future (within 1-3 years). ***It could therefore be argued that the cost of cataract surgery should not be included in assessment of effectiveness of Iluvien.*** Intravitreal steroid use does have approval in phakic patients for other retinal conditions. Iluvien has an effect on the retina whether there is cataract present in the eye or not (as demonstrated by OCT thickness changes in the FAME studies which showed a sustained reduction in central retinal thickness (Campochiaro PA, Brown DM, et al. Ophthalmology 2011; 118: 626-635. Campochiaro PA, Brown DM, et al. Ophthalmology 2012; 119: 2125-2131). The presence of cataract does not have any influence on the diabetic macular oedema, but does have an effect on visual acuity. Removal of a cataract results in improved visual acuity. Cataract surgery is low risk	Comment noted. The committee considered all the evidence submitted, including evidence from clinical trials, patient and clinical experts, the company's submissions and the ERG's critique. It also carefully considered the comments received in response to the ACD. The clinical evidence is discussed in sections 3.4, 3.5 and 3.6 of FAD). The committee was aware of the target population (see sections 3.1 and 3.2 of FAD).

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			with good visual outcomes. The National Ophthalmology Database Audit for 2018 shows that the overall rates of PC rupture is 1.1% and 0.9% for visual loss. From the clinical point of view there are a number of advantages in giving Iluvien treatment prior to cataract surgery. This allows the retina to be more stable with reduced/ no fluid prior to surgery and it reduces the inflammatory response and worsening macular oedema seen with cataract surgery in patients with diabetic macular oedema. It is considered good clinical practice to control macular oedema prior to cataract surgery. Persistent macular oedema risks permanent damage to the photoreceptors and results in poorer long term outcomes. A paper on the UK expert opinion of treatment for diabetic macular oedema recommends that ophthalmologists use steroids second line. "*Therefore, intravitreal steroids should only be considered as second-line therapy if the persistent oedema is responsible for the decline in vision and the patient is likely to be compliant with follow-up appointments."* (Translating evidence into practice: recommendations by a UK expert panel on the use of aflibercept in diabetic macular oedema Pearce I; Bailey C; Fletcher E; Ghanchi F; Rennie C; Santiago C; Napier J; Yang Y. In Press Eye.) The number of patients likely to be affected by this is relatively small. Iluvien is used second line to anti-VEGF treatment. Laser is not used often as first line treatment these days and this practice is supported by the results of the recent DRCRnet trial showing patients who have diabetic macular oedema and good vision who have deferred anti VEGF treatment do as well as those patients treated promptly (this was a US based trial where there is no OCT thickness restriction on treatment with anti-VEGF drugs). This supports the practice of many UK ophthalmologists to wait for patients to reach 400 microns thickness and treat with anti-VEGF rather than laser patients earlier.	
14	Consultee	The Royal College of Ophthalmologists	FAME is not an appropriate model of usual care for comparison. In clinical practice, the alternative to intravitreal steroid is continued anti-VEGF treatment even if the eye is suboptimally responding. In FAME the sham/usual care was no treatment or laser, with some eyes being treated with off protocol anti-VEGF treatment which will have led to the slight increase in vision seen in this arm of the study. The FAME Sham/usual care group does NOT reflect current standard clinical practice. Currently most patients will be receiving anti-VEGF treatment . Patients who are on anti-VEGF treatment with inadequate response will continue to have treatment because they have "insufficient" rather than no response to treatment	Comment noted. The committee concluded that FAME does not reflect NHS clinical practice (see sections 3.4). It was aware that there is an unmet need (see section 3.1 and 3.2 of FAD).

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			(that is continued treatment is not futile). We would not stop treatment as that would risk vision worsening and we would expect these patients to continue anti-VEGF treatment and our clinical experience indicates these patients require 4-6 injections a year. Their vision would not be expected to improve with this ongoing anti-VEGF treatment (rather it would help to prevent further decline) and that is different to the sham group in FAME which showed a modest increase in vision (due in part to the use in some cases of off protocol anti-VEGF treatment which these patients had not previously had available).	
15	Clinical expert		**Has all of the relevant evidence been taken into account?** Yes, except the current 'usual care' is confused with the sham arm treatment effect from the FAME study, which is completely different and hence skews the consultation. **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** On the whole yes, please refer to comments. **Are the recommendations sound and a suitable basis for guidance to the NHS?** Since the phakic DMO population that responds poorly to current usual care (antiVEGFinjections) is not the same as the Sham arm of FAME studies, the model using FAME sham arm can not form the basis of cost effectiveness analysis, hence recommendations based on such analysis need careful review.	Comment noted. The committee concluded that FAME does not reflect NHS clinical practice (see section 3.4 of FAD).
16	Clinical expert		**Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?** Population with cataract is usually elderly, who with multimorbidity (including diabetes in the current context) need access to better & equal care. **Recommendations:** This recommendation would unnecessarily increase disease burden ('unresponsive DMO') on the phakic patients; which potentially can lead to irreversible vision loss and increased treatment burden and social costs.	Comments noted. The committee concluded that there were no equality issues related to the recommendations (see section 3.18 of FAD).The committee was aware of the unmet need and the target population (see sections 3.1 and 3.2 of FAD).

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			The company's proposed population is narrower than that in the NICE scope for this appraisal: Clinicians can identify significant lens opacities in phakic patients with visual symptoms. The Royal College of Ophthalmologist's NICE accredited guidelines provides detailed guidance on the subject noting: "The presence of cataract causes disability and increases the likelihood that individuals will suffer adverse events such as falls."(https://www.rcophth.ac.uk/wp-content/uploads/2018/02/Cataract-Commissioning-Guide-January-2018.pdf) Not addressing visual comorbidity of 'unresponsive" DMO would be detrimental to such patients in long term.	
17	Clinical expert		**Both laser treatment and anti-VEFGs are appropriate comparators for decision making:** AnitVEGF injections are the mainstay for centre involving diabetic macular oedema in current clinical practice. The laser treatment option is limited to focal (localised) and usually early macular oedema that has not involved centre of macula. Thus, laser treatment is not a useful/ valid comparator in the present context of current clinical practice in UK.	Comment noted. Comparators are discussed in section 3.3 of the FAD.
18	Clinical expert		**The clinical evidence for people with phakic eyes with symptomatic cataractt is limited because of very small numbers:** The issue to address is the phakic patients where the usual care (antiVEGF injections) have had poor response and macular oedema had persisted. Persistent macular oedema can cause irreversible damage to retina, and lack of timely intervention would not only result in failure to improve vision later even with further treatment, but would also lead to higher rate of decline in vision in future. Browning DJ, Stewart MW, Lee C. Indian J Ophthalmol. 2018 Dec;66(12):1736-1750. doi: 10.4103/ijo.IJO_1240_18. The Pivotal ETDRS studies have provided very good natural history data on diabetic retinopathy. Rates of visual loss also increased according to baseline retinopathy severity, with eyes having more severe retinopathy losing vision at higher rates than eyes with less severe retinopathy. (Longer the duration worse the retinopathy - macular damage) Photocoagulation for diabetic macular edema. Early treatment diabetic retinopathy study report number 1. Early treatment diabetic retinopathy study research group.	Comments noted. The clinical evidence was considered by committee and is discussed in sections 3.4, 3.5 and 3.6 of the FAD.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			Arch Ophthalmol. 1985;103:1796–806. **The clinical evidence for people with phakic eyes with symptomatic cataract is limited because of very small numbers:** For most clinical trials on macular conditions (AMD, DMO, Retinal Vein occlusions etc), cataract that may require surgery within 6 months is considered an exclusion; hence clinical data on patients with cataract on any such trials is not readily available. Study protocols are therefore not likely to have plans for sub group analysis on patients with cataracts. Despite such limitations, antiVEGF treatments are approved for use in phakic as well as pseudophakic eyes. **Non-comparative evidence does not reduce uncertainty in the clinical outcomes because of the extremely small number of people included:** The biological response of drug injected intravitreally in the eye is not altered by phakic or pseudophakic state. Yang et al's paper reported positive response of Fluocinolone injection in pseudophakic eyes. This has been seen in clinical practice in eyes where fluocinilone was injected at the time of cataract surgery as well. Similarly clinical studies as well as real life experience has confirmed that AntiVEGF injections work equally well in phakic or pseudophakic eyes. Furthermore, steroid implants are approved for use in treatment of macular oedema in RVO as well as uveitis in phakic eyes and have been found to be effective. **Non-comparative evidence does not reduce uncertainty in the clinical outcomes because of the extremely small number of people included:** The usual care in the context of current consultation is antiVEGF injections that have been found to suboptimal response in phakic eyes. These patients have no access to rescue treatment and often continue to have repeated antiVEGF injections to maintain status quo until cataract surgery. Sequential, secondline rescue treatment with Fluocinolone has been shown to have positive effect on salvaging retina (reduction in macular oedema) as well as better chance of static or improved vision (Yang et al).	
19	Clinical expert		**The treatment effect caused by natural recovery and rescue treatments should be applied to both arms of the model:**	Comment noted. The FAD has been amended (see section 3.9).

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			The population of interest for this consultation is phakic DMO patients whose standard of care - antiVEGF injections have resulted in suboptimal response or no response. Such patients have no access to rescue and their vision is not likely to improve - in fact it is likely to deteriorate over time. These patients are not likely to have natural recovery due to chronicity of their DMO that may lead to irreversible retinal structural damage.	
20	Clinical expert		**About 42% of people with diabetic macular oedema in phakic eyes with symptomatic cataract might get a second implant after 3 years:** Clinical decision for reinjection of fluocinolone implant is based on whether the DMO has recurred as judged by using OCT scan based macular thickness and factoring in vision assessment.	Comment noted. No changes required.
21	Clinical expert		**It is implausible that the treatment effect is maintained for a lifetime after treatment has stopped:** Clinical experience from real life management of DMO has confirmed that with time treatment need declines and majority of patients do not need repeated injections (antiVEGF or steroids) after first 3 years. Thus it is NOT implausible that treatment effect can be maintained for lifetime.	Comment noted. Committee considered the long term effect of treatment after treatment stop (see section 3.14 of FAD).
22	Clinical expert		**The ICERs are highly uncertain, and there is no single most plausible ICER, but all plausible ICERs exceed £30,000 per quality-adjusted life year (QALY) gained:** The use of FAME 'sham' arm to represent current clinical standard of care (usual care) is flawed as noted previously. The phakic DMO patients who are not responding to current usual care (antiVEGF injections) do not have access to rescue treatment. These patients would not have any protection against continuos and progressive damage to their macula by persistent macular oedema and hence no natural recovery is usually expected, instead a decline in vision with risk of irreversibility with chronicity is expected. "In patients with chronic Diabetic Macular Edema, the likelihood of achieving vision ≥20/40 with treatment diminishes as the vision worsens." Chakravarthy et al. Retina. 2018 Feb;38(2):343-351	Comment noted. The committee concluded that FAME does not reflect NHS clinical practice (see sections 3.4, 3.5 and 3.6). It considered all the evidence for cost effectivness (see section 3.16).
23	Web comment	NHS professional 1	There is definite unmet need in treating Diabetic Macular Oedema not responding to anti VEGF therapy in phakic patients. FLucinalone implant does fulfil that space, especially if the patient already has early to symptomatic cataract. With lack of options, patients are undergoing cataract surgery first to become eligible for Iluvien implant but this poses dangers of worsening DMO. If approved Iluvien can	Comments noted. The committee understood that there is an unmet need (see sections 3.1 and 3.2 in FAD).

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			be implanted first to control DMO before performing cataract surgery, this will have the best visual and anatomical outcome. Even though the cost of Iluvien implant is high, if this can prevent multiple anti VEGF injections, over all it will be a saving. Also considering that most patients with symptomatic cataract need cataract surgery any way.	
24	Web comment	NHS professional 2	**Has all of the relevant evidence been taken into account?** The conclusion that vision will potentially improve spontaneously in eyes that failed anti-VEGF therapy is not based in evidence and clinical experience show that without further intervention the situation is likely to deteriorate. **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** Some conclusions are not really based in evidence and are assumptions rather than facts. **Are the recommendations sound and a suitable basis for guidance to the NHS?** My views were made clear in my comment below. **Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?** No. I certainly appreciate the fact that the lack of data makes the calculation of cost-effectiveness of Iluvien in phakic eyes with unresponsive DMO difficult. The issue I would like to raise is related to the fact that, as you pointed out, there are no other options beyond laser and anti-VEGF therapy for these patients. Currently a patient with DMO who fails 6 monthly injections of one of the anti-VEGF agents (excluding Bevacizumab) should be considered for steroid therapy. Laser is inferior to anti-VEGF therapy and does not represent an alternative in case of failure of this approach. There is no evidence that continuing with the same approach after 6 months will be beneficial and there is also no evidence that changing to another anti-VEGF will also result in improvement (again, not including Bevacizumab in this comment). At this point,	Comments noted. The clinical evidence was considered by the committee and is discussed in sections 3.4, 3.5 and 3.6 of FAD.

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			without steroids, the situation will not improve and is likely to deteriorate. Even though the lens status is relevant, the integrity of the macula is a lot more important since the damage to the macula will result in irreversible loss of visual function, unlike cataract which can be easily reversed. So, sacrificing macular function to prevent development of lens opacity does not represent a sensible alternative. Many patients will already have symptomatic cataracts and will require surgery in the near future. It is unlikely there will be many patients with asymptomatic lens opacity fitting this scenario. I think the option of Iluvien should be made available in this situation of reduced vision due to DMO that fails to respond to current standard of care after 6 months of anti-VEGF therapy. Ozurdex and Iluvien represent the only options these patients will have. Iluvien involves a longer effect, less procedures and should be cost-effective in this regard. I disclose that I have a consultancy agreement with Alimera. My views represent my own clinical analysis with the best for the patient in my heart. I am not receiving any payment from Alimera to write this and decided to express my views independently since I feel strongly about offering the patients the best option solution to prevent visual loss. **Has all of the relevant evidence been taken into account?** It would appear that all published evidence has been taken into account. **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** I am not convinced that the cost effectiveness is reflecting what is actually happening in the clinical practice. As mentioned in my comment, because the steroid implants cannot be used in phakic patients, clinician s will use unlicensed triamcinolone injections in these unfortunate patients, which in turn will accelerate the formation of cataract and will lead to cataract surgery sooner than otherwise perhaps expected. Is this an economy? **Are the recommendations sound and a suitable basis for guidance to the NHS?** Not for the particular group of patient afflicted by chronic macular oedema, unresponsive to anti-VEGF intravitreal injections.	
25	Web comment	NHS professional 3	**Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of**	Comments noted. The committee understood that

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			people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? Please refer to my answer in the next box; if we refer particular to the grounds above, then no there is not. It was disappointing to see that NICE has not recommended the use of Iluvien in phakic patients. It is well know that both a VEGF pathway and inflammatory pathway can contribute to the development of diabetic macular oedema and hence, makes this condition so much more challenging to control. Also, it is well documented that patient with diabetes will develop cataracts at a much earlier age compared with patients who do not have diabetes. So far, it is believed that the group of patients who have early macular oedema are much more responsive to anti-VEGF therapy and their needs appear to be met by the availability of anti-VEGF therapy. For the patients who have a more chronic type of macular oedema, if they are psudophakic, and are non-responsive or partially responsive to anti-VEGF,then they can have intravitreal steroid implants (Ozurdex or Iluvien) and their needs are met. However, for the group of patients who have chronic macular oedema, are phakic and anti-VEGF non-responsive there is no option available. Majority of clinicians will consider unlicensed Triamcinolone intravitreal injection to try and help stabilize their disease. Some of the patients may have grid laser, with associated side-effects (central visual field loss). Considering that the majority of these patients are working age group, having an intact visual field is very important for them. As a clinician, I feel that this group of patients is being let down by this recommendation, as they are at a disadvantage to what is available to them. In my opinion, if a patient with diabetic macular oedema had 6 anti-VEGF injections and has not responded or partially responded, then evidently the inflammatory pathway is the dominant pathway in causing the oedema and should be treated accordingly- intravitreal steroids. Also, it is well documented that diabetic patients will develop cataract much sooner than patients without diabetes, that multiple anti-VEGF injection will contribute to formation of cataract sooner and giving unlicenced intravitreal triamcinolone will have similar effect in contributing to cataract formation as using intravitreal steroids implants. It would appear that in the end, the economic model, which takes into account the cataract surgery cost induced by the steroids is a false economy, as these patients will have cataract surgery rather sooner than later, but by then a lot of other resources would have been used to try and control the	there is an unmet need (see section 3.2 in FAD) and considered the clinical evidence for fluocinolone in phakic eyes (the FAD has been amended in section 3.5).

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			disease and give these patients a reasonable quality of life. In my clinical experience, if the Iluvien implant could be used without these restrictions, the patients would benefit from the best available treatment algorithm for their particular case; the delay imposed on using the Iluvien implant means that by the time the patient is psudophake the disease has become even more chronic and possibly more difficult to control and instead of having visual gain, (which is more likely to occur in early stages of diabetic macular oedema), we are now looking for maintaining vision or stopping visual loss. As a clinician I feel frustrated that I cannot offer my patients what I consider to be the best algorithm of treatment for them.	
26	Web comment	NHS professional 3	In real world there are phakic patients with diabetic macular oedema which is sometimes difficult to be managed with anti-VEGFs: like pregnant women or people with recent cardiovascular event. We know that the Fluocinolone Acetonide (FAc) implant stays for almost 3 years inside the eye and it is likely to play part in cataractogenesis. I believe from personal, professional experience on steroids use on phakic patients in Sweden that the risk of cataractogenesis with FAc implant from use is counterbalanced from the actual effect of the steroid on the resistant multi-cystoid diabetic macular oedema, preventing further damage to the photoreceptors and ganglion cells from the chronicity of the retinal oedema. Cataract operation would happen much safer at a later stage when the DMO is stable treated for long time without significant fluctuations. There are no big studies on FAc implant except the FAME trial regarding safety and effectiveness and the IRISS UK investigation study group regarding safety. However, Metanalysis studies (RELDEX and PREDIAMEX) and Real world studies (BEVORDEX) on dexamethasone implant would show the similar effectiveness of steroid comparing to anti-VEGF. No meta-analysis study exists for the FAc use on phakic DMO patients; but it would be worth done if would it be possible in future. Moreover, an effectiveness cost-analysis would show that fluocinolone acetonide implant use would reduce both the burden of cost on the clinical visits and treatment with other drugs like anti-VEGFs	Comments noted. The committee understood that there is an unmet need (see section 3.2 in FAD) and considered the clinical evidence for fluocinolone in phakic eyes (the FAD has been amended in section 3.5). The committee concluded that the cost-effectiveness estimates were very uncertain (see section 3.16 of FAD).
27	Web comment	NHS professional 4	**Recommendations:** There is an unmet need within our diabetic patients; who suffer from chronic diabetic macular oedema that is insufficiently responsive to laser, Lucentis and Eylea - who would benefit from intravitreal steroid, but cannot be offered due to NICE guidance restriction. So I have to end up managing these patients with Off-Label and unlicensed intravitreal steroid till such time they can be offered cataract surgery; given the lack of available therapies given NICE restriction At present within the NHS, we have no available therapies for the phakic patient with	Comments noted. The committee understood that there is an unmet need (see section 3.2 in FAD).

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			DMO, who is insufficiently responsive to available therapies (antivegf and laser) I take this approach because the importance of saving the retina far outweighs the importance of saving a natural lens; and I am prepared to use off label treatments to achieve this goal However we have licensed intravitreal steroid already; and they should be made available for this small subset of patients who are difficult to manage. Even if their implantation was scheduled prior to planned cataract surgery to avoid any additional cost to the NHS.	
28	Web comment	NHS professional 5	**Has all of the relevant evidence been taken into account?** Please see below **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** They do not take into account the likely treatment needed for DMO after cataract surgery between those who have adequately controlled DMO pre cataract surgery & those who do not. It is likely that by restricting intravitreal fluocinolone acetonide to phakic patients, that the costs may be greater. **Are the recommendations sound and a suitable basis for guidance to the NHS?** I have patients under my care for whom all other treatments for diabetic macular oedema (DMO) have been exhausted, but they are still phakic, albeit with an early cataract. These patients are very likely to come to need cataract surgery in the future anyway and by not having the option of pre cataract surgery intravitreal fluocinolone acetonide, risk requiring more treatment for DMO after the cataract surgery. For these reasons, I do not agree with the guidance. **Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?** No. There is evidence that for patients with diabetic macular oedema & cataracts, that	Comments noted. The committee understood that there is an unmet need (see section 3.2 in FAD).

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			having effective treatment for the diabetic macular oedema (DMO) BEFORE the cataract surgery results in less DMO post operatively than those patients who have the cataract surgery first and treatment for the DMO afterwards. Therefore by restricting intravitreal fluocinolone acetonide to only pseudophakic patients (for whom other DMO treatments , such as intravitreal anti-VEGF agents have been ineffective), this may inadvertently result in patients requiring more intravitreal treatment after their cataract surgery, resulting in an increased risk to the patient & also increased treatment costs.	
29		RNIB (received as web comment)	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** See comment on 1 - Recommendations. RNIB would endorse the view of the Royal College of Ophthalmologists that the costs of cataract surgery should be removed from cost-effectiveness calculations. RNIB is concerned that by not recommending the Fluocinolone acetonide (FAc) implant for use in this case, a group of patients with a sight-threatening diabetic macular oedema (DMO) will be unable to access this treatment where no other second-line options exist, with consequent risk to their vision. Suitable phakic patients will be placed in an impossible catch-22 situation, in which they are unable to receive FAc treatment to control their DMO unless they have had cataract surgery, but unable to have cataract surgery because of the known risks of exacerbating their DMO. Given that many of the patients involved would go on to develop cataracts independently of use of FAc implants, in discussion with the Royal College of Ophthalmologists, we would therefore agree that the cost of cataract surgery should not be taken into consideration in cost-effectiveness calculations. We would also endorse the points made by the Royal College, that relate to the Pearce et al expert best practice recommendations, with regards second-line steroid use for DMO. RNIB's position is that, so long as the additional risks, including those of accelerated cataract development and increased intraocular pressure, are discussed with the patient, so that informed consent is obtained, the FAc implant meets a clinical need, and should be recommended for use in DMO patients with phakic lenses for whom	Comments noted. The committee understood that there is an unmet need (see section 3.2 in FAD).

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			first-line treatment options have been insufficiently effective. RNIB does agree that the uncertainty about the cost-effectiveness of FAc treatment does need to be resolved and research, as outlined in TA301 Section 6, must be commissioned, also to include analysis of the treatment for pseudophakic and phakic patients independently.	
30	Web comment	NHS professional 6	**Has all of the relevant evidence been taken into account?** No. **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** Only partly. Diabetic patients have a higher risk of cataract than the general population. (1. Pollreisz A, Schmidt-Erfuth U. Diabetic cataract – pathogenesis, epidemiology and treatment. J Ophthalmol 2010; 2010:608751. 2. American Diabetes Association. Eye complications [internet]. 2013 [cited: 2016 October]. Available from: www.diabetes.org/living-with-diabetes/complications/eyecomplications. 3) Klein BEK et al, Prevalence of cataracts in a population-based study of persons with diabetes mellitus. Ophthalmology 1985; 92: 1191-1196). Approximately 85% of phakic eyes included in the MEAD Study had cataracts at baseline, although a similar figure for the FAME Study is not readily available. It is known that some eyes with DMO do not respond completely to treatment with anti-VEGFs especially in cases of chronic DMO. (Amoaku et al, 2015). It is known that vision improvement following cataract surgery in diabetics especially those with DMO is significantly less than in non-diabetic patients. (Romero-Aroca ety al, 2006; Somaiya et al, 2002; Eriikson et al, 2011). Furthermore, it is known that some eyes with DR without DMO or with non-centre involving DMO will progress to centre-involving DMO following cataract surgery. (Baker et al, DRCRNet JAMA Ophthalmol. 2013 July; 131(7): 870–879. doi:10.1001/jamaophthalmol.2013.2313.) This is associated with visual loss. Similarly, eyes with DMO unresponsive to previous treatment will progress following cataract surgery with associated vision loss. It is unconceivable that eyes with DMO will have significant vision improvement following cataract surgery without adequate treatment for the macular oedema.	Comments noted. The committee considered all the evidence submitted, including evidence from clinical trials, patient and clinical experts, the company's submissions and the ERG's critique. It also carefully considered the comments received in response to the ACD. The clinical evidence was considered by committee and is discussed in sections 3.4, 3.5 and 3.6 of the FAD. No changes needed.
31			**Are the recommendations sound and a suitable basis for guidance to the NHS?** Only partly.	Comments noted. The committee was aware of the unmet need and the target

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			I believe that the NICE ACD as published is wrong in its recommendations re: treatment of eyes with DMO unresponsive to treatments with standard care (laser, anti-VEGFs as appropriate) and who have symptomatic cataract. I do not believe that such patients if continued on standard of care will get improvement in vision due to cataract removal and due to insufficient response to SoC therapies the retina would be further (irreversibly) damaged by diabetic macular oedema. NICE has, to date, restricted its recommendation on treatment of eyes with DMO to pseudophakic patients. In other words, patients with phakic eyes with DMO currently fall outside NICE TAs. **Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?** Eyes with diabetic macular oedema and significant cataract prior to cataract surgery. Such patients, as the cataract is significant, and will have subsequent surgery, should benefit from pre-surgical intravitreal Iluvien. That is because these patients will have progression of the DMO, and vision loss following cataract surgery alone. Care in such patients cannot be considered equal to that in others. I believe that the NICE ACD as published is wrong in its recommendations re: treatment of eyes with DMO unresponsive to treatments with standard care (laser, anti-VEGFs as appropriate) and who have symptomatic cataract. I do not believe that such patients if continued on standard of care will get improvement in vision due to cataract removal alone as, as a result of insufficient response to SoC therapies, the retina would be further (irreversibly) damaged by diabetic macular oedema. NICE has, to date, restricted its recommendation on treatment of eyes with DMO to pseudophakic patients. In other words, patients with phakic eyes with DMO currently fall outside NICE TAs. Diabetic patients have a higher risk of cataract than the general population. (1. Pollreisz A, Schmidt-Erfuth U. Diabetic cataract – pathogenesis, epidemiology and treatment. J Ophthalmol 2010; 2010:608751. 2. American Diabetes Association. Eye complications [internet]. 2013 [cited: 2016 October]. Available from: www.diabetes.org/living-with-diabetes/complications/eyecomplications. 3) Klein BEK et al, Prevalence of cataracts in a population-based study of persons with diabetes mellitus. Ophthalmology 1985; 92: 1191-1196). Approximately 85% of phakic eyes included in the MEAD Study had cataracts at	population (see sections 3.1 and 3.2).

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			baseline, although a similar figure for the FAME Study is not readily available. It is known that some eyes with DMO do not respond completely to treatment with anti-VEGFs especially in cases of chronic DMO. (Amoaku et al, 2015). It is known that vision improvement following cataract surgery in diabetics especially those with DMO is significantly less than in non-diabetic patients. (Romero-Aroca ety al, 2006; Somaiya et al, 2002; Eriikson et al, 2011). Furthermore, it is known that some eyes with DR without DMO or with non-centre involving DMO will progress to centre-involving DMO following cataract surgery. (Baker et al, DRCRNet JAMA Ophthalmol. 2013 July; 131(7): 870–879. doi:10.1001/jamaophthalmol.2013.2313.) This is associated with visual loss. Similarly, eyes with DMO unresponsive to previous treatment will progress following cataract surgery with associated vision loss. It is unconceivable that eyes with DMO will have significant vision improvement following cataract surgery without adequate treatment for the macular oedema. Furthermore, administration of intravitreal steroids preoperatively is known to reduce/prevent the progression of postoperative macular oedema (Mehta et al, 2015. I would suggest that it, in my clinical judgement, it is implausible to suggest that that if a patient presents with centre involving DMO, and insufficient response to available therapies, treatment a day or more 1 day(s) before cataract surgery with ILUVIEN implant would not be cost effective, whereas that treatment with the same ILUVIEN implant on the day of / or soon after cataract surgery as has already been agreed by NICE to be cost-effective? Amoaku WM, Saker S, Stewart EA. A review of therapies for diabetic macular oedema and rationale for combination therapy. Eye (Lond). 2015 Jun 26. doi: 10.1038/eye.2015.110. Review Romero-Aroca P, Fernandez-Ballart J, Almena-Garcia M, Mendez-Marin I, Salvat-Serra M, Buil- Calvo JA. Nonproliferative diabetic retinopathy and macular edema progression after phacoemulsification: prospective study. J Cataract Refract Surg. 2006; 32(9):1438–44. Somaiya MD, Burns JD, Mintz R, Warren RE, Uchida T, Godley BF. Factors affecting visual outcomes after small-incision phacoemulsification in diabetic patients. J Cataract Refract Surg. 2002; 28(8):1364–71. Eriksson U, Alm A, Bjarnhall G, Granstam E, Matsson AW. Macular edema and visual outcome following cataract surgery in patients with diabetic retinopathy and controls. Graefes Arch Clin Exp Ophthalmol. 2011; 249(3):349–59. Mehta H, Gillies M, Fraser-Bell S. Perspective on the role of Ozurdex (dexamethasone intravitreal implant) in the management of diabetic macular oedema. Ther Adv Chronic Dis. 2015 Sep;6(5):234-45. doi: 10.1177/2040622315590319.	

NICE National Institute for Health and Care Excellence

Fluocinolone acetonide intravitreal implant for treating chronic diabetic macular oedema (part review of TA301) [ID1421]

Consultation on the appraisal consultation document – deadline for comments 5pm on **Wednesday 21 August 2019 email:** TACommC@nice.org.uk/NICE DOCS

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Alimera Sciences Limited Royal Pavilion Wellesley Road Aldershot Hampshire GU11 1PZ United Kingdom
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[None]

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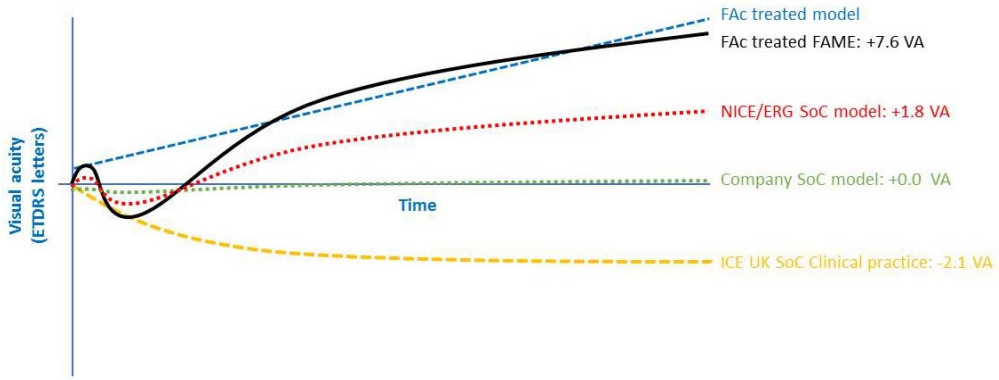
Consultation on the appraisal consultation document – deadline for comments 5pm on **Wednesday 21 August 2019 email:** TACommC@nice.org.uk/NICE DOCS

Name of commentator person completing form:	[redacted]
Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1. Body of evidence on subpopulation "phakic with symptomatic cataract" "*The company submitted evidence for people with phakic eyes and symptomatic cataracts."* *(Page 3)*	The company feel strongly that whenever 'symptomatic cataract' is mentioned it should be made clear to the reader that this refers to the group of patients eligible for cataract surgery according to NICE guidance 77 and deemed cost effective. This is important as it is clear guidance to clinicians on the patient group and surgical options approved by NICE. In the context of referring a patient for cataract surgery, NICE guidance 77 states, "…the decision to refer a person with a cataract for surgery on a discussion with them (and their family members or carers, as appropriate)…" and to "…not restrict access to cataract surgery on the basis of visual acuity."[1] **NICE guidance 77:** In phakic eyes with symptomatic cataract (NICE guidance 77) there is a clear unmet need as vision is declining. Furthermore, NICE guidance 77 can be used as a basis and a means to identify and treat DMO patients that are insufficiently responding to anti-VEGF therapy provided they have a symptomatic cataract. **ICE-UK study[2]:** This study demonstrated that in people with 'phakic eyes and symptomatic cataracts after an insufficient response to anti-VEGF therapy' there was declining vision in spite of on-going treatment.
2. Clinical evidence of broader trial DMO population relevant for phakic eyes insufficiently responsive to anti-VEGF and with symptomatic cataract *"Only very few people had anti-VEGFs before the trial..."* *(page 3)*	It is important that NICE is clear that the FAME control arm (active treatment) and treatment arm do not represent the outcome of usual care in the target population. Indeed, at the time of the trial (2005 to 2009) anti-VEGFs were not a standard of care and this is why only very few people had anti-VEGFs before the trial. Alimera Sciences believes that data in ICE-UK in the 12 months prior to ILUVIEN is representative of current clinical practice. ICE-UK collated data from current clinical practices where anti-VEGF was being used as a first-line therapy and prior to the use of ILUVIEN.
3. Clinical evidence of broader trial DMO population relevant for phakic eyes insufficiently responsive to anti-VEGF and with symptomatic cataract *"The clinical evidence for people with phakic*	Alimera Sciences would like to clarify that the discussion is about an existing unmet need and that the population in question is an identifiable population from the FAME trial and suitable for cataract surgery according to NICE guidance 77. Alimera Sciences believes that following cataract surgery the effectiveness of ILUVIEN is no different in VA outcomes in patients with a phakic or pseudophakic lens at baseline as the majority of evidence pertains to the 3 years of therapy rather than the period of time between cataract diagnosis and cataract removal (i.e. 0 and 3 months in the ICE-UK study). Furthermore, having a steroid in the eye has clear advantages at the time of cataract surgery in people at increased risk of cystoid macular oedema (e.g. people with diabetes or uveitis).[1]

eyes with symptomatic cataract is limited because of very small numbers" *(page 7)*	Alimera Sciences would also like to make it clear that DMO is a progressive disease and detrimental to the retina irrespective of the status of the patient's lens. An untreated or insufficiently responsive DMO eye is at risk of damage and subsequent loss of vision as shown in the 12-months prior to ILUVIEN in the ICE-UK study. Following ILUVIEN administration, the retinal protective effect was demonstrated by the improvement in visual acuity.
4. Plausibility of cost-effectiveness estimates *"Even the lowest clinically plausible cost-effectiveness estimates are substantially higher than what NICE normally considers as acceptable" (page 4)*	**The vision outcomes calculated by Alimera Sciences are very conservative** DMO is a progressive disease and detrimental to the retina irrespective of the status of the patient's lens. This is shown in the ICE-UK study where in current UK clinical practice there was a progressive loss in visual acuity during the 12 months preceding the injection of the ILUVIEN implant (*represented by the yellow line in the schematic below*). As a progressive disease, however, visual acuity would be expected to worsen over the long-term if ineffective medicines continued to be given and the small losses in visual acuity observed in the ICE-UK study would quickly become much larger over several years. **Figure. Schematic showing visual acuity outcomes in patients treated with the fluocinolone acetonide (FAc) implant (both model and actual values from the FAME study) and standard of care (models and ICE-UK)**  In contrast to Alimera Sciences view, NICE / ERG argue that the sham treated arm in the FAME trial actually reflects usual care (*represented by the red line in the schematic above*). This is incorrect as it does not reflect current clinical practice in the UK (*represented by the yellow line in the schematic above*). In looking at the scenarios, therefore, it was calculated that visual acuity would remain stable (*represented by the green line in the schematic above*), which is unlikely according to ICE-UK data but accounts for possible improvements in visual acuity following cataract surgery. Alimera Sciences believes that this assumption is very conservative considering the progressive nature of DMO. **Alimera Sciences' model is very conservative** The company would like to highlight that the base case ICER from the company was actually £2,187 and was based on a very conservative model of the net treatment effect versus the control arm. Alimera Sciences acknowledges that there is uncertainty around some assumptions and inputs considered in the company base case, we disagree that this scenario should be discarded as "not plausible". We note that the ERG presented a similar scenario with assumption of constant best-corrected visual acuity in the usual care arm, resulting in a

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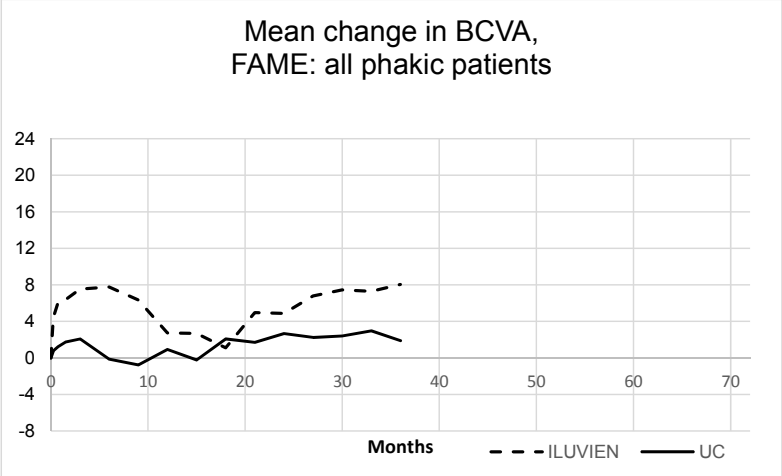
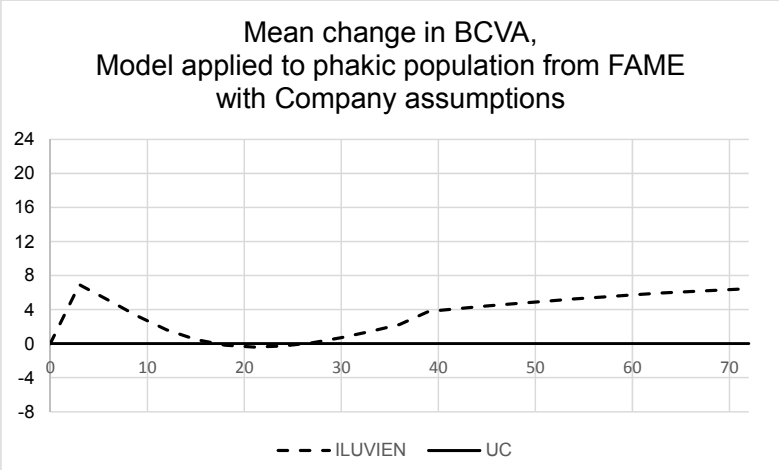
	cost effective ICER of £18,710. We believe this to be plausible. **Reasons why NICE's position is implausible** Firstly, in eyes without prior ILUVIEN treatment and with symptomatic cataract (i.e. eligible for cataract surgery per NICE guidance 77), the extraction of the cataract is clearly unrelated to ILUVIEN treatment and considered cost-effective. Secondly, NICE's position on the mildly improved vision over the long-term is also implausible. Indeed, whilst cataract surgery is expected to provide a transient gain in visual acuity, patients with an insufficient response will continue to be treated with ineffective first-line therapies and thus the retina will remain under-treated and vision will continue to decline. Thirdly, in patients with a pseudophakic eye with chronic DMO insufficiently responsive to available therapies (i.e. predominantly anti-VEGF), ILUVIEN implantation has been shown to be cost-effective in TA301.[3] Yet, NICE has concluded that if a cataract surgery unrelated to ILUVIEN was conducted one day earlier, the therapy would not be cost-effective. This argument seems completely nonsensical as the cataract is unrelated to ILUVIEN and treatment would be equivalent to current guidance outlined in TA301.[3]
5. Rescue treatments and natural recovery within 3 years *"The treatment effect caused by natural recovery and rescue treatments should be applied to both arms of the model" (page 10)* *"The company included the full treatment effectiveness in the FAME treatment arm in their model but assumed no change in BCVA in the usual care arm. The company explained that this approach is taken because the sham arm of FAME does not represent current NHS clinical practice and that there is no natural recovery seen in usual care. Because rescue therapy was used in both arms in FAME, the ERG suggested modelling the net effect between*	The "*effect caused by natural recovery and rescue treatments*" does not exist in the target population. Patients selected for treatment with ILUVIEN have an "insufficient response to available treatments" (the label) due to increasing damage to the retina caused by DMO irrespective of lens status. The clinical expert at the NICE committee meeting clearly stated that this proposed "natural" recovery was improbable in this patient group. The ICE-UK clinical data showed a BCVA decreased by 2 letters over 12 months before FAc administration of whom 56 eyes underwent cataract surgery during 12 months prior to implant. In total, 185 (89%) of 208 eyes were pseudophakic before injection of the FAc implant.[4] Alimera Sciences agrees with the Decision Committee that the "net gain" in best-corrected visual acuity in FAME is the best estimate of treatment effect. However, the net gain predicted in the company model is in fact much closer to the net gain estimated in FAME than the gain predicted in the ERG model adaptation, while remaining conservative, as shown below. The Decision Committee did not take note of an essential argument made by the Company to justify the assumption of constant best-corrected visual acuity in the sham arm. Also, we would like to detail this argument here. The company presented in its submission a scenario assuming constant best-corrected visual acuity in the usual care arm of FAME and a scenario where the transition probabilities for usual care were based on the sham arm of FAME. The comparison of the net gain in best-corrected visual acuity in the trial to the model predictions for the phakic population showed that the model predictions were much closer to the trial results in the former scenario. This was a major reason supporting the choice of constant best-corrected visual acuity in usual care arm as base case scenario. The graphs below show: - the mean change in best-corrected visual acuity for the phakic population from the FAME study. - model predictions for the trial phakic population in the scenario with constant best-corrected visual acuity in the usual care arm (scenario considered in Company

treatment and sham arm […] [The committee] noted that both arms included people who had rescue therapies and agreed that the same issue applied to the treatment arm. The committee concluded that modelling the net effect was more appropriate than assuming no change in BCVA for the usual care arm" *(page 10)*	submission). - model predictions for the trial phakic population in scenario with transition probabilities for usual care based on sham arm of FAME (base case scenario considered by ERG). As shown by these graphs, the base case scenario in Company submission is more consistent with the results of FAME trial, especially in terms of the net gain in best-corrected visual acuity following treatment with the FAc implant. In both the trial results and the company model, there is a net gain in best-corrected visual acuity reaching approximately 8 letters after treatment administration, followed by a decrease in net gain to approximately zero around 20 months, and then a progressive increase in the net gain over time. The curves generated by the company model do not follow very closely those from the trials, but the model actually provides a very conservative prediction of the net gain in best-corrected visual acuity over time. The model with transition probabilities obtained based on sham arm of FAME (ERG scenario) does not reflect the trial results. In particular, this model predicted that best-corrected visual acuity would be worse in the fluocinolone arm than in the sham arm after 10 months, for the phakic trial population.  

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	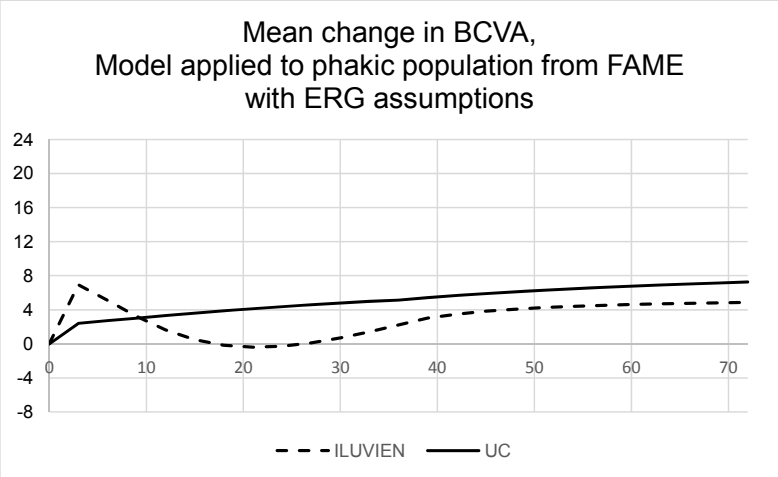 Looking at patients with cataract, the estimates of net gain in best-corrected visual acuity (FAc vs. sham/usual care) are: - in FAME trial, using phakic patients at baseline undergoing surgery cataract during the study as a proxy (95 patients in fluocinolone 0.2 mcg arm, 23 patients in sham arm): +3.2 letters at 12 months and +3.2 letters at 36 months. - in Company base case scenario: +2.6 letters at 12 months and +3.6 letters at 36 months. - in ERG base case scenario: -1.6 letters at 12 months and -2.7 letters at 36 months. While the company provides plausible estimates of the net gain in best-corrected visual acuity, the ERG adaptation of the model clearly does not. As regards "natural recovery and rescue treatments", it should be noted that: • the use of rescue treatments was significantly lower in the FAc arm, so any effect of rescue treatments would also be lower: as reported in Campochiaro *et al*.[5] after 6 weeks in the study, patients were allowed to undergo additional laser treatments, and subsequently treatments were allowed as frequently as every 3 months for persistent or recurrent DME. A significantly higher percentage of patients in the sham group (60.7%) received rescue focal grid laser than in the FAc treatment arm (40.7%) Also, a greater percentage of patients were given repeated focal/grid laser treatments in the sham group; 11.9% of patients in the sham group received 3 treatments during the trial compared with 6.6% FAc treatment arm.
6. Reinjection rate within 3 years *"In their model, the company assumed an average of 1.06 implants per person over the first 3 years in line with non-comparative data from the Medisoft study. […] Non-comparative data from the IRISS*	We agree that a very small proportion of people will have a second implant within the first 3 years. The IRISS study estimates a re-injection rate of 1.13 implants but not specific to the UK as this figure is based on usage in the UK, Germany and Portugal. Focusing on only the UK, analyses reveals the most plausible re-injection rate to be a value of 1.06 (n=462 eyes treated with 491 ILUVIEN implants over a mixed follow-up period). This is consistent with the Medisoft study (n=93 eyes treated with 99 ILUVIEN implants over a three year period) and independent of lens status as the majority of patients are pseudophakic due to current UK practice and market restrictions (IRISS safety report published 23rd July 2019).

study suggested that this number is 1.13 implants over the first 3 years. The ERG included the number from the IRISS study in their base-case model. […] The committee concluded that it is reasonable to assume people may have more than 1 implant during the first 3 years and accepted the ERG's base-case model assumption." *(page 11)*	
7. Real-world clinical practice evidence from ICE-UK "*The committee concluded that there were not enough data to establish if fluocinolone acetonide intravitreal implant worked better than usual care in phakic eyes with symptomatic cataract."* *(page 8)*	This point has been made previously that there are only two therapies that can currently be used in phakic eyes – these are laser and anti-VEGF therapy. However, in the target population (i.e. patients with chronic DMO that are insufficiently responsive and a symptomatic cataract) these therapies would have already been shown to be ineffective. If left untreated or treatment continued with ineffective therapies, the patient risks further retinal damage and long-term vision loss. The above point is reflected in the ICE-UK study where there was a gradual decline in visual acuity with standard of care (i.e. primarily anti-VEGF therapy and the current standard of care) in the 12 months prior to ILUVIEN. Further, the presence of persistent macular oedema could theoretically lead to delays in cataract surgery due to the risk of pseudophakic cystoid macula oedema. In this scenario, an intravitreal steroid prior to cataract surgery would help to dry the oedema and reduce the potential for pseudophakic cystoid macula oedema. As mentioned previously, the majority of the clinical evidence in the UK has been accrued following the approval of TA301 and so the majority of real-world evidence pertains to a 3 year of therapy following ILUVIEN administration. There is less data for the 3 month period (based on ICE-UK) between cataract diagnosis and cataract removal, although the study by Yang *et al*.[6] shows a similar visual acuity outcome being achieved after 3 years of ILUVIEN therapy irrespective of the lens status at baseline.
8. NICE TA301 restricts use to pseudophakic eyes in UK patients "*Also, noncomparative studies used to support the company's submission only include few people with phakic eyes and symptomatic cataract."* *(page 3)*	At the time TA301 was approved it was suggested by NICE that the company collect data from current clinical practices where anti-VEGF is being used before ILUVIEN - acknowledging that anti-VEGF's were not widely used at the time the pivotal trial was conducted. For this reason, Alimera Sciences set-up and conducted the ICE-UK study and from this it is possible to assess the effect of the FAc implant after an insufficient response to anti-VEGF.[2] ICE-UK showed that during the 12 months before ILUVIEN was administered there was a gradual decline in visual acuity with standard of care (i.e. primarily anti-VEGF therapy). Following the injection of the ILUVIEN implant there was an overall improvement of +4.3 letters at 12 months. The company also feels strongly that ICE-UK as ground-breaking non-comparative study should not be dismissed and instead be given more weight as this study was recommended by NICE at the time TA301 was approved and since that time has collected

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	data from current clinical practices where anti-VEGF is being used before ILUVIEN.
9. Uncertainty of FAME and ICE-UK *"Non-comparative evidence does not reduce uncertainty in the clinical outcomes because of the extremely small number of people included" (page 8)*	**NICE guidance 77 is useful for identifying the target population** The discussion here is not about the number of eyes, it's a question of whether the target population is a clear and identifiable cohort of patients. Based on the FAME trial, a small proportion of phakic eyes did have 'symptomatic cataract' and there is NICE guidance (i.e. NG77) on clinical decision making once a diagnosis has been made. Furthermore, the ICE-UK study shows that patients with a phakic lens at the start of ILUVIEN therapy are likely to undergo a cataract operation between 0 and 3 months after the ILUVIEN implant is administered. Hence NICE guidance 77 is useful in identifying the target population and can be used as a basis for commencement of ILUVIEN therapy knowing that cataract surgery is likely to occur relatively soon after the ILUVIEN implant is administered. Speaking from a pragmatic point of view, NICE guidance 77 will help deliver ILUVIEN therapy more efficiently to patients where there is an unmet need. It also means that, as acknowledged in section 3.2 of the ACD, patients do not need "…to wait until after cataract surgery before they are offered intravitreal steroid implants" and that they are treated as effectively as possible thus helping to reduce "…anxiety and stress because of the chronic nature of the disease and potential sight loss."
10. Uncertainty of FAME and ICE-UK *No gain/no loss (to ILUVIEN/prior to ILUVIEN) in BCVA is not right assumption according to ICE UK*	**ICE shows an improvement in VA when ILUVIEN is administered at the same time as cataract removal** The submission presented evidence from 14 patients from ICE-UK and 10 patients from retro-IDEAL who had cataract surgery and FAc implant administration at the same time. Results from the ICE-UK study showed a real-world mean gain of 13 letters over a 12-month period following concurrent cataract removal and FAc implant administration.
11. Applicability and definition of Usual Care as Comparator *"This makes it difficult to establish if fluocinolone acetonide intravitreal implant works better than usual care for these people, especially in the long term." (page 4)*	Usual care in patients that are insufficiently responsive to anti-VEGFs is ineffective from a cost and clinical perspective. This is openly stated in section 3.2 of the ACD where it is mentioned that "clinical experts confirmed that in some cases, people continue to have anti-vascular endothelial growth factors (anti-VEGFs), even if they do not work well," an observation supported by the fellow eye arm of the ICE-UK study." By allowing this practice to continue, NICE is condoning this practice and the wasteful use of NHS England and Wales resources. Alimera Sciences would like to reiterate that the ILUVIEN implant is only administered after an insufficient response to prior therapy. The ICE-UK study confirmed this was primarily after anti-VEGF, so by definition the ILUVIEN implant works better than usual care as this reflects continued therapy with an ineffective treatment option. The recommendation being sought by Alimera Sciences relates specifically to patients with 'symptomatic cataract' and eligible for cataract surgery according to NICE guidance 77, which has been deemed cost effective. Further, the presence of persistent macular oedema may delay the decision to perform cataract surgery due to the thickening of the macula. Without cataract surgery, the ILUVIEN implant cannot be used (according to TA 301). Therefore, these patients would have no access to an effective treatment. Of course, the above scenario could be overcome if the patient had been indicated for cataract surgery according to NICE guidance 77. A further benefit to the patient is the macula drying effect of the intravitreal

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	steroid, which helps to reduce oedema before cataract surgery and reduce the risk of cystoid macula oedema after the cataract surgery.
12. Clinically relevant comparator "*…both laser treatment and anti-VEGFs are appropriate comparators for decision making."* *(page 6)*	Alimera Sciences acknowledges that laser and anti-VEGF may be suitable comparators provided it is clear that the model accounts for these being ineffective therapies as they are being used in patients with chronic DMO that are insufficiently responsive. This fact has been confirmed in the ICE-UK study where it was shown that during the 12 months before ILUVIEN was administered there was a gradual decline in visual acuity with standard of care (i.e. primarily anti-VEGF therapy and the current standard of care). Following the injection of the ILUVIEN implant there was an overall improvement of +4.3 letters at 12 months. This point was made in the consultation meeting but is not properly reflected in the ACD. Whilst the choice of comparator is not under debate, the outcomes associated with it are, and have a large influence on the cost-effectiveness. Modelling any gain or maintenance in vision whilst patients receive 'standard care', in this case continuing ineffective anti-VEGF and laser treatment, is contrary to the observations in ICE-UK of a decline in VA in the study eye in the period before ILUVIEN treatment, and a continuing decline in VA in the fellow eye when continuing on 'standard care'.[7]

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

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REFERENCES

1. NICE. Recommendations | Cataracts in adults: management | Guidance NG77. *Guideline NG77* (2017). at <https://www.nice.org.uk/guidance/ng77>
2. Holden, S. E., Currie, C. J. & Owens, D. R. Evaluation of the clinical effectiveness in routine practice of fluocinolone acetonide 190 µg intravitreal implant in people with diabetic macular edema. *Curr. Med. Res. Opin.* **33,** 5–17 (2017).
3. NICE. Technology appraisal guidance [TA301]. Fluocinolone acetonide intravitreal implant for treating chronic diabetic macular oedema after an inadequate response to prior therapy. *27 Nov 2013* (2013). at <https://www.nice.org.uk/guidance/ta301>
4. Holden, S. E., Currie, C. J. & Owens, D. R. Health-economic evaluation of fluocinolone acetonide 190 µg implant in people with diabetic macular edema. *Curr. Med. Res. Opin.* **33,** 45–52 (2017).
5. Campochiaro, P. A. *et al.* Sustained delivery fluocinolone acetonide vitreous inserts provide benefit for at least 3 years in patients with diabetic macular edema. *Ophthalmology* **119,** 2125–2132 (2012).
6. Yang, Y. *et al.* Long-term outcomes of phakic patients with diabetic macular oedema treated with intravitreal fluocinolone acetonide (FAc) implants. *Eye* **29,** 1173–80 (2015).
7. Currie, C. J., Holden, S. E., Berni, E. & Owens, D. R. Evaluation of the clinical effectiveness of fluocinolone acetonide 190 µg intravitreal implant in diabetic macular edema: a comparison between study and fellow eyes. *Curr. Med. Res. Opin.* **33,** 19–31 (2017).

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	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	The Royal College of Ophthalmologists
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A
Name of commentator person completing form:	[redacted]

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	Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	We feel that the data analysis has lost sight of how the drug is used clinically. The clinical opinion (and what is being requested) is to use Iluvien in patients who have cataracts before they come to have cataract surgery, not in patients who have no cataract. These patients would come to need cataract surgery whether Iluvien was used or not. The issue is whether Iluvien is given pre or post cataract surgery. Currently we have to operate on patients before using Iluvien so the cost of cataract surgery is not included in the model for pseudophakic patients. In the situation of giving Iluvien pre cataract surgery we assume that the cost of this surgery has been included in the model. However, these are all patients who have cataracts and will be having surgery in the near future (within 1-3 years). ***It could therefore be argued that the cost of cataract surgery should not be included in assessment of effectiveness of Iluvien.*** Intravitreal steroid use does have approval in phakic patients for other retinal conditions. Iluvien has an effect on the retina whether there is cataract present in the eye or not (as demonstrated by OCT thickness changes in the FAME studies which showed a sustained reduction in central retinal thickness (Campochiaro PA, Brown DM, et al. Ophthalmology 2011; 118: 626-635. Campochiaro PA, Brown DM, et al. Ophthalmology 2012; 119: 2125-2131). The presence of cataract does not have any influence on the diabetic macular oedema, but does have an effect on visual acuity. Removal of a cataract results in improved visual acuity. Cataract surgery is low risk with good visual outcomes. The National Ophthalmology Database Audit for 2018 shows that the overall rates of PC rupture is 1.1% and 0.9% for visual loss. From the clinical point of view there are a number of advantages in giving Iluvien treatment prior to cataract surgery. This allows the retina to be more stable with reduced/ no fluid prior to surgery and it reduces the inflammatory response and worsening macular oedema seen with cataract surgery in patients with diabetic macular oedema. It is considered good clinical practice to control macular oedema prior to cataract surgery. Persistent macular oedema risks permanent damage to the photoreceptors and results in poorer long term outcomes. A paper on the UK expert opinion of treatment for diabetic macular oedema recommends that ophthalmologists use steroids second line. "*Therefore, intravitreal steroids should only be considered as second-line therapy if the persistent oedema is responsible for the decline in vision and the patient is likely to be compliant with follow-up appointments."* (Translating evidence into practice: recommendations by a UK expert panel on the use of aflibercept in diabetic macular oedema Pearce I; Bailey C; Fletcher E; Ghanchi F; Rennie C; Santiago C; Napier J; Yang Y. In Press Eye.) The number of patients likely to be affected by this is relatively small. Iluvien is used second line to anti-VEGF treatment. Laser is not used often as first line treatment these days and this practice is supported by the results of the recent DRCRnet trial showing patients who have diabetic macular oedema and good vision who have deferred anti VEGF treatment do as well as those patients treated promptly (this was a US based trial where there is no OCT thickness restriction on treatment with anti-VEGF drugs). This supports the practice of many UK ophthalmologists to wait for patients to reach 400 microns thickness and treat with anti-VEGF rather than laser patients earlier.
2	FAME is not an appropriate model of usual care for comparison. In clinical practice, the alternative to intravitreal steroid is continued anti-VEGF treatment even if the eye is suboptimally responding. In FAME the sham/usual care was no treatment or laser, with some

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	eyes being treated with off protocol anti-VEGF treatment which will have led to the slight increase in vision seen in this arm of the study. The FAME Sham/usual care group does NOT reflect current standard clinical practice. Currently most patients will be receiving anti-VEGF treatment . Patients who are on anti-VEGF treatment with inadequate response will continue to have treatment because they have "insufficient" rather than no response to treatment (that is continued treatment is not futile). We would not stop treatment as that would risk vision worsening and we would expect these patients to continue anti-VEGF treatment and our clinical experience indicates these patients require 4-6 injections a year. Their vision would not be expected to improve with this ongoing anti-VEGF treatment (rather it would help to prevent further decline) and that is different to the sham group in FAME which showed a modest increase in vision (due in part to the use in some cases of off protocol anti-VEGF treatment which these patients had not previously had available).
3	
4	
5	
6	

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
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	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Dr Faruque Ghanchi
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None.
Name of commentator person completing form:	Dr Faruque Ghanchi

Comment number	**Comments**

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	Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	**Has all of the relevant evidence been taken into account?** Yes, except the current 'usual care' is confused with the sham arm treatment effect from the FAME study, which is completely different and hence skews the consultation. **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** On the whole yes, please refer to comments. **Are the recommendations sound and a suitable basis for guidance to the NHS?** Since the phakic DMO population that responds poorly to current usual care (antiVEGFinjections) is not the same as the Sham arm of FAME studies, the model using FAME sham arm can not form the basis of cost effectiveness analysis, hence recommendations based on such analysis need careful review. **Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?** Population with cataract is usually elderly, who with multimorbidity (including diabetes in the current context) need access to better & equal care. **Recommendations:** This recommendation would unnecessarily increase disease burden ('unresponsive DMO') on the phakic patients; which potentially can lead to irreversible vision loss and increased treatment burden and social costs. **The company's proposed population is narrower than that in the NICE scope for this appraisal:** Clinicians can identify significant lens opacities in phakic patients with visual symptoms. The Royal College of Ophthalmologist's NICE accredited guidelines provides detailed guidance on the subject noting: "The presence of cataract causes disability and increases the likelihood that individuals will suffer adverse events such as falls."(https://www.rcophth.ac.uk/wp-content/uploads/2018/02/Cataract-Commissioning-Guide-January-2018.pdf) Not addressing visual comorbidity of 'unresponsive" DMO would be detrimental to such patients in long term.

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	Both laser treatment and anti-VEFGs are appropriate comparators for decision making: AnitVEGF injections are the mainstay for centre involving diabetic macular oedema in current clinical practice. The laser treatment option is limited to focal (localised) and usually early macular oedema that has not involved centre of macula. Thus, laser treatment is not a useful/ valid comparator in the present context of current clinical practice in UK. **The clinical evidence for people with phakic eyes with symptomatic 3ataractt is limited because of very small numbers:** The issue to address is the phakic patients where the usual care (antiVEGF injections) have had poor response and macular oedema had persisted. Persistent macular oedema can cause irreversible damage to retina, and lack of timely intervention would not only result in failure to improve vision later even with further treatment, but would also lead to higher rate of decline in vision in future. Browning DJ, Stewart MW, Lee C. Indian J Ophthalmol. 2018 Dec;66(12):1736-1750. doi: 10.4103/ijo.IJO_1240_18. The Pivotal ETDRS studies have provided very good natural history data on diabetic retinopathy. Rates of visual loss also increased according to baseline retinopathy severity, with eyes having more severe retinopathy losing vision at higher rates than eyes with less severe retinopathy. (Longer the duration worse the retinopathy - macular damage) Photocoagulation for diabetic macular edema. Early treatment diabetic retinopathy study report number 1. Early treatment diabetic retinopathy study research group. Arch Ophthalmol. 1985;103:1796–806. **The clinical evidence for people with phakic eyes with symptomatic cataract is limited because of very small numbers:** For most clinical trials on macular conditions (AMD, DMO, Retinal Vein occlusions etc), cataract that may require surgery within 6 months is considered an exclusion; hence clinical data on patients with cataract on any such trials is not readily available. Study protocols are therefore not likely to have plans for sub group analysis on patients with cataracts. Despite such limitations, antiVEGF treatments are approved for use in phakic as well as pseudophakic eyes. **Non-comparative evidence does not reduce uncertainty in the clinical outcomes because of the extremely small number of people included:** The biological response of drug injected intravitreally in the eye is not altered by phakic or pseudophakic state. Yang et al's paper reported positive response of Fluocinolone injection in pseudophakic eyes. This has been seen in clinical practice in eyes where fluocinilone was injected at the time of cataract surgery as well. Similarly clinical studies as well as real life experience has confirmed that AntiVEGF injections work equally well in phakic or pseudophakic eyes. Furthermore, steroid implants are approved for use in treatment of macular oedema in RVO as well as uveitis in phakic eyes and have been found to be effective.

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	Non-comparative evidence does not reduce uncertainty in the clinical outcomes because of the extremely small number of people included: The usual care in the context of current consultation is antiVEGF injections that have been found to suboptimal response in phakic eyes. These patients have no access to rescue treatment and often continue to have repeated antiVEGF injections to maintain status quo until cataract surgery. Sequential, secondline rescue treatment with Fluocinolone has been shown to have positive effect on salvaging retina (reduction in macular oedema) as well as better chance of static or improved vision (Yang et al). **The treatment effect caused by natural recovery and rescue treatments should be applied to both arms of the model:** The population of interest for this consultation is phakic DMO patients whose standard of care - antiVEGF injections have resulted in suboptimal response or no response. Such patients have no access to rescue and their vision is not likely to improve - in fact it is likely to deteriorate over time. These patients are not likely to have natural recovery due to chronicity of their DMO that may lead to irreversible retinal structural damage. **About 42% of people with diabetic macular oedema in phakic eyes with symptomatic cataract might get a second implant after 3 years:** Clinical decision for reinjection of fluocinolone implant is based on whether the DMO has recurred as judged by using OCT scan based macular thickness and factoring in vision assessment. **It is implausible that the treatment effect is maintained for a lifetime after treatment has stopped:** Clinical experience from real life management of DMO has confirmed that with time treatment need declines and majority of patients do not need repeated injections (antiVEGF or steroids) after first 3 years. Thus it is NOT implausible that treatment effect can be maintained for lifetime. **The ICERs are highly uncertain, and there is no single most plausible ICER, but all plausible ICERs exceed £30,000 per quality-adjusted life year (QALY) gained:** The use of FAME 'sham' arm to represent current clinical standard of care (usual care) is flawed as noted previously. The phakic DMO patients who are not responding to current usual care (antiVEGF injections) do not have access to rescue treatment. These patients would not have any protection against continuos and progressive damage to their macula by persistent macular oedema and hence no natural recovery is usually expected, instead a decline in vision with risk of irreversibility with chronicity is expected. "In patients with chronic Diabetic Macular Edema, the likelihood of achieving vision ≥20/40 with treatment diminishes as the vision worsens." Chakravarthy et al. Retina. 2018 Feb;38(2):343-351

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Comments on the ID1421 Fluocinolone ACD received from the public through the NICE Website

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	No
Notes	
Comments on the ACD:	
There is definite unmet need in treating Diabetic Macular Oedema not responding to anti VEGF therapy in phakic patients. FLucinalone implant does fulfil that space, especially if the patient already has early to symptomatic cataract. With lack of options, patients are undergoing cataract surgery first to become eligible for Iluvien implant but this poses dangers of worsening DMO. If approved Iluvien can be implanted first to control DMO before performing cataract surgery, this will have the best visual and anatomical outcome. Even though the cost of Iluvien implant is high, if this can prevent multiple anti VEGF injections, over all it will be a saving. Also considering that most patients with symptomatic cataract need cataract surgery any way.	

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	No
Notes	

Comments on the ACD:

Has all of the relevant evidence been taken into account?

The conclusion that vision will potentially improve spontaneously in eyes that failed anti-VEGF therapy is not based in evidence and clinical experience show that without further intervention the situation is likely to deteriorate.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Some conclusions are not really based in evidence and are assumptions rather than facts.

Are the recommendations sound and a suitable basis for guidance to the NHS?

My views were made clear in my comment below.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

No.

I certainly appreciate the fact that the lack of data makes the calculation of cost-effectiveness of Iluvien in phakic eyes with unresponsive DMO difficult. The issue I would like to raise is related to the fact that, as you pointed out, there are no other options beyond laser and anti-VEGF therapy for these patients. Currently a patient with DMO who fails 6 monthly injections of one of the anti-VEGF agents (excluding Bevacizumab) should be considered for steroid therapy. Laser is inferior to anti-VEGF therapy and does not represent an alternative in case of failure of this approach. There is no evidence that continuing with the same approach after 6 months will be beneficial and there is also no evidence that changing to another anti-VEGF will also result in improvement (again, not including Bevacizumab in this comment). At this point, without steroids, the situation will not improve and is likely to deteriorate. Even though the lens status is relevant, the integrity of the macula is a lot more important since the damage to the macula will result in irreversible loss of visual function, unlike cataract which can be easily reversed. So, sacrificing macular function to prevent development of lens opacity does not represent a sensible alternative. Many patients will already have symptomatic cataracts and will require surgery in the near future. It is unlikely there will be many patients with asymptomatic lens opacity fitting this scenario. I think the option of Iluvien should

be made available in this situation of reduced vision due to DMO that fails to respond to current standard of care after 6 months of anti-VEGF therapy. Ozurdex and Iluvien represent the only options these patients will have. Iluvien involves a longer effect, less procedures and should be cost-effective in this regard. [redacted] My views represent my own clinical analysis with the best for the patient in my heart. [redacted] and decided to express my views independently since I feel strongly about offering the patients the best option solution to prevent visual loss.

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	No
Notes	
Comments on the ACD:	

Has all of the relevant evidence been taken into account?

It would appear that all published evidence has been taken into account.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

I am not convinced that the cost effectiveness is reflecting what is actually happening in the clinical practice. As mentioned in my comment, because the steroid implants cannot be used in phakic patients, clinician s will use unlicensed triamcinolone injections in these unfortunate patients, which in turn will accelerate the formation of cataract and will lead to cataract surgery sooner than otherwise perhaps expected. Is this an economy?

Are the recommendations sound and a suitable basis for guidance to the NHS?

Not for the particular group of patient afflicted by chronic macular oedema, unresponsive to anti-VEGF intravitreal injections.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Please refer to my answer in the next box; if we refer particular to the grounds above, then no there is not.

It was disappointing to see that NICE has not recommended the use of Iluvien in phakic patients.
It is well know that both a VEGF pathway and inflammatory pathway can contribute to the development of diabetic macular oedema and hence, makes this condition so much more challenging to control. Also, it is well documented that patient with diabetes will develop cataracts at a much earlier age compared with patients who do not have diabetes.
So far, it is believed that the group of patients who have early macular oedema are much more responsive to anti-VEGF therapy and their needs appear to be met by the availability of anti-VEGF therapy. For the patients who have a more chronic type of macular oedema, if they are psudophakic, and are non-responsive or partially responsive to anti-VEGF,then they can have intravitreal steroid implants (Ozurdex or Iluvien) and their needs are met.
However, for the group of patients who have chronic macular oedema, are phakic and anti-VEGF non-responsive there is no option available. Majority of clinicians will consider unlicensed Triamcinolone intravitreal injection to try and help stabilize their disease. Some of the patients may have grid laser, with associated side-

effects (central visual field loss). Considering that the majority of these patients are working age group, having an intact visual field is very important for them.
As a clinician, I feel that this group of patients is being let down by this recommendation, as they are at a disadvantage to what is available to them.
In my opinion, if a patient with diabetic macular oedema had 6 anti-VEGF injections and has not responded or partially responded, then evidently the inflammatory pathway is the dominant pathway in causing the oedema and should be treated accordingly- intravitreal steroids. Also, it is well documented that diabetic patients will develop cataract much sooner than patients without diabetes, that multiple anti-VEGF injection will contribute to formation of cataract sooner and giving unlicenced intravitreal triamcinolone will have similar effect in contributing to cataract formation as using intravitreal steroids implants. It would appear that in the end, the economic model, which takes into account the cataract surgery cost induced by the steroids is a false economy, as these patients will have cataract surgery rather sooner than later, but by then a lot of other resources would have been used to try and control the disease and give these patients a reasonable quality of life.
In my clinical experience, if the Iluvien implant could be used without these restrictions, the patients would benefit from the best available treatment algorithm for their particular case; the delay imposed on using the Iluvien implant means that by the time the patient is psudophake the disease has become even more chronic and possibly more difficult to control and instead of having visual gain, (which is more likely to occur in early stages of diabetic macular oedema), we are now looking for maintaining vision or stopping visual loss. As a clinician I feel frustrated that I cannot offer my patients what I consider to be the best algorithm of treatment for them.

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	No
Notes	

Comments on the ACD:

In real world there are phakic patients with diabetic macular oedema which is sometimes difficult to be managed with anti-VEGFs: like pregnant women or people with recent cardiovascular event.

We know that the Fluocinolone Acetonide (FAc) implant stays for almost 3 years inside the eye and it is likely to play part in cataractogenesis. I believe from personal, professional experience on steroids use on phakic patients in Sweden that the risk of cataractogenesis with FAc implant from use is counterbalanced from the actual effect of the steroid on the resistant multi-cystoid diabetic macular oedema, preventing further damage to the photoreceptors and ganglion cells from the chronicity of the retinal oedema. Cataract operation would happen much safer at a later stage when the DMO is stable treated for long time without significant fluctuations.

There are no big studies on FAc implant except the FAME trial regarding safety and effectiveness and the IRISS UK investigation study group regarding safety. However, Metanalysis studies (RELDEX and PREDIAMEX) and Real world studies (BEVORDEX) on dexamethasone implant would show the similar effectiveness of steroid comparing to anti-VEGF. No meta-analysis study exists for the FAc use on phakic DMO patients; but it would be worth done if would it be possible in future. Moreover, an effectiveness cost-analysis would show that fluocinolone acetonide implant use would reduce both the burden of cost on the clinical visits and treatment with other drugs like anti-VEGFs

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	No
Notes	
Comments on the ACD:	

Recommendations:

There is an unmet need within our diabetic patients; who suffer from chronic diabetic macular oedema that is insufficiently responsive to laser, Lucentis and Eylea - who would benefit from intravitreal steroid, but cannot be offered due to NICE guidance restriction. So I have to end up managing these patients with Off-Label and unlicensed intravitreal steroid till such time they can be offered cataract surgery; given the lack of available therapies given NICE restriction
At present within the NHS, we have no available therapies for the phakic patient with DMO, who is insufficiently responsive to available therapies (antivegf and laser)
I take this approach because the importance of saving the retina far outweighs the importance of saving a natural lens; and I am prepared to use off label treatments to achieve this goal
However we have licensed intravitreal steroid already; and they should be made available for this small subset of patients who are difficult to manage. Even if their implantation was scheduled prior to planned cataract surgery to avoid any additional cost to the NHS.

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	No
Notes	
Comments on the ACD:	

Has all of the relevant evidence been taken into account?

Please see below

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

They do not take into account the likely treatment needed for DMO after cataract surgery between those who have adequately controlled DMO pre cataract surgery & those who do not.
It is likely that by restricting intravitreal fluocinolone acetonide to phakic patients, that the costs may be greater.

Are the recommendations sound and a suitable basis for guidance to the NHS?

I have patients under my care for whom all other treatments for diabetic macular oedema (DMO) have been exhausted, but they are still phakic, albeit with an early cataract. These patients are very likely to come to need cataract surgery in the future anyway and by not having the option of pre cataract surgery intravitreal fluocinolone acetonide, risk requiring more treatment for DMO after the cataract surgery.
For these reasons, I do not agree with the guidance.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

No.

There is evidence that for patients with diabetic macular oedema & cataracts, that having effective treatment for the diabetic macular oedema (DMO) BEFORE the cataract surgery results in less DMO post operatively than those patients who have the cataract surgery first and treatment for the DMO afterwards.
Therefore by restricting intravitreal fluocinolone acetonide to only pseudophakic patients (for whom other DMO treatments , such as intravitreal anti-VEGF agents have been ineffective), this may inadvertently result in patients requiring more intravitreal treatment after their cataract surgery, resulting in an increased risk to the patient & also increased treatment costs.

Name	[redacted]
Role	
Other role	
Organisation	RNIB
Location	
Conflict	No
Notes	

Comments on the ACD:

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

See comment on 1 - Recommendations. RNIB would endorse the view of the Royal College of Ophthalmologists that the costs of cataract surgery should be removed from cost-effectiveness calculations.

RNIB is concerned that by not recommending the Fluocinolone acetonide (FAc) implant for use in this case, a group of patients with a sight-threatening diabetic macular oedema (DMO) will be unable to access this treatment where no other second-line options exist, with consequent risk to their vision.

Suitable phakic patients will be placed in an impossible catch-22 situation, in which they are unable to receive FAc treatment to control their DMO unless they have had cataract surgery, but unable to have cataract surgery because of the known risks of exacerbating their DMO.

Given that many of the patients involved would go on to develop cataracts independently of use of FAc implants, in discussion with the Royal College of Ophthalmologists, we would therefore agree that the cost of cataract surgery should not be taken into consideration in cost-effectiveness calculations.

We would also endorse the points made by the Royal College, that relate to the Pearce et al expert best practice recommendations, with regards second-line steroid use for DMO.

RNIB's position is that, so long as the additional risks, including those of accelerated cataract development and increased intraocular pressure, are discussed with the patient, so that informed consent is obtained, the FAc implant meets a clinical need, and should be recommended for use in DMO patients with phakic lenses for whom first-line treatment options have been insufficiently effective.

RNIB does agree that the uncertainty about the cost-effectiveness of FAc treatment does need to be resolved and research, as outlined in TA301 Section 6, must be commissioned, also to include analysis of the treatment for pseudophakic and phakic patients independently.

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	No
Notes	
Comments on the ACD:	

Has all of the relevant evidence been taken into account?

No.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Only partly.
Diabetic patients have a higher risk of cataract than the general population. (1. Pollreisz A, Schmidt-Erfuth U. Diabetic cataract – pathogenesis, epidemiology and treatment. J Ophthalmol 2010; 2010:608751. 2. American Diabetes Association. Eye complications [internet]. 2013 [cited: 2016 October]. Available from: www.diabetes.org/living-with-diabetes/complications/eyecomplications. 3) Klein BEK et al, Prevalence of cataracts in a population-based study of persons with diabetes mellitus. Ophthalmology 1985; 92: 1191-1196).
Approximately 85% of phakic eyes included in the MEAD Study had cataracts at baseline, although a similar figure for the FAME Study is not readily available. It is known that some eyes with DMO do not respond completely to treatment with anti-VEGFs especially in cases of chronic DMO. (Amoaku et al, 2015). It is known that vision improvement following cataract surgery in diabetics especially those with DMO is significantly less than in non-diabetic patients. (Romero-Aroca ety al, 2006; Somaiya et al, 2002; Eriikson et al, 2011). Furthermore, it is known that some eyes with DR without DMO or with non-centre involving DMO will progress to centre-involving DMO following cataract surgery. (Baker et al, DRCRNet JAMA Ophthalmol. 2013 July; 131(7): 870–879. doi:10.1001/jamaophthalmol.2013.2313.) This is associated with visual loss. Similarly, eyes with DMO unresponsive to previous treatment will progress following cataract surgery with associated vision loss. It is unconceivable that eyes with DMO will have significant vision improvement following cataract surgery without adequate treatment for the macular oedema.

Are the recommendations sound and a suitable basis for guidance to the NHS?

Only partly.
I believe that the NICE ACD as published is wrong in its recommendations re: treatment of eyes with DMO unresponsive to treatments with standard care (laser, anti-VEGFs as appropriate) and who have symptomatic cataract. I do not believe that such patients if continued on standard of care will get improvement in vision due to cataract removal and due to insufficient response to SoC therapies the retina would be further (irreversibly) damaged by diabetic macular oedema.
NICE has, to date, restricted its recommendation on treatment of eyes with DMO to pseudophakic patients. In other words, patients with phakic eyes with DMO currently fall outside NICE TAs.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Eyes with diabetic macular oedema and significant cataract prior to cataract surgery.
Such patients, as the cataract is significant, and will have subsequent surgery, should benefit from pre-surgical intravitreal Iluvien. That is because these patients will have progression of the DMO, and vision loss following cataract surgery alone. Care in such patients cannot be considered equal to that in others.

I believe that the NICE ACD as published is wrong in its recommendations re: treatment of eyes with DMO unresponsive to treatments with standard care (laser, anti-VEGFs as appropriate) and who have symptomatic cataract. I do not believe that such patients if continued on standard of care will get improvement in vision due to cataract removal alone as, as a result of insufficient response to SoC therapies, the retina would be further (irreversibly) damaged by diabetic macular oedema.
NICE has, to date, restricted its recommendation on treatment of eyes with DMO to pseudophakic patients. In other words, patients with phakic eyes with DMO currently fall outside NICE TAs.
Diabetic patients have a higher risk of cataract than the general population. (1. Pollreisz A, Schmidt-Erfuth U. Diabetic cataract – pathogenesis, epidemiology and treatment. J Ophthalmol 2010; 2010:608751. 2. American Diabetes Association. Eye complications [internet]. 2013 [cited: 2016 October]. Available from: www.diabetes.org/living-with-diabetes/complications/eyecomplications. 3) Klein BEK et al, Prevalence of cataracts in a population-based study of persons with diabetes mellitus. Ophthalmology 1985; 92: 1191-1196).
Approximately 85% of phakic eyes included in the MEAD Study had cataracts at baseline, although a similar figure for the FAME Study is not readily available. It is known that some eyes with DMO do not respond completely to treatment with anti-VEGFs especially in cases of chronic DMO. (Amoaku et al, 2015). It is known that vision improvement following cataract surgery in diabetics especially those with DMO is significantly less than in non-diabetic patients. (Romero-Aroca ety al, 2006; Somaiya et al, 2002; Eriikson et al, 2011). Furthermore, it is known that some eyes with DR without DMO or with non-centre involving DMO will progress to centre-involving DMO following cataract surgery. (Baker et al, DRCRNet JAMA Ophthalmol. 2013 July; 131(7): 870–879. doi:10.1001/jamaophthalmol.2013.2313.) This is associated with visual loss. Similarly, eyes with DMO unresponsive to previous treatment will progress following cataract surgery with associated vision loss. It is unconceivable that eyes with DMO will have significant vision improvement following cataract surgery without adequate treatment for the macular oedema. Furthermore, administration of intravitreal steroids preoperatively is known to reduce/prevent the progression of postoperative macular oedema (Mehta et al, 2015.
I would suggest that it, in my clinical judgement, it is implausible to suggest that that if a patient presents with centre involving DMO, and insufficient response to available therapies, treatment a day or more 1 day(s) before cataract surgery with ILUVIEN implant would not be cost effective, whereas that treatment with the same ILUVIEN implant on the day of / or soon after cataract surgery as has already been agreed by NICE to be cost-effective?

Amoaku WM, Saker S, Stewart EA. A review of therapies for diabetic macular oedema and rationale for combination therapy. Eye (Lond). 2015 Jun 26. doi: 10.1038/eye.2015.110. Review
Romero-Aroca P, Fernandez-Ballart J, Almena-Garcia M, Mendez-Marin I, Salvat-Serra M, Buil- Calvo JA. Nonproliferative diabetic retinopathy and macular edema progression after phacoemulsification: prospective study. J Cataract Refract Surg. 2006; 32(9):1438–44.
Somaiya MD, Burns JD, Mintz R, Warren RE, Uchida T, Godley BF. Factors affecting visual outcomes after small-incision phacoemulsification in diabetic patients. J Cataract Refract Surg. 2002; 28(8):1364–71.
Eriksson U, Alm A, Bjarnhall G, Granstam E, Matsson AW. Macular edema and visual outcome following cataract surgery in patients with diabetic retinopathy and controls. Graefes Arch Clin Exp Ophthalmol. 2011; 249(3):349–59.
Mehta H, Gillies M, Fraser-Bell S. Perspective on the role of Ozurdex (dexamethasone intravitreal implant) in the management of diabetic macular oedema. Ther Adv Chronic Dis. 2015 Sep;6(5):234-45. doi: 10.1177/2040622315590319.

Fluocinolone acetonide intravitreal implant for treating chronic diabetic macular oedema (part review of TA301) [ID1421]

ERG commentary on ACD and company ACD response

NICE ID1421

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The ERG would like to acknowledge the clinical advice and input from Professor Norman Waugh, Professor of Public Health, Warwick Medical School.

1. **Clinical Effectiveness**

*Comment 1 company ACD response: The company state **ICE-UK study:** This study demonstrated that in people with 'phakic eyes and symptomatic cataracts after an insufficient response to anti-VEGF therapy' there was declining vision in spite of on-going treatment."*

ERG clinical comment: The Holden paper did not provide such data. There were only 26 phakic eyes (11% of the total), of which 19 would probably fit the company's "target population"). However results are not given separately for this small subgroup for the year before fluocinolone implantation. Also if vision were declining, it might have been because of symptomatic cataract. Note that cataract extraction was undertaken in 14 of these eyes on the same day as fluocinolone insertion, and a in a further 5 within 3 months.

Comment 5 company ACD response: The ICE-UK clinical data showed a BCVA decreased by 2 letters over 12 months before FAc administration of whom 56 eyes underwent cataract surgery during 12 months prior to implant. In total, 185 (89%) of 208 eyes were pseudophakic before injection of the FAc implant

ERG clinical comment: The company states that 185 (89%) of 208 eyes were pseudophakic before fluocinolone injection. However in their paper Holden et al confuse eyes and patients. In addition, Holden et al state that 207 eyes were pseudophakic in the clinical effectiveness paper but that 205 were pseudophakic in the health economics paper, both in CMRO 2017. The company provide graphs of results from FAME for eyes which were phakic at baseline, but this is not relevant to the new target group.

Comment 7 company ACD response: The majority of the clinical evidence in the UK has been accrued following the approval of TA301 and so the majority of real-world evidence pertains to a 3 year of therapy following ILUVIEN administration. There is less data for the 3 month period (based on ICE-UK) between cataract diagnosis and cataract removal, although the study by Yang et al.[6] shows a similar visual acuity outcome being achieved after 3 years of ILUVIEN therapy irrespective of the lens status at baseline.

ERG clinical comment: The company states "the majority of real-world evidence pertains to a 3 year period following Iluvien administration." This is incorrect because there is very little

data for 3 year results. The ICE-UK report data only to 12 months. The Medisoft study had a mean follow-up of 428 days, and only 17% had data at 24 months.

Comment 8 company ACD response: Alimera Sciences set-up and conducted the ICE-UK study and from this it is possible to assess the effect of the FAc implant after an insufficient response to anti-VEGF.[2] ICE-UK showed that during the 12 months before ILUVIEN was administered there was a gradual decline in visual acuity with standard of care (i.e. primarily anti-VEGF therapy). Following the injection of the ILUVIEN implant there was an overall improvement of +4.3 letters at 12 months. The company also feels strongly that ICE-UK as ground-breaking non-comparative study should not be dismissed and instead be given more weight as this study was recommended by NICE at the time TA301 was approved and since that time has collected data from current clinical practices where anti-VEGF is being used before ILUVIEN.

ERG clinical comment: As noted earlier, 89% of eyes in the ICE-UK study, were pseudophakic at baseline. Only about 19 eyes were relevant to the new target group. Overall results from ICE-UK are not relevant.

Comment 10 company ACD response: The submission presented evidence from 14 patients from ICE-UK and 10 patients from retro-IDEAL who had cataract surgery and FAc implant administration at the same time.

ERG clinical comment: This refers to evidence from the 14 patients who had cataract extraction and Iluvien implant on the same day. They gained [redacted], but the relative contributions of cataract extraction and fluocinolone implant cannot be distinguished at that point.

Comment 12 company ACD response: Alimera Sciences acknowledges that laser and anti-VEGF may be suitable comparators provided it is clear that the model accounts for these being ineffective therapies as they are being used in patients with chronic DMO that are insufficiently responsive. This fact has been confirmed in the ICE-UK study where it was shown that during the 12 months before ILUVIEN was administered there was a gradual decline in visual acuity with standard of care (i.e. primarily anti-VEGF therapy and the

current standard of care). Following the injection of the ILUVIEN implant there was an overall improvement of +4.3 letters at 12 months. This point was made in the consultation meeting but is not properly reflected in the ACD. Whilst the choice of comparator is not under debate, the outcomes associated with it are, and have a large influence on the cost-effectiveness.

ERG clinical comment: This notes an overall improvement in ICE-UK of 4.3 letters at 12 months. This is less than the 5 letter change regarded by NICE in ACD para 3.5 as clinically significant.
It is likely that without fluocinolone, there would be a further decline due to DMO, of perhaps 2 letters (based on the 12 month trajectory before fluocinolone), so the 4.3 could be 6.3 letters. However these figures apply to the whole ICE-UK population, most of whom were pseudophakic before entry to the study. The results in the phakic at baseline group might be different. Firstly, their decline in the previous 12 months could be partly due to developing cataract, partly to DMO. If fluocinolone was not available, their vision would of course anyway be improved by cataract extraction.

2. Health Economics

Comment 3.5 ACD: The clinical expert explained that people with cataract are often excluded from clinical trials in DMO because their retinas cannot be assessed.

ERG economic comment: It should be borne in mind that the original scope was not restricted to those with cataract at baseline. The scope specifies phakic patients who are insufficiently responsive to available therapies. The 1st company submission addressed this population. The company themselves further restricted the scope to those with cataract at baseline.

Comment 3.7 ACD: The company model structure is acceptable for decision making.

ERG economic comment: Both the company and the ERG agree that the company model implementation is bad at predicting patients' BCVA as acknowledged in ACD section 3.8 (see below).

Comment 3.8 ACD: Most company model inputs are from FAME with a minority from non-comparative studies. The usual care arm should be modelled in line with FAME results. The company model validation BCVA outputs show poor alignment with FAME BCVA results, which introduces uncertainty during extrapolation.

ERG economic comment: This is as per the ERG report, the company model validation data are reproduced below (Table 1).

Table 1: Company model validation data

	FAME recorded values			Company model outputs		
	Fluo.	Sham	Net	Fluo.	Usual Care	Net
12 mth	+2.7	+0.9	+1.8	+2.6	+4.2	-1.6
36 mth	+8.1	+1.9	+6.2	+3.6	+6.4	-2.7

It should be stressed that the company model validation data relates to the company model set up to replicate the FAME trial phakic patients, and so uses the FAME trial proportion of phakic patients with symptomatic cataract at baseline. It should also be stressed that the model inputs that relate to estimating BCVA in the above are drawn from FAME. The other input sources only really affect QALY and cost estimates. As a consequence, even when modelling the FAME phakic population the company model results in BCVA estimates that bear little relation to those who are phakic in FAME at 36 months. This raises further major uncertainties about the accuracy of extrapolation beyond 36 months, even when only attempting to model the FAME phakic population.

The modelling of the company submissions takes two major steps away from the FAME phakic population:

- The 1st company submission revised the patient group to be aligned with the scope: phakic patients who have failed to respond to existing treatments, most being assumed to have failed to respond to anti-VEGF.
- The 2nd company submission further restricted the patient group to those with symptomatic cataracts at baseline.

If the company model cannot reasonably replicate the FAME phakic population at 36 months, it seems very doubtful that it can take the two major steps above to provide accurate 36

month estimates for the position(s) sought. Extrapolation beyond the 36 months becomes even more concerning.

Comment 3.9 ACD: Both arms of FAME are affected by rescue treatments and possibly also natural recovery. It is appropriate to company model the net effect.

ERG economic comment: This is as per the ERG revised base case. It should be borne in mind that the 2nd company submission assumes all have symptomatic cataract at baseline. However in this submission the benefits of symptomatic cataract removal are included only in the fluocinolone arm, not in the usual care arm.

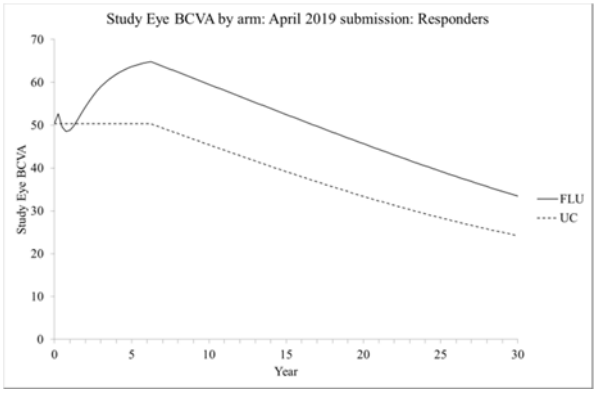
Comment 3.10 ACD: A mean of 1.13 fluocinolone implants over 3 years as derived from IRISS is appropriate.

ERG economic comment: This is as per the ERG revised base case.

Comment 3.11 ACD: A 2nd fluocinolone implant may not just maintain gains in BCVA but may cause additional gains in BCVA.

ERG economic comment: ERG expert opinion remains that a 2nd fluocinolone implant is likely to act more to maintain than to further improve BCVA. The ACD does not comment on the size of the additional BCVA gains that should be anticipated. Neither Alimera nor the clinical expert presented actual data on the gains after a second fluocinolone implant at 36 months or later. The ERG is not aware of any such data.

Figure 1: Company modelled BCVA among those receiving a 2nd fluocinolone implant



As per the ERG report, the company modelling anticipates additional BCVA gains in the 36 months after the 2nd implant that are around two thirds those that occur in the 36 months after the 1st implant. This is in the context of the large majority of patients in both arms being modelled by the company as having their symptomatic cataracts removed during the 36 months after the 1st implant.

Comment 3.12 ACD: For the target group the best estimate of the proportion who would receive a 2nd fluocinolone implant is 42%.

ERG economic comment: This is as per the ERG revised base case.

Comment 3.13 ACD: Anti-VEGF monitoring for those on established treatment should be 8 in the 1st year and 4 annually thereafter.

ERG economic comment: This is as per the ERG revised base case.

Comment 3.14 ACD: It is implausible to assume that the treatment effect would last a lifetime.

ERG economic comment: As per the ERG report given the company model structure this can only be explored by restricting the company model time horizon. Restricting the company model time horizon somewhat worsens the cost effectiveness estimate.

Comment 3.15 ACD: The quality of life estimated from the NEI-VFQ-25 is acceptable.

ERG economic comment: This is as per the ERG revised base case.

Comment 3.16 ACD: There is no most plausible ICER but all plausible ICERs exceed £30k per QALY.

ERG economic comment: The ERG agrees that it is difficult to establish a most plausible ICER.

Comment 2 company ACD response: It is important that NICE is clear that the FAME control arm (active treatment) and treatment arm do not represent the outcome of usual care in the target population. Indeed, at the time of the trial (2005 to 2009) anti-VEGFs were not a standard of care and this is why only very few people had anti-VEGFs before the trial.

ERG economic comment: It is not immediately clear if the company is arguing that both arms of the FAME trial are not relevant to the position sought, or if only the FAME control arm is not relevant to the position sought. Even if only the latter, given possible natural recovery, placebo effect and the rates of rescue in both arms of FAME, asserting that the FAME control arm is not relevant begs the question of whether the FAME fluocinolone arm is also not relevant. The economics in the company submission rests almost entirely upon data from the FAME trial.

Comment 4 company ACD response: In contrast to the company's view, NICE / ERG argue that the sham treated arm in the FAME trial actually reflects usual care.

ERG economic comment: This is incorrect and was explained in some detail during the 1st AC. The ERG argues that during FAME there may have been natural recovery or even a pure trial or placebo effect in both arms, but more significantly that there were significant rates of rescue therapy in both arms. The ERG accepts that these effects may well not apply in the position sought, and that it may be appropriate to remove them from the modelling. The company argues that these effects should be retained in the fluocinolone arm but removed from the usual care arm. The ERG argues that they should be removed from both arms. But the company model does not permit this. The closest approximation to removing them in both arms that is possible in the company model is to retain them in both arms; i.e. to company model the net effect.

Comment 4 company ACD response: The company figure presents data on BCVA changes.

ERG economic comment: The figure is not helped by not specifying the time axis. Obviously, the pre and post implant ICE-UK data is limited to one year. It would be more correct to present the ICE-UK pre-implant data to the left of the vertical axis. The figure also omits the ICE-UK post implant data. This is inexplicable in the context of the company arguing in favour of the importance of the ICE-UK data. The March 2019 ERG report noted

that "*The most useful of the observational studies are in patients with chronic DMO that has not responded to previous treatment, including with anti-VEGF drugs. The improvements in BCVA are not dramatic – a mean 5.3 letters at 24 months in the Medisoft study, and a mean of about 3 letters at 12 months in the ICE-UK study. However these results are mainly in pseudophakic patients*."

Comment 4 company ACD response: The company would like to highlight that the base case ICER from the company was actually £2,187 and was based on a very conservative company model of the net treatment effect versus the control arm.

ERG economic comment: The company cost effectiveness estimate is not relative to a control arm but to a usual care arm in which it is assumed there is no change in BCVA. Alimera Sciences in its ACD response notes that for the revised target group the usual care arm would receive benefits from cataract surgery but suggests that these would be transient and that further deterioration would occur in the longer term. The benefits of cataract surgery in the usual care arm are not included in the company modelling. The company modelling is also not conservative inassuming that any natural recovery and rescue treatment effects apply only in the FAME fluocinolone arm.

Comment 4 company ACD response: The company repeatedly states that the NICE position is implausible, and that fluocinolone would be deemed cost effective 1 day after cataract surgery but not 1 day before it.

ERG economic comment: The company argument appears to allude to a different patient group tothe revised scope. During the 2nd set of clarification questions the ERG asked the company to clarify if the revised target group was either (a) patients with symptomatic cataracts or (b) patients referred for cataract surgery. The company response was that it was patients with symptomatic cataracts suggesting that the company thinks the two groups differ. Within the target group for ICE-UK most had cataract extraction at baseline. How much the two groups differ is open to debate; if they differ by only a little the company argument has force, if they differ by more than a little the company argument loses its force.

Comment 5 company ACD response: The company net gain assuming no change in BCVA in the usual care arm results in a company modelled net gain at 36 months that more closely reflects the FAME trial.

ERG economic comment: To the ERG the first question that needs to be addressed is whether the company model validation data suggests that the company model can accurately predict BCVA for the FAME trial population. If the company model cannot predict the BCVA of the FAME trial at 36 months, extrapolations made using the company model are unlikely to be reliable. Furthermore, is the company appears to assume that it is reasonable to use the company model to extrapolate to the patient group specified in the scope, and to then further extrapolate to the restricted patient population of those with symptomatic cataracts at baseline. If the company model is not reliable when trying to model the FAME trial phakic patients, there are reasons to believe it may be even less reliable when trying to model the specified patient populations during the 1st and 2nd submissions.

Comment 5 company ACD response: The company suggests a UK specific rate of 1.06 implants rather than 1.13 since IRISS includes patients from, Germany and Portugal as well as the UK.

ERG economic comment: It is unclear why implant rates from Germany and Portugal are not relevant, if they extend the data set. But whether it is 1.06 implants or 1.13 implants is unlikely to determine the final decision, as shown in the ERG sensitivity analysis SA05b. The ERG in its June 2019 report noted "The company selects 1.06 derived from the MEDISOFT data as its preferred revised estimate. This is presented in the clarification response as a mean of 1.06 over 14.3 months. In table 12 of the April 2019 Document B, it appears that 5 of the original 93 eyes were followed up between 24 and 36 months and had an additional implant. If the MEDISOFT mean follow-up was 14.3 months the company choice of the MEDISOFT value of 1.06 does not seem reasonable".

Other comments on the ACD as they relate to the economics

[redacted] *comment*: *The costs of cataract surgery should not be included.*

[redacted] *comment*: M*akes a similar point about the cost of cataract surgery.*

[redacted] *comment: Makes a similar point about the cost of cataract surgery.*

ERG economic comment: The revised population is those with symptomatic cataracts. Cataract surgery is modelled in both arms. The costs of it largely cancel out. Setting the cost of cataract surgery to zero barely changes the costs effectiveness estimates, including the company 2nd submission base case.

[redacted] *comment: Even though the cost of Iluvien implant is high, if this can prevent multiple anti VEGF injections, over all it will be a saving.*
[redacted] *comment: A similar point is made about the costs of anti-VEGF.*

ERG economic comment: The company 2nd submission base case does not estimate that fluocinolone will save money, and this is without taking into account the ranibizumab PAS. It can also be noted that ranibizumab will shortly be coming off patent, though NICE processes may not permit a formal evaluation of the probable effects of this. The original ERG report also noted that continuing with anti-VEGFs for the patient group of the original scope was unlikely to be cost effective.

[redacted] *comment*: *Usual care is confused with the sham arm of FAME.*

ERG economic comment: This is a reasonable point but is not the ERG argument. The ERG argument is accepted under ACD points 3.4 and 3.9.

[redacted] *comment*: Laser is not a relevant comparator.

ERG economic comment: The ERG was concerned about the company using a composite comparator and has presented cost effectiveness estimates for fluocinolone compared to laser and for fluocinolone compared to anti-VEGF. Restricting the comparison from the composite comparator to anti-VEGF does not appear to change the main thrust of the economics. But NICE guidance suggests that laser remains a relevant comparator and the company appears to accept this, given the composite comparator of its base case.

[redacted] *comment: Clinical experience from real life management of DMO has confirmed that with time treatment need declines and majority of patients do not need*

repeated injections (anti-VEGF or steroids) after first 3 years. Thus it is NOT implausible that treatment effect can be maintained for lifetime.

ERG economic comment: The ICE-UK data suggested ongoing anti-VEGF use in the year prior to fluocinolone implant, and continued use for a substantial minority in the year subsequent to the fluocinolone implant. The median disease duration in ICE-UK was 2.7 years, with a range of 1.1-4.8 years. The base case of both the company and the ERG do in effect assume that the net treatment effect at 6 years is maintained for a further 24 years at no additional cost, however company and ERG scenario analyses that restrict the time horizon significantly worsen the cost effectiveness estimates.

3. Conclusions

At its simplest the company submitted a model which relies upon FAME data for the transition probabilities that yield the BCVA estimates though the BCVA estimates that result will be affected by the proportion of patients who are assumed to have symptomatic cataracts at baseline. Inputs that were not available or not applied during TA301 mainly relate to:

- ICE-UK resource use data which suggests that among those with an insufficient response to anti-VEGF in the year prior to fluocinolone implant around 4 anti-VEGF injections were received. In the year after the fluocinolone implant the proportion receiving anti-VEGF injections fell to a little under a third, but the frequency of treatment was still around 4 anti-VEGF injections per year.
- The analysis of NEI-VFQ-25 data to estimate quality of life values for bilateral health states. The resulting quality of life values result in smaller QALY gains than the previous approach of using the Czoski-Murray values and assuming that changes in the BCVA of the WSE have 15% of the QoL impact of the same change in BCVA of the BSE.

There seems to be relatively little that is new in terms of model inputs compared to TA301. In the ERGs opinion new material is liable to worsen the cost effectiveness estimate.

The company model validation data at 36 months is poor. The reasons for this are unknown. Extrapolating using this company model for a further 3 years' treatment effect is questionable, and further extrapolation to the narrower patient population is more questionable. The company position appears to be to ignore the logic of its model as derived

by the company from FAME data and it is difficult to establish a most plausible ICER with the company model.

The outlook for this group of people in whom anti-VEGFs and laser have failed to prevent progression of visual loss is poor. Many will suffer progressive loss of vision. The failure of anti-VEGFs in chronic DMO is perhaps not surprising, since there is evidence that the processes within the retina may change from a VEGF-driven one to an inflammatory one (main ERG report dated 6th March 2019). In that case, steroids would be more effective. The ERG thinks that there is a high probability that a better evidence base and better economic modelling would show that fluocinolone is cost-effective in this group. It is unfortunate therefore that Alimera did not follow the FDA recommendation to do a trial of fluocinolone in patients in whom anti-VEGFs had failed.

The ERG recommends that:

1. There should be research into the possibility of identifying, at an early stage, which patients have DMO driven by VEGF and which have a more inflammatory process. This might be commissioned by the HTA Programme
2. There should be a systematic review of predictors of response and non-response to anti-VEGF drugs
3. NICE should recommend (a) a stopping rule for anti-VEGF treatment and (b) guidance on the use of combination therapy with laser treatment after an initial course of anti-VEGF injections have reduced retinal thickness. Such a combination would be less expensive and less invasive.
4. Further modelling research would be valuable in order to (a) estimate how much of an effect would be required to make fluocinolone cost-effective in phakic patients, including both those with symptomatic cataract at baseline, and those without such cataract and (b) consider the plausibility of an effect of that size being achieved by steroids, taking into account trials of other steroids.