NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Fluocinolone acetonide ocular implant for treating recurrent non-infectious uveitis [ID1039]

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
   - Birdshot Uveitis Society
   - International Uveitis Study Group
   - The Royal College of Ophthalmologists
   - Allergan

3. **Comments on the Appraisal Consultation Document from experts:**
   - Dr Archana Pradeep, clinical expert – nominated by Olivia's Vision

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

5. **Appendix of new evidence –** submitted by Alimera Sciences
   - Updated response to modelling request

6. **Evidence Review Group critique of company response** – prepared by Kleijnen Systematic Reviews

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

Appraisal title

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	1) Uncertainty associated with clinical trial results: "The clinical trial results are difficult to interpret and very uncertain. The trial didn't measure health-related quality of life and the number of recurrences reported may be overestimated." • The study design of PSV-FAI-001 ensured that the effect of treatment with the FAc implant is estimated in a conservative manner. To this end, any use of any medication that could affect the course of patient's NIU-PS was considered a recurrence in the trial, to ensure that any reduction in recurrence rate observed were attributable only to the FAc implant and not to other medications the patient may have received. This approach to quantifying the recurrence endpoint was satisfactory for regulatory agencies, including the US FDA and the MHRA. • An important clarification point is that data imputation usually refers to imputed missing data, e.g. in patients who did not have the required eye examinations. However, in the PSV-FAI-001 trial this common understanding is misleading, as the vast majority of imputed recurrences was due to the use of medications that could affect the course of NIU-PS. The trial allowed clinicians to treat patients if there was any sign of uveitis that they considered required treatment (even if the protocol-defined criteria for recurrence have not been met) and such treatment administered at any time point post 7 days* was classified as an 'imputed recurrence'. Therefore, imputed recurrence recorded any deterioration of the patient's condition, even if it did not meet the protocol-defined criteria for recurrence.	Comments noted. The company's response to clarification agreed that recurrence was likely overestimated in the trial. The committee understood that this affected both arms of the trial. In the model, treatment effectiveness was defined by time to recurrence, so there was some uncertainty as to how this was affected by the overestimated recurrence rates in the trial. No changes to the FAD required.

			• The use of imputed recurrences can be seen as a pragmatic approach to study design, resembling real-world practice, since clinicians could treat patients for uveitis at their discretion and these patients remained on study. It also represents a very stringent evaluation of the FAc implant effect, as it allows any deterioration in the patient's condition to be captured in the analysis, rather than just those events that meet pre-defined recurrence criteria. • Although missing eye examination data also resulted in an 'imputed recurrence', at 36 months only 4 out of 52 patients with imputed recurrences had missing eye examination data, while the remaining patients had a recurrence imputed due to the use of local or systemic steroids/ immunosuppressants. • Although the aforementioned conservative approach could result in recurrence rates being somewhat overestimated, this affected both arms of the trial equally without favouring the FAc implant in any way, as the same non-study treatments were permitted in both arms. Supporting this notion was the fact the FAc implant showed a very clear and statistically significant reduction in recurrence rate not only in the ITT population, but also in the per-protocol population, where only observed (and not imputed) recurrences were considered. Therefore, the benefits of the FAc implant observed in the trial were independent of, and unbiased by, the conservative imputation approach described above. • Overall, both a flare of NIU-PS meeting the protocol-defined recurrence criteria and treatment given at early signs of recurrence (and before these criteria were met) led to the patient being recognised as experiencing a recurrence. Therefore, the trial results should not be interpreted as uncertain, but rather as providing a conservative estimate of FAc implant effect, which nonetheless provided a statistically significant reduction in the rate of uveitis recurrence, as well as a clear effect on reducing a number of other measures of NIU-PS activity (please refer to the Company Submission, and	

			Clarification Document for details of the results). * Recurrence in days 0–7 could be treated, but was not included in the analysis due to potential symptom overlap with an inflammatory reaction from implant injection.	
2	Consultee	Alimera Sciences	2) Applicability of PSV-FAI-001 to the UK setting "People in the control group didn't have any treatment after 3 months in the trial, which is not what is likely to happen in the NHS in England." • The company believes that the NICE committee and ERG have misinterpreted the design of the PSV-FAI-001 trial, which impacts on the perceived relevance of the trial to UK clinical practice. • Patients recruited into the PSV-FAI-001 trial had prior history of recurrent NIU-PS, but also relatively quiescent disease at enrolment. Patients on any systemic medication with a potential effect on NIU-PS (approximately 50% of trial participants) were tapered off these medications within 3 months from study entry; however, this taper was not enforced if disease recurred and patients could have the tapering stopped (or dose increased) at clinical signs of recurrence. • Importantly, the trial did permit treatment of NIU-PS at any point during the study (also after the initial 3-month taper) in both arms of the study. In fact, any trial not permitting treatment over the course of 3 years in a chronic disease would be likely considered unethical, and this was not the case for PSV-FAI-001 trial. • If the investigators perceived there was clinical evidence of uveitis recurring, they were allowed to treat the patient before the patients NIU-PS flared up enough to reach the protocol-defined recurrence threshold of an >2 step increase in anterior chamber cells (ACC) or vitreous haze (VH), or a 15+ letter loss of best corrected visual acuity (BCVA). PSV-FAI-001 results clearly showed that, in both the FAc implant and control arms, the majority of recurrences reported were due to the use of these adjunctive/rescue treatments (termed imputed recurrences, see the first clarification comment) rather than for patients reaching the protocol-defined recurrence threshold. This suggests clinicians opted for prompt rescue treatment at	Comments noted. The committee understood that treatment could be given at any point during the study if required, but that if local or systemic treatment was given that was prohibited as part of the trial, this would have been recorded as a recurrence of uveitis. The committee agreed that it was plausible that people with unilateral disease may have corticosteroid treatment tapered off and receive no treatment until recurrence. However the committee considered that it was unlikely that people with bilateral disease would receive no treatment. The FAD has been updated to reflect that before recurrence in the trial, trial investigators were encouraged to use systemic treatment only after local treatment had failed. See section 3.3.

			early signs of uveitis recurrence, irrespective of the treatment arm to which the patient was randomised as the study was double-blind. • Therefore, patients in the sham arm could be seen as receiving "on-demand" treatment for uveitis recurrences, while patients in the FAc implant arm received a background low-dose local treatment with FAc in addition to "on-demand" treatment for recurrences. The degree to which this background treatment reduced the incidence of recurrence was of key interest in PSV-FAI-001, which primary endpoint was the incidence of uveitis recurrence. • In both arms, permitted treatment of NIU-PS recurrences was local (topical drops or intra-ocular /intravitreal treatments) or systemic (steroids or immunosuppressants). These adjunctive or rescue treatments were therefore allowed in both study arms, but also counted as evidence of NIU-PS recurrence. Of note, the trial protocol advised clinicians to attempt local therapy first and then move onto systemic treatment if required, but did not stop them from prescribing systemic medications where these were necessary to treat the patient effectively. Therefore, the ACD was incorrect in stating that "before recurrence in the trial, systemic treatment could only be used after local treatment had failed." • Only if topical drops/intra-ocular or intravitreal treatments or systemic immunosuppressants were used for indications OTHER than uveitis they were classed as prohibited. These had to be discussed with clinical trial monitors. • The local and systemic treatment options used for managing NIU-PS recurrences in PSV-FAI-001 are also available to patients and clinicians in England. Advice from clinical experts provided to the company and, indeed, the clinical expert speaking at the Committee meeting, also suggests that the trial is similar to the UK clinical practice in several respects: o In UK patients treated with systemic corticosteroids, clinicians would attempt to taper these off once an acute uveitis flare is under control, so as to reduce AEs.	

			Similarly, in PSV-FAI-001 approximately half of the enrolled patients received systemic steroids or immunosuppressants at baseline. These were tapered off after study entry, but could be re-introduced in case of NIU-PS recurrence. o Clinicians in the UK would also attempt to discontinue local treatments once acute uveitis is under control, so as to establish minimal treatment necessary to manage the patient's uveitis, thus avoiding potential AEs associated with over-treatment. Again, the approach was similar in PSV-FAI-001, where local treatments could be used to treat acute uveitis flares/recurrences and were discontinued when the disease was again controlled. • The company acknowledges that the treatments used for uveitis recurrence in the trial are only a sample (rather than a full reflection) of the heterogenous uveitis treatment landscape. Since a national guideline for the treatment of NIU-PS in England does not exist, treatment may depend on the number of affected eyes, underlying aetiology or even local protocols. Given the resulting complexity of NIU-PS treatment landscape, it would be extremely difficult, if not impossible, to completely replicate it within any trial. This issue is well illustrated by the heterogeneity of additional treatment options permitted in PSV-FAI-001, the HURON trial of dexamethasone and the VISUAL I trial of adalimumab. Each of these trials took a different approach to additional treatments.	
3	Consultee	Alimera Sciences	3) Comparison versus the dexamethasone implant • Dexamethasone is available as an implant and is used in the treatment of active uveitis. As such, it could be considered recommended as a treatment of recurrence of non-infectious uveitis, however, the effectiveness in preventing relapse of recurrent NIU-PS has not been studied. Thus, no data exists in relation to dexamethasone as a prevention of uveitis recurrence. In summary, dexamethasone is not explicitly recommended (according to TA460) or used to prevent relapse of recurrent NIU-PS, nor does evidence exist with regards to its	Comments noted. The committee understood that the marketing authorisation for the dexamethasone implant is different to that of the fluocinolone acetonide. However it heard from clinical experts that they may choose to use the fluocinolone acetonide implant at the point in the treatment pathway that they may currently use the dexamethasone implant. Therefore the committee concluded that the dexamethasone implant was a relevant comparator. See FAD section 3.2. The committee understood that there is limited data

			efficacy as a preventative treatment. • Despite this, the company recognised that, in some patients, the dexamethasone implant is likely to be considered a relevant comparator. However, clinical experts at the Committee meeting considered the two implants would be used in different (albeit possibly overlapping in some cases) patient populations. This is also well reflected in the different indications of the two implants. NICE TA460 resulted in a recommendation of the dexamethasone implant for patients with active disease (that is, current inflammation in the eye) and worsening vision with a risk of blindness. Conversely, marketing authorisation for the FAc implant is for prevention of relapse in recurrent NIU-PS, reflecting the pivotal PSV-FAI-001 study where any acute uveitis flares were treated prior to enrolment to obtain a relatively quiet eye. • However, the primary reason for the company not conducting an analysis versus the dexamethasone implant was the lack of appropriate data to inform this comparison in the economic model. • The company would like to highlight that the ERG report also did not consider the comparison vs the dexamethasone implant to be appropriate, and this was based on different trial designs and patient populations. These points are reflected in the following statements that have been extracted from page 82 of the ERG report: o "The most notable difference between the HURON trial and PSV-FAI-00135 was the difference in primary and secondary outcomes. PSV-FAI-00135 was powered to detect the recurrence of uveitis in the study eye at six months and three years (primary and secondary outcomes, respectively). HURON was powered to find the proportion of patients with a vitreous haze score of 0 at 8 weeks, the proportion of patients with a ≥ 15 letter improvement in BCVA and the proportion of patients with a ≥ 10 point improvement in VFQ-25 score	to enable a comparison of the fluocinolone acetonide implant and the dexamethasone implant. However, as described in the methods guide section 6.2.2, the availability of data is not a consideration when selecting relevant comparators. The committee understood that both the company's and the ERG's methods of comparing the fluocinolone acetonide implant with the dexamethasone implant were based on assumptions, but concluded that the ERG's method was more plausible. See FAD section 3.9. The quotes presented in the consultee's comments are taken from the company's submission rather than the ERG report.

			change (primary and secondary outcomes, respectively)." o "…dexamethasone is not considered to be a comparator to ILUVIEN. Additionally, an indirect treatment comparison is inappropriate given that these trials are not powered to evaluate the same endpoints and the (L)CP arms are not comparable. In the absence of direct and indirect comparative effectiveness data, a naïve treatment comparison versus dexamethasone was considered, however, this was not preferred due to the lack of clinical efficacy data available to support an accurate evaluation of dexamethasone." • At the explicit request from NICE, an informal analysis versus the dexamethasone implant has now been provided. The results should be interpreted with caution, due to the large number of important assumptions that had to be implemented in the absence of source data, including: o Dexamethasone was assumed to be as efficacious over 6 months as the FAc implant is over 3 years in the prevention of relapse of recurrent NIU-PS; the efficacy profile demonstrated in PSV-FAI-001 was compressed to a 6-month period for this modelling approach. o It is critical to understand that there are no data to support this assumption of dexamethasone effectiveness. Furthermore, clinical opinion is that dexamethasone implant is effective for up to 4 months, so an assumption of 6 months is highly conservative. However, in order to fulfil the goal of preventing relapse of recurrent NIU-PS, the use of dexamethasone implant would be required on an empirical basis, being injected into eyes without signs or symptoms of NIU-PS at the time of administration. o Consequently, a range of treatment comparisons have been evaluated, where ILUVIEN has been compared against 1, 2 and 3, dexamethasone injections. This	

			provides a range of outcomes for consideration, which can be judged against the clinical plausibility in each case. o It was assumed that a patient may fail treatment up to three times on either the FAc implant or dexamethasone where this option is selected by the user. o It was assumed that the efficacy profile would not change with multiple treatments for both the FAc implant and for dexamethasone. Note, there is no available study data on the effectiveness of the dexamethasone implant in terms of prevention of relapse of recurrent NIU-PS. o It was assumed that on both treatment regimens the rates of movement (attributed to blindness, death or treatment failure) would not change dependent with treatment line. o Finally, in this model, it is assumed that dexamethasone implant would be administered to asymptomatic eyes in order to fulfil the goal of preventing relapse. This is use outside of the licensed indication for the dexamethasone implant and also current NICE recommendations for use.	
4	Consultee	Alimera Sciences	4) Visual acuity • As the company has previously informed, the statistical analysis plan for PSV-FAI-001 stated that change from baseline BCVA would be analysed using descriptive statistics only; thus, statistical testing for this endpoint was performed post-hoc rather than included in the trial as a planned analysis. The company did not present it in the initial submission as it could be considered “data dredging”, i.e. looking for statistical significance where the data appears favourable at first glance. • As NICE has specifically requested statistical analysis of this endpoint to be provided, this is presented in the Table below. **Table: Mean Change from Baseline in BCVA in the Study Eye (ITT**	Thank you for your comment. The FAD has been updated. See section 3.5.

<table>
<tr>
<td></td>
<td></td>
<td></td>
<td>
Population): PSV-FAI-001
<table>
<tr><td></td><td colspan="2">6 Months</td><td colspan="2">12 Months</td><td colspan="2">36 Months</td></tr>
<tr><td>Arm</td><td>FAI Insert</td><td>Sham Injection</td><td>FAI Insert</td><td>Sham Injection</td><td>FAI Insert</td><td>Sham Injection</td></tr>
<tr><td>N</td><td>[redacted]</td><td>[redacted]</td><td>87</td><td>42</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Mean Change (SD)</td><td>[redacted]</td><td>[redacted]</td><td>5.8 (14.36)</td><td>3.3 (12.78)</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Median</td><td>[redacted]</td><td>[redacted]</td><td>5.0</td><td>4.0</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Min, max</td><td>[redacted]</td><td>[redacted]</td><td>(-39, 49)</td><td>(-52, 25)</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Difference from sham injection*</td><td colspan="2"></td><td colspan="2"></td><td colspan="2"></td></tr>
<tr><td>Estimate</td><td colspan="2">[redacted]</td><td colspan="2">2.5</td><td colspan="2">[redacted]</td></tr>
<tr><td>95% CI</td><td colspan="2">[redacted]</td><td colspan="2">(-2.81, 7.82)</td><td colspan="2">[redacted]</td></tr>
<tr><td>P-value</td><td colspan="2">[redacted]</td><td colspan="2">0.353</td><td colspan="2">[redacted]</td></tr>
</table>
Abbreviations: BCVA, best corrected visual acuity; CI, confidence interval; ITT, intent-to-treat; SD, standard deviation.
*Estimate, 95% CI, and P values were based on one-way analysis of variance.
</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Consultee</td>
<td>Alimera Sciences</td>
<td>5) Modelling bilateral disease

• The company has now provided a revised model where both eyes are considered independently. It is worth noting at this point that an FAc implant administered in one eye does not affect any uveitis that may be present in the other eye, since the small daily dose (0.2 µg/day) of FAc is not detectable in blood samples and therefore extremely unlikely to affect the fellow, untreated eye. Hence, both eyes should be considered separately for treatment with the FAc implant in the real-world setting. Bilateral treatment should not be performed at the same visit; instead a second implant should only be used when the patient's ocular and systemic response to the first implant is known (see the SPC for more details).</td>
<td>Comments noted. The committee would have preferred to have seen both eyes taken into account in the modelling and cost-effectiveness results. See FAD section 3.7.</td>
</tr>
</table>

			• Initially, the model focused only on unilateral treatment, since bilateral treatment with the FAc implant was not permitted in the PSV-FAI-001 trial. Hence, several important assumptions were made to model bilateral treatment: o The model and evidence were only able to make estimates about unilateral treatment and therefore the effect in the other eye is assumed to be as modelled. o Costs and effect for the second eye were assumed to be as for the modelled eye.	
6	Consultee	Birdshot Uveitis Society	1.1: The Birdshot Uveitis Society is very disappointed that the NICE appraisal committee has not recommended fluocinolone acetonide implant as an option for preventing relapse in recurrent non-infectious uveitis affecting the posterior segment of the eye in adults.	Comment noted. The fluocinolone acetonide intravitreal implant is recommended, within its marketing authorisation, as an option for preventing relapse in recurrent non-infectious uveitis affecting the posterior segment of the eye. See FAD section 1.
7	Consultee	Birdshot Uveitis Society	1.2, 3.17, 3.18 Birdshot Uveitis Society asks that NICE gives careful consideration to the further clarification and analysis of evidence requested by the appraisal committee from the manufacturers.	Comment noted. The fluocinolone acetonide intravitreal implant is recommended, within its marketing authorisation, as an option for preventing relapse in recurrent non-infectious uveitis affecting the posterior segment of the eye. See FAD section 1.
8	Consultee	Birdshot Uveitis Society	3.16 Birdshot Uveitis Society hopes that this new information will lead to a recommendation by NICE for the use of this 'potentially promising treatment'.	Comment noted. The fluocinolone acetonide intravitreal implant is recommended, within its marketing authorisation, as an option for preventing relapse in recurrent non-infectious uveitis affecting the posterior segment of the eye. See FAD section 1.
9	Consultee	Birdshot Uveitis Society	3.1, 3.2, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 3.10, 3.11, 3.19: Birdshot Uveitis Society agrees with the committee's conclusions on these points.	Comment noted. No change to the FAD required.
10	Consultee	Birdshot Uveitis Society	3.3. Birdshot Uveitis Society disagrees with the committee's conclusion on this point. The PSV-FAI-001 trial was not designed 'to reflect NHS clinical practice in England': it was designed to test the effectiveness of the fluocinolone acetonide intravitreal implant compared with a sham implant. Patients in both treatment groups had their previous treatments tapered off during the first three months of the trial. They were all monitored for recurrence of uveitis and recurrences were treated. This is what happens in NHS England clinical	Comment noted. The committee agreed that it was plausible that people with unilateral disease may have corticosteroid treatment tapered off and receive no treatment until recurrence. However the committee considered that it was unlikely that people with bilateral disease would receive no treatment.

			practice as part of the routine monitoring and treatment of uveitis patients.	
11	Consultee	Birdshot Uveitis Society	3.13, 3.14, 3.15: Birdshot Uveitis Society is unable to comment on the committee's conclusions on these points.	Comment noted. No action required.
12	Consultee	Birdshot Uveitis Society	4.1 Birdshot Uveitis Society would welcome an earlier review date when relevant information is gathered by NICE.	Comment noted. The review date is a suggested date. Guidance may be reviewed before the suggested review time when there is significant new evidence that is likely to change the recommendations. See the Guide to the processes of technology appraisal, section 6.2.
13	Consultee	International Uveitis Study Group	We appreciate that the PSV-FAI-001 study may not have been as 'exact' as other sponsored clinical trials in uveitis (anecdotally some IUSG members have remarked about various aspects of the trial), perhaps due to the naivety (or over enthusiasm) of the company and the lack of undertaking previous studies in uveitis. Nevertheless, the study design etc. should not be used to penalise patients. Did the treatment work? The answer is 'Yes'. The study provides evidence for this and from patient comments. Would having it available as another treatment option for uveitis benefit patients in the real-world setting? Again, the answer is 'Yes'.	Comment noted. As described in the Guide to the methods of technology appraisal, section 6.2.7, the committee's judgements on clinical effectiveness need to take into account the nature and quality of the evidence presented. The committee understood that people with recurrent non-infectious uveitis affecting the posterior segment of the eye would welcome an additional treatment option and took into account the statements of patients and patient organisations in its decision making. See FAD section 3.17.
14	Consultee	International Uveitis Study Group	We feel that it would be appropriate to compare to the dexamethasone implant (ozurdex). There will be patients who have disease in only one eye and also may not have an underlying systemic disease, thus they would be denied adalimumab (TA 460). There is increasing evidence that the effect of the dexamethasone implant may wear off after 4-5 months (it was previously thought to be 6 months). In theory, over a two-year period, patients could require 4-5 dexamethasone implants whereas a single fluocinolone acetonide implant may have the same effect over a similar time period. Adverse events have been commented on, but every intravitreal injection has the potential for infection (endophthalmitis is a well-recognised and feared complication of anti-VEGF injections for AMD), cataract formation, and possibly raised intraocular pressure. These injections are frequently given in Theatre and repeated dexamethasone implants (apart from the cost of numerous implants) would add additional costs and take up slots that could have been used for cataract surgery and improving vision in those patients. In the real world 4-5 dexamethasone implants over 2 years would be unlikely as the ophthalmologist and patient may decide that more than 3 injections over a 12-18-month period may not be	Thank you for your comment. The committee agreed that the dexamethasone implant was a relevant comparator. See FAD section 3.2.

			acceptable. Then the only alternative would be systemic corticosteroid +/- systemic immunosuppression with all their well-known side effects. Having the option of a local treatment that may last 2-3 years, that could be repeated may save the patient having frequent intravitreal dexamethasone implants and possibly systemic therapy with all the side-effects and costs associated with them. There is some analogy with the Retisert studies where the majority of patients had IOP rises and some needed glaucoma surgery, but they stated this would be much preferable than staying on systemic therapy.	
15	Consultee	International Uveitis Study Group	We are concerned that if this treatment was not approved at this time point and the guidance re-evaluated after 3 years, it is highly unlikely patients will have access to it during this period. Ophthalmologists would still have to submit IFRs to NHS England and we envisage that 99-100% of applications will be rejected on the grounds that there was not enough evidence (that may be based on this NICE recommendation) and that patients would not be classed as exceptional. There are no other official pathways to obtain the treatment. The only options would be a DTC in an NHS Trust funding it or the company providing it on compassionate grounds (or stock about to expire). We understand that it will require time for more robust data to be produced and there needs to be discussions with the company to see if the meaningful data NICE requires can be made available in a shorter time period so that the guidance could be re-evaluated within the next 2 years. Nevertheless, there needs to be a better mechanism for individual patients to have an opportunity to obtain this drug during this time.	Comment noted. The fluocinolone acetonide intravitreal implant is recommended, within its marketing authorisation, as an option for preventing relapse in recurrent non-infectious uveitis affecting the posterior segment of the eye. See FAD section 1. The review date is a suggested date. Guidance may be reviewed before the suggested review time when there is significant new evidence that is likely to change the recommendations. See the Guide to the processes of technology appraisal, section 6.2.
16	Consultee	The Royal College of Ophthalmologists	We are very disappointed that NICE may not recommend this treatment for patients in the NHS with chronic, sight-threatening uveitis who currently have unmet clinical need including patients who have one or more needs: -Inadequate respond /do not tolerate standard treatment with immunosuppression or biologic therapy - Have demonstrated responded to currently available intravitreal steroid medications but demonstrate recurrence of activity including sight-threatening complications such as flare up of uveitis or recurrence of macular oedema as treatment wears off (typically <6 months)	Comment noted. The fluocinolone acetonide intravitreal implant is recommended, within its marketing authorisation, as an option for preventing relapse in recurrent non-infectious uveitis affecting the posterior segment of the eye. See FAD section 1.
17	Consultee	The Royal College of Ophthalmologists	Multiple clinical experts have recommended in the consultation and during the appraisal meeting that withdrawal of systemic therapy, as the clinical trial for Iluvien included, is representative of treatment in NHS practice. It is standard care to withdraw treatment, particularly corticosteroid and systemic immunosuppression is withdrawn if	Comment noted. The committee agreed that it was plausible that people with unilateral disease may have corticosteroid treatment tapered off and receive no treatment until recurrence. However the committee considered

			ineffective after an adequate clinical trial, not tolerate or adverse event occurs.	that it was unlikely that people with bilateral disease would receive no treatment.
18	Consultee	The Royal College of Ophthalmologists	We agree that the rate of recurrence may be overestimated with missing data imputed as a recurrence.	Comment noted. No change to the FAD required.
19	Consultee	The Royal College of Ophthalmologists	A well designed, randomised trial comparing Ozurdex with Iluvien would be welcomed and would inform the valid question of comparisons between intravitreal therapies. However, we have significant concerns regarding comparisons between the currently available HURON Ozurdex trial and Iluvien trial data. Comparing two differently designed trials, with different entry criteria (particularly with significantly different disease activity measures and levels) and endpoints and heterogenous cohorts of patients does not provide robust data to allow comparisons on efficacy and safety. The HURON study entry was entirely based on a cohort of patients with active disease at baseline based on a strict entry vitreous haze grade at baseline whereas the Iluvien trial incorporated patients with inactive and active uveitis and had different entry criteria. A comparison on purely economic terms does not take account the disutility to the patient (in time and unpleasantness of having multiple Ozurdexes vs one Iluvien) and cost to the NHS of managing disease activity and flare ups between injections. Also, multiple Iluvien injections means modelling out to 6 years at least. The Huron licensing trial for Ozurdex was only 6 months and the Iluvien trial did not include repeat Iluvien injections. Multiple clinical experts have recommended that our real-world experience of the duration of action of Ozurdex is not 6months as modelled in the calculations. This is felt to be an over-estimation and using this timescale does not reflect clinical practice with Ozurdex. In reality: 1. Patients do not routinely have 6months effect from Ozurdex (patient experts verified this) 2. Patients have fluctuating control and disease recurrence sooner with more frequent visits, need for repeat treatments at less than 6mo with costs to NHS of provision of treatment and follow up in clinic 3. The long-term visual impact of fluctuating control should be considered	Comment noted. The committee understood that there is limited data to enable a comparison of the fluocinolone acetonide implant and the dexamethasone implant. However, as described in the methods guide section 6.2.2, the availability of data is not a consideration when selecting relevant comparators. Comment noted. The committee understood from the patient experts that the dexamethasone implant may last for less than 6 months and took this into account. See FAD section 3.1.
20	Consultee	The Royal	Economic modelling:	Comment noted. The committee recognised

		College of Ophthalmologists	The model seems unduly sensitive to adverse events (disutilities):" When the ERG included a disutility of 0.10 for all adverse events, the ICER increased from £12,325 to £85,084 per QALY gained" a 7-fold increase for AEs. This is not concordant with the earlier statement: "But overall, the committee considered that the fluocinolone acetonide implant is well tolerated compared with other treatments for uveitis and that the adverse effects are manageable in clinical practice. "	that the ERG's analysis including disutilities for adverse events was speculative and not reliable for decision making. The committee considered that the company's new method was more reliable than the ERG's exploratory analyses. See FAD section 3.13.
21	Consultee	The Royal College of Ophthalmologists	A point for clarification: "When the ERG assumed equal efficacy for the fluocinolone acetonide and dexamethasone implants, the dexamethasone implant was dominant compared with the fluocinolone acetonide implant (that is, it was both less costly and more effective)." How can there be an assumption of equal effectiveness but Ozurdex come out more effective? How many Ozurdexes did this include? Assumption of equal efficacy means there will be periods of sub-optimal effectiveness for multiple Ozurdexes as each implant wears off over 3 years. "When the ERG assumed that the dexamethasone implant was more effective than the fluocinolone acetonide implant, the fluocinolone acetonide implant was extendedly dominated" Not an unreasonable assumption given that Ozurdex will give sub-optimal effectiveness as each one wears off during 3 years. Making Iluvien more effective and less costly than the approved comparator.	Thank you for your comment. The incremental costs and QALYs gained are commercial in confidence and cannot be reported here or in the FAD. The FAD has been updated, see section 3.16.
22	Clinical expert	Archana Pradeep	I have no concerns regarding this Technology implementation	Thank you for your comment. No changes to the FAD required.
23	Clinical expert	Archana Pradeep	The only consideration is that the evidence for re treatment after the implant effect wears off could be verified with further research to establish treatment protocols and to qualify treatment failure.	Comment noted. No evidence was available to the committee on these issues at the time when it made its decision. The guidance on this technology will be considered for review by the guidance executive 3 years after publication of the guidance. NICE is keen to hear about any new evidence that becomes available before the time of review. See the process guide section 6.
24	Commentator	Allergan	Allergan concurs with NICE Appraisal Committee's feedback on the limitations of the economic model of fluocinolone acetonide implant for treating recurrent non-infectious uveitis. • As was noted by the Committee the visual acuity outcome was	Comments noted. In response to the appraisal consultation

			a secondary outcome in the clinical trial and no formal statistical evaluation of change in visual acuity was performed that made it unsuitable for the inclusion in the health economic evaluation. • The economic model was a one-eye model that evaluated the study eye using a state transition Markov approach with five heath states. This could potentially underestimate the impact of bilateral disease on costs and health related quality of life of patients. • Extrapolation of the treatment effect beyond the three-year time horizon of the trial creates additional uncertainty within the model since it is not supported by the clinical evidence. Allergan agrees that inclusion of the length of the duration of adverse events will provide a more accurate estimate of the disutility, compared to using a fixed decrement of 0.05 or 0.10 for every adverse event. Allergan has not been granted access to any technical documentation that fully describes the economic modelling approach. However, we understand from the ACD document that the disutility of monocular blindness was not modelled in the base case, with the utility value of 0.57 from Brown et al. (1999) being preferred for the permanent blindness. In the trial however, 67.8% in the fluocinolone acetonide implant group and 73.8% in the control group had bilateral disease at baseline. As was noted by NICE in the technology appraisal for adalimumab and dexamethasone (TA460), the effect of blindness may depend on whether disease is unilateral or bilateral as the utility loss of blindness in both eyes is likely to be much higher than in unilateral blindness. The treatment failure and associated discontinuation rate wasn't explicitly discussed in the documents; therefore, it remains unclear whether this important aspect has been considered within the model. The Committee considered that dexamethasone implant should be considered as a relevant comparator. However head to head clinical trial evidence is not available. Furthermore, the different efficacy endpoints assessed in the HURON and PSV-FAI-001 studies makes indirect comparison challenging and this is likely to have a significant impact on the quality of the economic model results derived from any such comparison. Allergan is not aware of any data comparing long-term fluocinolone treatment v dexamethasone implant, so that modelling	document, the company presented post-hoc statistical analyses of visual acuity. However the committee noted that visual acuity was not included in the model. See FAD section 3.5. The committee agreed that it would have preferred to have seen a model that took both eyes into account. See FAD section 3.7. Comment noted. No change to the FAD required. Comment noted. The committee agreed that the company's new method of incorporating disutilities for adverse events was more reliable than the ERG's exploratory analyses. See FAD section 3.13. Comment noted. Treatment effectiveness was modelled using time to first uveitis recurrence in the study eye from the trial. The data on time to recurrence is academic in confidence and cannot be reported. Comment noted. The committee understood that there is limited data to enable a comparison of the fluocinolone acetonide implant and the dexamethasone implant. However, as described in the methods guide section 6.2.2, the availability of data is not a consideration when selecting relevant

			long-term outcomes for these two treatments would require a set of extrapolation outcomes that would further amplify uncertainty in the modelling.	comparators.
25	Web comment	NHS Professional	**Commenting on 1 Recommendations:** There is no data from the RCTs looking into both eyes use. No device study carried out until now has looked into this. Analysis will always be theoretical extrapolating findings from the one eye use to both eyes. I don't think this was requested for the analysis of the Ozurdex. **Commenting on 1 Recommendations:** The dexamethasone implant was not approved for the prevention of non-infectious posterior uveitis and no trial data exists to give data on this aspect of the use of this device. Even though the Huron study suggested a six-month effect, real-world experience is showing a shorter duration of the effect (median of 4.5 months in the OPUS data (unpublished). I don't think the devices are actually comparable in what they have been designed to do. I would never consider Ozurdex an option to prevent recurrence of uveitis in a patient who has been brought under control by other treatments. It is used to treat active disease, especially if not responding to other options or in cases where systemic therapy is not possible. The only device that could be comparable to Iluvien would be the Retisert, also releasing Fluocinolone acetonide over 3 years, but this device was never approved by the EMA for use in Europe. **Commenting on the following text:** *'The clinical trial results are difficult to interpret and very uncertain. The trial didn't measure health-related quality of life and the number of recurrences reported may be overestimated. Also, people in the control group didn't have any treatment after 3 months in the trial, which is not what is likely to happen in the NHS in England.'* This is the same situation for the Huron study, when the fellow eye was not treated. No trial will replicate what happens in the NHS since the criteria for inclusion and exclusion don't match our clinical decisions and the design is not a comparative study to standard of care. It is important to remember that standard of care does not actually exist for Uveitis. We all use variations of the use of the different options available. most	Comment noted. The committee would have preferred to have seen a model that took both eyes into account, particularly because of the proportion of people with bilateral disease in the trial. See FAD section 3.7. Comment noted. The committee understood that the marketing authorisation for the dexamethasone implant is different to that of the fluocinolone acetonide. However it heard from clinical experts that they may choose to use the fluocinolone acetonide implant at the point in the treatment pathway that they may currently use the dexamethasone implant. Therefore the committee concluded that the dexamethasone implant was a relevant comparator. See FAD section 3.2. Comment noted. The committee understood that the treatment pathway for non-infectious uveitis is complex (see FAD section 3.2). However, as described in the Guide to the methods of technology appraisal, section 6.2.7, the committee's judgements on clinical effectiveness need to take into account the nature and quality of the evidence presented.

			of which is not based on evidence. The patients in the study will offered rescue whenever a recurrence was identified and there was a very strict control for patient safety.	

Comment number	Comments
The company response below focuses on 5 key issues identified in the ACD and clarifies important misunderstandings that appear to have arisen during the TA process. Its aim is to discuss data interpretation, as actual data and all supporting references have already been provided to NICE at this stage.	
1) Uncertainty associated with clinical trial results: "The clinical trial results are difficult to interpret and very uncertain. The trial didn't measure health-related quality of life and the number of recurrences reported may be overestimated."	• The study design of PSV-FAI-001 ensured that the effect of treatment with the FAc implant is estimated in a conservative manner. To this end, any use of any medication that could affect the course of patient's NIU-PS was considered a recurrence in the trial, to ensure that any reduction in recurrence rate observed were attributable only to the FAc implant and not to other medications the patient may have received. This approach to quantifying the recurrence endpoint was satisfactory for regulatory agencies, including the US FDA and the MHRA. • An important clarification point is that data imputation usually refers to imputed missing data, e.g. in patients who did not have the required eye examinations. However, in the PSV-FAI-001 trial this common understanding is misleading, as the vast majority of imputed recurrences was due to the use of medications that could affect the course of NIU-PS. The trial allowed clinicians to treat patients if there was any sign of uveitis that they considered required treatment (even if the protocol-defined criteria for recurrence have not been met) and such treatment administered at any time point post 7 days* was classified as an 'imputed recurrence'. Therefore, imputed recurrence recorded any deterioration of the patient's condition, even if it did not meet the protocol-defined criteria for recurrence. • The use of imputed recurrences can be seen as a pragmatic approach to study design, resembling real-world practice, since clinicians could treat patients for uveitis at their discretion and these patients remained on study. It also represents a very stringent evaluation of the FAc implant effect, as it allows any deterioration in the patient's condition to be captured in the analysis, rather than just those events that meet pre-defined recurrence criteria. • Although missing eye examination data also resulted in an 'imputed recurrence', at 36 months only 4 out of 52 patients with imputed recurrences had missing eye examination data, while the remaining patients had a recurrence imputed due to the use of local or systemic steroids/ immunosuppressants. • Although the aforementioned conservative approach could result in recurrence rates being somewhat overestimated, this affected both arms of the trial equally without favouring the FAc implant in any way, as the same non-study treatments were permitted in both arms. Supporting this notion was the fact the FAc implant showed a very clear and statistically significant reduction in recurrence rate not only in the ITT population, but also in the per-protocol population,

	where only observed (and not imputed) recurrences were considered. Therefore, the benefits of the FAc implant observed in the trial were independent of, and unbiased by, the conservative imputation approach described above. • Overall, both a flare of NIU-PS meeting the protocol-defined recurrence criteria and treatment given at early signs of recurrence (and before these criteria were met) led to the patient being recognised as experiencing a recurrence. Therefore, the trial results should not be interpreted as uncertain, but rather as providing a conservative estimate of FAc implant effect, which nonetheless provided a statistically significant reduction in the rate of uveitis recurrence, as well as a clear effect on reducing a number of other measures of NIU-PS activity (please refer to the Company Submission, and Clarification Document for details of the results). * Recurrence in days 0–7 could be treated, but was not included in the analysis due to potential symptom overlap with an inflammatory reaction from implant injection.
2) Applicability of PSV-FAI-001 to the UK setting "People in the control group didn't have any treatment after 3 months in the trial, which is not what is likely to happen in the NHS in England."	• The company believes that the NICE committee and ERG have misinterpreted the design of the PSV-FAI-001 trial, which impacts on the perceived relevance of the trial to UK clinical practice. • Patients recruited into the PSV-FAI-001 trial had prior history of recurrent NIU-PS, but also relatively quiescent disease at enrolment. Patients on any systemic medication with a potential effect on NIU-PS (approximately 50% of trial participants) were tapered off these medications within 3 months from study entry; however, this taper was not enforced if disease recurred and patients could have the tapering stopped (or dose increased) at clinical signs of recurrence. • Importantly, the trial did permit treatment of NIU-PS at any point during the study (also after the initial 3-month taper) in both arms of the study. In fact, any trial not permitting treatment over the course of 3 years in a chronic disease would be likely considered unethical, and this was not the case for PSV-FAI-001 trial. • If the investigators perceived there was clinical evidence of uveitis recurring, they were allowed to treat the patient before the patients NIU-PS flared up enough to reach the protocol-defined recurrence threshold of an >2 step increase in anterior chamber cells (ACC) or vitreous haze (VH), or a 15+ letter loss of best corrected visual acuity (BCVA). PSV-FAI-001 results clearly showed that, in both the FAc implant and control arms, the majority of recurrences reported were due to the use of these adjunctive/rescue treatments (termed imputed recurrences, see the first clarification comment) rather than for patients reaching the protocol-defined recurrence threshold. This suggests clinicians opted for prompt rescue treatment at early signs of uveitis recurrence, irrespective of the treatment arm to which the patient was randomised as the study was double-blind. • Therefore, patients in the sham arm could be seen as receiving "on-demand" treatment for uveitis recurrences, while patients in the FAc implant arm received a background low-dose local treatment with FAc in addition to "on-demand" treatment for recurrences. The degree to which this background treatment reduced the incidence of recurrence was of key interest in PSV-FAI-001, which primary endpoint was the incidence of uveitis recurrence.

	• In both arms, permitted treatment of NIU-PS recurrences was local (topical drops or intra-ocular /intravitreal treatments) or systemic (steroids or immunosuppressants). These adjunctive or rescue treatments were therefore allowed in both study arms, but also counted as evidence of NIU-PS recurrence. Of note, the trial protocol advised clinicians to attempt local therapy first and then move onto systemic treatment if required, but did not stop them from prescribing systemic medications where these were necessary to treat the patient effectively. Therefore, the ACD was incorrect in stating that "before recurrence in the trial, systemic treatment could only be used after local treatment had failed." • Only if topical drops/intra-ocular or intravitreal treatments or systemic immunosuppressants were used for indications OTHER than uveitis they were classed as prohibited. These had to be discussed with clinical trial monitors. • The local and systemic treatment options used for managing NIU-PS recurrences in PSV-FAI-001 are also available to patients and clinicians in England. Advice from clinical experts provided to the company and, indeed, the clinical expert speaking at the Committee meeting, also suggests that the trial is similar to the UK clinical practice in several respects: o In UK patients treated with systemic corticosteroids, clinicians would attempt to taper these off once an acute uveitis flare is under control, so as to reduce AEs. Similarly, in PSV-FAI-001 approximately half of the enrolled patients received systemic steroids or immunosuppressants at baseline. These were tapered off after study entry, but could be re-introduced in case of NIU-PS recurrence. o Clinicians in the UK would also attempt to discontinue local treatments once acute uveitis is under control, so as to establish minimal treatment necessary to manage the patient's uveitis, thus avoiding potential AEs associated with over-treatment. Again, the approach was similar in PSV-FAI-001, where local treatments could be used to treat acute uveitis flares/recurrences and were discontinued when the disease was again controlled. • The company acknowledges that the treatments used for uveitis recurrence in the trial are only a sample (rather than a full reflection) of the heterogenous uveitis treatment landscape. Since a national guideline for the treatment of NIU-PS in England does not exist, treatment may depend on the number of affected eyes, underlying aetiology or even local protocols. Given the resulting complexity of NIU-PS treatment landscape, it would be extremely difficult, if not impossible, to completely replicate it within any trial. This issue is well illustrated by the heterogeneity of additional treatment options permitted in PSV-FAI-001, the HURON trial of dexamethasone and the VISUAL I trial of adalimumab. Each of these trials took a different approach to additional treatments.
3) Comparison versus the dexamethasone implant	• Dexamethasone is available as an implant and is used in the treatment of active uveitis. As such, it could be considered recommended as a treatment of recurrence of non-infectious uveitis, however, the effectiveness in preventing relapse of recurrent NIU-PS has not been studied. Thus, no data exists in relation to dexamethasone as a prevention of uveitis recurrence. In summary, dexamethasone is not explicitly recommended (according to TA460) or used to prevent relapse of recurrent NIU-PS, nor does evidence exist with regards to its efficacy as a preventative treatment.

	• Despite this, the company recognised that, in some patients, the dexamethasone implant is likely to be considered a relevant comparator. However, clinical experts at the Committee meeting considered the two implants would be used in different (albeit possibly overlapping in some cases) patient populations. This is also well reflected in the different indications of the two implants. NICE TA460 resulted in a recommendation of the dexamethasone implant for patients with active disease (that is, current inflammation in the eye) and worsening vision with a risk of blindness. Conversely, marketing authorisation for the FAc implant is for prevention of relapse in recurrent NIU-PS, reflecting the pivotal PSV-FAI-001 study where any acute uveitis flares were treated prior to enrolment to obtain a relatively quiet eye. • However, the primary reason for the company not conducting an analysis versus the dexamethasone implant was the lack of appropriate data to inform this comparison in the economic model. • The company would like to highlight that the ERG report also did not consider the comparison vs the dexamethasone implant to be appropriate, and this was based on different trial designs and patient populations. These points are reflected in the following statements that have been extracted from page 82 of the ERG report: o "The most notable difference between the HURON trial and PSV-FAI-00135 was the difference in primary and secondary outcomes. PSV-FAI-00135 was powered to detect the recurrence of uveitis in the study eye at six months and three years (primary and secondary outcomes, respectively). HURON was powered to find the proportion of patients with a vitreous haze score of 0 at 8 weeks, the proportion of patients with a ≥ 15 letter improvement in BCVA and the proportion of patients with a ≥ 10 point improvement in VFQ-25 score change (primary and secondary outcomes, respectively)." o "…dexamethasone is not considered to be a comparator to ILUVIEN. Additionally, an indirect treatment comparison is inappropriate given that these trials are not powered to evaluate the same endpoints and the (L)CP arms are not comparable. In the absence of direct and indirect comparative effectiveness data, a naïve treatment comparison versus dexamethasone was considered, however, this was not preferred due to the lack of clinical efficacy data available to support an accurate evaluation of dexamethasone." • At the explicit request from NICE, an informal analysis versus the dexamethasone implant has now been provided. The results should be interpreted with caution, due to the large number of important assumptions that had to be implemented in the absence of source data, including: o Dexamethasone was assumed to be as efficacious over 6 months as the FAc implant is over 3 years in the prevention of relapse of recurrent NIU-PS; the efficacy profile demonstrated in PSV-FAI-001 was compressed to a 6-month period for this modelling approach. o It is critical to understand that there are no data to support this assumption of dexamethasone effectiveness. Furthermore, clinical opinion is that dexamethasone implant is effective for up to 4 months, so an assumption of

6 months is highly conservative. However, in order to fulfil the goal of preventing relapse of recurrent NIU-PS, the use of dexamethasone implant would be required on an empirical basis, being injected into eyes without signs or symptoms of NIU-PS at the time of administration.

- Consequently, a range of treatment comparisons have been evaluated, where ILUVIEN has been compared against 1, 2 and 3, dexamethasone injections. This provides a range of outcomes for consideration, which can be judged against the clinical plausibility in each case.
- It was assumed that a patient may fail treatment up to three times on either the FAc implant or dexamethasone where this option is selected by the user.
- It was assumed that the efficacy profile would not change with multiple treatments for both the FAc implant and for dexamethasone. Note, there is no available study data on the effectiveness of the dexamethasone implant in terms of prevention of relapse of recurrent NIU-PS.
- It was assumed that on both treatment regimens the rates of movement (attributed to blindness, death or treatment failure) would not change dependent with treatment line.
- Finally, in this model, it is assumed that dexamethasone implant would be administered to asymptomatic eyes in order to fulfil the goal of preventing relapse. This is use outside of the licensed indication for the dexamethasone implant and also current NICE recommendations for use.

4) Visual acuity

- As the company has previously informed, the statistical analysis plan for PSV-FAI-001 stated that change from baseline BCVA would be analysed using descriptive statistics only; thus, statistical testing for this endpoint was performed post-hoc rather than included in the trial as a planned analysis. The company did not present it in the initial submission as it could be considered "data dredging", i.e. looking for statistical significance where the data appears favourable at first glance.
- As NICE has specifically requested statistical analysis of this endpoint to be provided, this is presented in the Table below.

Table: Mean Change from Baseline in BCVA in the Study Eye (ITT Population): PSV-FAI-001

	6 Months		12 Months		36 Months	
Arm	**FAI Insert**	**Sham Injection**	**FAI Insert**	**Sham Injection**	**FAI Insert**	**Sham Injection**
N	[redacted]	[redacted]	87	42	[redacted]	[redacted]
Mean Change (SD)	[redacted]	[redacted]	5.8 (14.36)	3.3 (12.78)	[redacted]	[redacted]

	Median	[redacted]	[redacted]	5.0	4.0	[redacted]	[redacted]
	Min, max	[redacted]	[redacted]	(-39, 49)	(-52, 25)	[redacted]	[redacted]
	Difference from sham injection*						
	Estimate	[redacted]		2.5		[redacted]	
	95% CI	[redacted]		(-2.81, 7.82)		[redacted]	
	P-value	[redacted]		0.353		[redacted]	

Abbreviations: BCVA, best corrected visual acuity; CI, confidence interval; ITT, intent-to-treat; SD, standard deviation.
*Estimate, 95% CI, and P values were based on one-way analysis of variance.

5) Modelling bilateral disease	• The company has now provided a revised model where both eyes are considered independently. It is worth noting at this point that an FAc implant administered in one eye does not affect any uveitis that may be present in the other eye, since the small daily dose (0.2 µg/day) of FAc is not detectable in blood samples and therefore extremely unlikely to affect the fellow, untreated eye. Hence, both eyes should be considered separately for treatment with the FAc implant in the real-world setting. Bilateral treatment should not be performed at the same visit; instead a second implant should only be used when the patient's ocular and systemic response to the first implant is known (see the SPC for more details). • Initially, the model focused only on unilateral treatment, since bilateral treatment with the FAc implant was not permitted in the PSV-FAI-001 trial. Hence, several important assumptions were made to model bilateral treatment: o The model and evidence were only able to make estimates about unilateral treatment and therefore the effect in the other eye is assumed to be as modelled. o Costs and effect for the second eye were assumed to be as for the modelled eye.

NICE National Institute for Health and Care Excellence

Fluocinolone acetonide ocular implant for treating recurrent non-infectious uveitis [ID1039]

Consultation on the appraisal consultation document – deadline for comments 5pm on **Wednesday 24 April 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):	**Birdshot Uveitis Society**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**No disclosures**
Name of commentator person completing form:	[redacted]

Please return to: TACommC@nice.org.uk/**NICE DOCS**

NICE National Institute for Health and Care Excellence

Fluocinolone acetonide ocular implant for treating recurrent non-infectious uveitis [ID1039]

Consultation on the appraisal consultation document – deadline for comments 5pm on **Wednesday 24 April 2019 email:** TACommC@nice.org.uk/NICE DOCS

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	1.1: The Birdshot Uveitis Society is very disappointed that the NICE appraisal committee has not recommended fluocinolone acetonide implant as an option for preventing relapse in recurrent non-infectious uveitis affecting the posterior segment of the eye in adults.
2	1.2, 3.17, 3.18 Birdshot Uveitis Society asks that NICE gives careful consideration to the further clarification and analysis of evidence requested by the appraisal committee from the manufacturers.
3	3.16 Birdshot Uveitis Society hopes that this new information will lead to a recommendation by NICE for the use of this 'potentially promising treatment'.
4	3.1, 3.2, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 3.10, 3.11, 3.19: Birdshot Uveitis Society agrees with the committee's conclusions on these points.
5	3.3. Birdshot Uveitis Society disagrees with the committee's conclusion on this point. The PSV-FAI-001 trial was not designed 'to reflect NHS clinical practice in England': it was designed to test the effectiveness of the fluocinolone acetonide intravitreal implant compared with a sham implant. Patients in both treatment groups had their previous treatments tapered off during the first three months of the trial. They were all monitored for recurrence of uveitis and recurrences were treated. This is what happens in NHS England clinical practice as part of the routine monitoring and treatment of uveitis patients.
6	3.13, 3.14, 3.15: Birdshot Uveitis Society is unable to comment on the committee's conclusions on these points.
7	4.1 Birdshot Uveitis Society would welcome an earlier review date when relevant information is gathered by NICE.

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

Please return to: TACommC@nice.org.uk/**NICE DOCS**

NICE National Institute for Health and Care Excellence

Fluocinolone acetonide ocular implant for treating recurrent non-infectious uveitis [ID1039]

Consultation on the appraisal consultation document – deadline for comments 5pm on **Wednesday 24 April 2019 email:** TACommC@nice.org.uk/NICE DOCS

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.

Comments received during our consultations 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 comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

Fluocinolone acetonide ocular implant for treating recurrent non-infectious uveitis [ID1039]

Consultation on the appraisal consultation document – deadline for comments 5pm on **Wednesday 24 April 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):	International Uveitis Study Group
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:	[redacted]

Comment number	Comments

Please return to: TACommC@nice.org.uk/**NICE DOCS**

NICE National Institute for Health and Care Excellence

Fluocinolone acetonide ocular implant for treating recurrent non-infectious uveitis [ID1039]

Consultation on the appraisal consultation document – deadline for comments 5pm on **Wednesday 24 April 2019 email:** TACommC@nice.org.uk/NICE DOCS

	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 appreciate that the PSV-FAI-001 study may not have been as 'exact' as other sponsored clinical trials in uveitis (anecdotally some IUSG members have remarked about various aspects of the trial), perhaps due to the naivety (or over enthusiasm) of the company and the lack of undertaking previous studies in uveitis. Nevertheless, the study design etc. should not be used to penalise patients. Did the treatment work? The answer is 'Yes'. The study provides evidence for this and from patient comments. Would having it available as another treatment option for uveitis benefit patients in the real-world setting? Again, the answer is 'Yes'.
2	We feel that it would be appropriate to compare to the dexamethasone implant (ozurdex). There will be patients who have disease in only one eye and also may not have an underlying systemic disease, thus they would be denied adalimumab (TA 460). There is increasing evidence that the effect of the dexamethasone implant may wear off after 4-5 months (it was previously thought to be 6 months). In theory, over a two-year period, patients could require 4-5 dexamethasone implants whereas a single fluocinolone acetonide implant may have the same effect over a similar time period. Adverse events have been commented on, but every intravitreal injection has the potential for infection (endophthalmitis is a well-recognised and feared complication of anti-VEGF injections for AMD), cataract formation, and possibly raised intraocular pressure. These injections are frequently given in Theatre and repeated dexamethasone implants (apart from the cost of numerous implants) would add additional costs and take up slots that could have been used for cataract surgery and improving vision in those patients. In the real world 4-5 dexamethasone implants over 2 years would be unlikely as the ophthalmologist and patient may decide that more than 3 injections over a 12-18-month period may not be acceptable. Then the only alternative would be systemic corticosteroid +/- systemic immunosuppression with all their well-known side effects. Having the option of a local treatment that may last 2-3 years, that could be repeated may save the patient having frequent intravitreal dexamethasone implants and possibly systemic therapy with all the side-effects and costs associated with them. There is some analogy with the Retisert studies where the majority of patients had IOP rises and some needed glaucoma surgery, but they stated this would be much preferable than staying on systemic therapy.
3	We are concerned that if this treatment was not approved at this time point and the guidance re-evaluated after 3 years, it is highly unlikely patients will have access to it during this period. Ophthalmologists would still have to submit IFRs to NHS England and we envisage that 99-100% of applications will be rejected on the grounds that there was not enough evidence (that may be based on this NICE recommendation) and that patients would not be classed as exceptional. There are no other official pathways to obtain the treatment. The only options would be a DTC in an NHS Trust funding it or the company providing it on compassionate grounds (or stock about to expire). We understand that it will require time for more robust data to be produced and there needs to be discussions with the company to see if the meaningful data NICE requires can be made available in a shorter time period so that the guidance could be re-evaluated within the next 2 years. Nevertheless, there needs to be a better mechanism for individual patients to have an opportunity to obtain this drug during this time.

Please return to: TACommC@nice.org.uk/**NICE DOCS**

NICE National Institute for Health and Care Excellence

Fluocinolone acetonide ocular implant for treating recurrent non-infectious uveitis [ID1039]

Consultation on the appraisal consultation document – deadline for comments 5pm on **Wednesday 24 April 2019 email:** TACommC@nice.org.uk/NICE DOCS

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.
- 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.

Comments received during our consultations 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 comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

Fluocinolone acetonide ocular implant for treating recurrent non-infectious uveitis [ID1039]

Consultation on the appraisal consultation document – deadline for comments 5pm on **Wednesday 24 April 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):	**The Royal College of Ophthalmologists**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[redacted]

NICE National Institute for Health and Care Excellence

Fluocinolone acetonide ocular implant for treating recurrent non-infectious uveitis [ID1039]

Consultation on the appraisal consultation document – deadline for comments 5pm on **Wednesday 24 April 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.
Example 1	We are concerned that this recommendation may imply that ……..
1	We are very disappointed that NICE may not recommend this treatment for patients in the NHS with chronic, sight-threatening uveitis who currently have unmet clinical need including patients who have one or more needs: -Inadequate respond /do not tolerate standard treatment with immunosuppression or biologic therapy - Have demonstrated responded to currently available intravitreal steroid medications but demonstrate recurrence of activity including sight-threatening complications such as flare up of uveitis or recurrence of macular oedema as treatment wears off (typically <6 months)
2	Multiple clinical experts have recommended in the consultation and during the appraisal meeting that withdrawal of systemic therapy, as the clinical trial for Iluvien included, is representative of treatment in NHS practice. It is standard care to withdraw treatment, particularly corticosteroid and systemic immunosuppression is withdrawn if ineffective after an adequate clinical trial, not tolerate or adverse event occurs.
3	We agree that the rate of recurrence may be overestimated with missing data imputed as a recurrence.
4	A well designed, randomised trial comparing Ozurdex with Iluvien would be welcomed and would inform the valid question of comparisons between intravitreal therapies. However, we have significant concerns regarding comparisons between the currently available HURON Ozurdex trial and Iluvien trial data. Comparing two differently designed trials, with different entry criteria (particularly with significantly different disease activity measures and levels) and endpoints and heterogenous cohorts of patients does not provide robust data to allow comparisons on efficacy and safety. The HURON study entry was entirely based on a cohort of patients with active disease at baseline based on a strict entry vitreous haze grade at baseline whereas the Iluvien trial incorporated patients with inactive and active uveitis and had different entry criteria. A comparison on purely economic terms does not take account the disutility to the patient (in time and unpleasantness of having multiple Ozurdexes vs one Iluvien) and cost to the

Fluocinolone acetonide ocular implant for treating recurrent non-infectious uveitis [ID1039]

Consultation on the appraisal consultation document – deadline for comments 5pm on **Wednesday 24 April 2019 email:** TACommC@nice.org.uk/NICE DOCS

	NHS of managing disease activity and flare ups between injections. Also, multiple Iluvien injections means modelling out to 6 years at least. The Huron licensing trial for Ozurdex was only 6 months and the Iluvien trial did not include repeat Iluvien injections. Multiple clinical experts have recommended that our real-world experience of the duration of action of Ozurdex is not 6months as modelled in the calculations. This is felt to be an over-estimation and using this timescale does not reflect clinical practice with Ozurdex. In reality: 1. Patients do not routinely have 6months effect from Ozurdex (patient experts verified this) 2. Patients have fluctuating control and disease recurrence sooner with more frequent visits, need for repeat treatments at less than 6mo with costs to NHS of provision of treatment and follow up in clinic 3. The long-term visual impact of fluctuating control should be considered
5	Economic modelling: The model seems unduly sensitive to adverse events (disutilities):" When the ERG included a disutility of 0.10 for all adverse events, the ICER increased from £12,325 to £85,084 per QALY gained" a 7-fold increase for AEs. This is not concordant with the earlier statement: "But overall, the committee considered that the fluocinolone acetonide implant is well tolerated compared with other treatments for uveitis and that the adverse effects are manageable in clinical practice. "
6	A point for clarification: "When the ERG assumed equal efficacy for the fluocinolone acetonide and dexamethasone implants, the dexamethasone implant was dominant compared with the fluocinolone acetonide implant (that is, it was both less costly and more effective)." How can there be an assumption of equal effectiveness but Ozurdex come out more effective? How many Ozurdexes did this include? Assumption of equal efficacy means there will be periods of sub-optimal effectiveness for multiple Ozurdexes as each implant wears off over 3 years. "When the ERG assumed that the dexamethasone implant was more effective than the fluocinolone acetonide implant, the fluocinolone acetonide implant was extendedly dominated" Not an unreasonable assumption given that Ozurdex will give sub-optimal effectiveness as each one wears off during 3 years. Making Iluvien more effective and less costly than the approved comparator.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).

Please return to: TACommC@nice.org.uk/**NICE DOCS**

NICE National Institute for Health and Care Excellence

Fluocinolone acetonide ocular implant for treating recurrent non-infectious uveitis [ID1039]

Consultation on the appraisal consultation document – deadline for comments 5pm on **Wednesday 24 April 2019 email:** TACommC@nice.org.uk/NICE DOCS

- 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.

Comments received during our consultations 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 comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

Fluocinolone acetonide ocular implant for treating recurrent non-infectious uveitis [ID1039]

Consultation on the appraisal consultation document – deadline for comments 5pm on **Wednesday 24 April 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):	Allergan Ltd
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:	[redacted]

Comment number	Comments

Please return to: TACommC@nice.org.uk/**NICE DOCS**

NICE National Institute for Health and Care Excellence

Fluocinolone acetonide ocular implant for treating recurrent non-infectious uveitis [ID1039]

Consultation on the appraisal consultation document – deadline for comments 5pm on **Wednesday 24 April 2019 email:** TACommC@nice.org.uk/NICE DOCS

	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	
1	Allergan concurs with NICE Appraisal Committee's feedback on the limitations of the economic model of fluocinolone acetonide implant for treating recurrent non-infectious uveitis. • As was noted by the Committee the visual acuity outcome was a secondary outcome in the clinical trial and no formal statistical evaluation of change in visual acuity was performed that made it unsuitable for the inclusion in the health economic evaluation. • The economic model was a one-eye model that evaluated the study eye using a state transition Markov approach with five heath states. This could potentially underestimate the impact of bilateral disease on costs and health related quality of life of patients. • Extrapolation of the treatment effect beyond the three-year time horizon of the trial creates additional uncertainty within the model since it is not supported by the clinical evidence. Allergan agrees that inclusion of the length of the duration of adverse events will provide a more accurate estimate of the disutility, compared to using a fixed decrement of 0.05 or 0.10 for every adverse event. Allergan has not been granted access to any technical documentation that fully describes the economic modelling approach. However, we understand from the ACD document that the disutility of monocular blindness was not modelled in the base case, with the utility value of 0.57 from Brown et al. (1999) being preferred for the permanent blindness. In the trial however, 67.8% in the fluocinolone acetonide implant group and 73.8% in the control group had bilateral disease at baseline. As was noted by NICE in the technology appraisal for adalimumab and dexamethasone (TA460), the effect of blindness may depend on whether disease is unilateral or bilateral as the utility loss of blindness in both eyes is likely to be much higher than in unilateral blindness. The treatment failure and associated discontinuation rate wasn't explicitly discussed in the documents; therefore, it remains unclear whether this important aspect has been considered within the model. The Committee considered that dexamethasone implant should be considered as a relevant comparator. However head to head clinical trial evidence is not available. Furthermore, the different efficacy endpoints assessed in the HURON and PSV-FAI-001 studies makes indirect comparison challenging and this is likely to have a significant impact on the quality of the economic model results derived from any such comparison. Allergan is not aware of any data comparing long-term fluocinolone treatment v dexamethasone implant, so that modelling long-term outcomes for these two treatments would require a set of extrapolation outcomes that would further amplify uncertainty in the modelling.

NICE National Institute for Health and Care Excellence

Fluocinolone acetonide ocular implant for treating recurrent non-infectious uveitis [ID1039]

Consultation on the appraisal consultation document – deadline for comments 5pm on **Wednesday 24 April 2019 email:** TACommC@nice.org.uk/NICE DOCS

2	
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.
- 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.

Comments received during our consultations 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 comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

Fluocinolone acetonide ocular implant for treating recurrent non-infectious uveitis [ID1039]

Consultation on the appraisal consultation document – deadline for comments 5pm on **Wednesday 24 April 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):	NHS
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:	Archana Pradeep

Comment number	**Comments**

Please return to: TACommC@nice.org.uk**/NICE DOCS**

NICE National Institute for Health and Care Excellence

Fluocinolone acetonide ocular implant for treating recurrent non-infectious uveitis [ID1039]

Consultation on the appraisal consultation document – deadline for comments 5pm on **Wednesday 24 April 2019 email:** TACommC@nice.org.uk/NICE DOCS

	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	
1	I have no concerns regarding this Technology implementation
2	The only consideration is that the evidence for re treatment after the implant effect wears off could be verified with further research to establish treatment protocols and to qualify treatment failure.
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.
- 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.

Comments received during our consultations 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 comments we received, and are not endorsed by NICE, its officers or advisory committees.

Please return to: TACommC@nice.org.uk/**NICE DOCS**

NICE National Institute for Health and Care Excellence

Fluocinolone acetonide ocular implant for treating recurrent non-infectious uveitis [ID1039]

Consultation on the appraisal consultation document – deadline for comments 5pm on **Wednesday 24 April 2019 email:** TACommC@nice.org.uk/NICE DOCS

Please return to: TACommC@nice.org.uk**/NICE DOCS**

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

Name	[redacted]
Conflict	Before I start my comments I want to declare that I have a consultancy contract with Alimera.
Comments on the ACD:	

Commenting on 1 Recommendations:
There is no data from the RCTs looking into both eyes use. No device study carried out until now has looked into this. Analysis will always be theoretical extrapolating findings from the one eye use to both eyes. I don't think this was requested for the analysis of the Ozurdex.

Commenting on 1 Recommendations:
The dexamethasone implant was not approved for the prevention of non-infectious posterior uveitis and no trial data exists to give data on this aspect of the use of this device. Even though the Huron study suggested a six-month effect, real-world experience is showing a shorter duration of the effect (median of 4.5 months in the OPUS data (unpublished). I don't think the devices are actually comparable in what they have been designed to do. I would never consider Ozurdex an option to prevent recurrence of uveitis in a patient who has been brought under control by other treatments. It is used to treat active disease, especially if not responding to other options or in cases where systemic therapy is not possible.
The only device that could be comparable to Iluvien would be the Retisert, also releasing Fluocinolone acetonide over 3 years, but this device was never approved by the EMA for use in Europe.

Commenting on the following text: *'The clinical trial results are difficult to interpret and very uncertain. The trial didn't measure health-related quality of life and the number of recurrences reported may be overestimated. Also, people in the control group didn't have any treatment after 3 months in the trial, which is not what is likely to happen in the NHS in England.'*

This is the same situation for the Huron study, when the fellow eye was not treated. No trial will replicate what happens in the NHS since the criteria for inclusion and exclusion don't match our clinical decisions and the design is not a comparative study to standard of care. It is important to remember that standard of care does not actually exist for Uveitis. We all use variations of the use of the different options available. most of which is not based on evidence. The patients in the study will offered rescue whenever a recurrence was identified and there was a very strict control for patient safety.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Fluocinolone acetonide ocular implant for treating recurrent non-infectious uveitis [ID1039]

Company Response to ACD Modelling Requests

Contents

Tables and figures

ACD Model Adaptations

Dear Committee Members,

We would like to thank you for the opportunity to present additional analysis following the conduct of the ACD meeting. The following analysis takes on board comments made by the ERG and ACD and includes a comparison to dexamethasone. These analyses show that:

- Where ILUVIEN alone is compared to dexamethasone, ILUVIEN would be considered cost effective at a willingness to pay threshold of £20,000
- Bilateral treatment with ILUVIEN compared with bilateral treatment with dexamethasone implants always results in a blindness reduction over five years.
- Regardless of whether a transition to blindness from a state of positive treatment response is allowed, ILUVIEN remains cost-effective when compared to dexamethasone.

We appreciate that decision making is difficult, particularly where the evidence base is limited. We hope therefore, that these additional estimates may be informative.

Philip Ashman | Chief Operating Officer & SVP Commercial Operations Europe
Alimera Sciences Limited

A.1 Methodology

The ERG adapted cost-effectiveness model was further adapted to consider dexamethasone as a comparator to the FAc implant using a different methodology than was presented by the ERG. A number of ERG settings were included in the base case analysis as recommended by the committee; these are as follows:

- Error fixing (ERG 1-4)
- Use of IPD in estimating FAc efficacy (ERG 5)
- Violations corrected (ERG 6 – 9)
- Removal of the remission health state (ERG 10)

Additionally, as recommended by the committee:

- No efficacy after 3 years for ILUVIEN or 6 months for dexamethasone (the “active” time)
- Disutilities for selected adverse events (AEs) are considered
- Results were included where a transition to permanent blindness is possible from the “On Treatment” health state

Additionally, now that repeated treatments are being considered, a disutility associated with the anxiety of repeated intraocular injections is included. Pochopien (2019)[1] included a disutility for patients with chronic diabetic macular oedema of 0.071 per year, expecting approximately 17.3% of patients to experience this. The same methodology has been applied to patients who are receiving treatment in the scenarios presented here.

It was also requested that bilateral disease was considered. Given the absence of data regarding bilateral disease, it was not considered possible to do anything other than replicate the model for the additional eye. The limitations of the data are described in the original Company Submission (CS) and the Company response to the ERG. In addition, the data that underpins the efficacy of ILUVIEN and now of dexamethasone in the model is specific to the study eye only and the relationship that this data has to any other eye is not documented. In an attempt to ascertain the costs and benefits associated with treatment in both eyes, a cost and benefit summary is reported for a number of scenarios.

A.2 Dexamethasone Efficacy

No evidence was available to model the efficacy of dexamethasone without considerable assumptions as it was described in the CS, the ERG report and the Company’s response to the ERG. The Company does not consider it appropriate to assume that treatment with dexamethasone over three years would show the same profile of efficacy as ILUVIEN over three years. The ILUVIEN efficacy profile shows a constantly decreasing proportion of patients experiencing recurrence over three years, whereas the dexamethasone implant is only effective for up to six months. Thus, a similar profile may be expected but confined to six months only to capture the possible failures over this period of time. Therefore, for this analysis it was assumed that the efficacy for dexamethasone and ILUVIEN is the same during the period the respective implant was considered “active” and that after this time there was no efficacy. To implement this, the efficacy profile selected for ILUVIEN in the model is scaled down from three years to six months for use for the dexamethasone arm.

Adverse Events

Disutilities for relevant AEs were not included in the original analysis as the informing trial did not provide information regarding the duration of each AE. Additionally, it is assumed only

those AEs considered severe would likely contribute to a reduction in a patients expected health-related quality of life (HRQoL). Thus, disutilities for this subset of AEs only were sourced. More of these selected AEs were recorded in the original comparator arm than in ILUVIEN, so omission was a conservative approach.

The information available to inform the rates of AEs for a dexamethasone implant are sparse. AEs related to treatment with dexamethasone were as reported in the HURON trial (Lowder 2011) and were as follows:

- 15% experienced cataract during 26 weeks (9/62)
- 30% conjunctival haemorrhage (23/72)
- 12% eye pain (9/76)
- 9% iridocyclitis (7/76)

The following AEs (from PSV-FAI-001) were considered to impact a patient's quality of life:

- Anterior chamber flare
- Cataract (and cataract subscapular)
- Conjunctival haemorrhage
- Macular oedema (incl cystoid macular oedema)
- Iridocyclitis
- Macular fibrosis
- Posterior capsule opacification
- Uveitis
- Visual acuity reduced
- Visual impairment
- Vitreous Opacities
- IOP increased
- Viral upper respiratory infection
- Hypertension

Of those listed, the HURON trial (Lowder 2011) reported rates for:

- Cataract

- Conjunctival Haemorrhage
- Iridocyclitis

Disutilities were identified through an extensive literature search. Values were identified for four of the selected AEs. These and the indications they were recorded in are shown in the table below:

Table 1. Disutilities of selected AEs applied in the model

Adverse Event	Disutility (Annual – assumed where not reported)	Indication	Source
Cataract	-0.016	Type 2 Diabetes	Lee (2012)[2]
Macular oedema	-0.04	Diabetic Retinopathy and Diabetic Macular Edema	Fenwick (2012)[3]
Visual Impairment	-0.063	Type 2 Diabetes	Solli (2010)[4]
Hypertension	-0.009	Mixed	Wang (2014)[5]

To account for the missing values, the average of the values was used for any missing disutilities (-0.032). Where rates of AEs were not available for dexamethasone, it was assumed that the cyclical rates were the same for ILUVIEN and for dexamethasone as this is consistent with the approach taken by the ERG for inclusion of AE costs. This is also consistent with the assumption taken here that the efficacy is the same for both ILUVIEN and dexamethasone.

The total decrement per year on treatment is therefore 0.0006 and 0.0017 for ILUVIEN and dexamethasone, respectively.

A.3 Departures from ERG methods

As described in the Company's Response to the ERG report, not all of the approaches used in the ERG's comparison between ILUVIEN and dexamethoasone were considered appropriate by the Company. Therefore, departures from those methods were deemed necessary in this analysis. These are described below:

- The ERG's method of estimating efficacy assumed a constantly decreasing probability of recurrence over three years, though in this time a patient would have to have 6 implants with dexamethasone to comply with the same restrictions regarding the "active" time of ILUVIEN that the ERG placed on the ILUVIEN arm.
    - To represent a more clinically plausible profile, the company conservatively assumed that the efficacy profile that ILUVIEN shows over three years (while the implant is "active"), is the same in dexamethasone in its "active" period.
- To accommodate this, the Company's revised model allows patients to move be retreated upon failure, rather than wait for the next implant (be it another six months or three years) which the Company considers more clinically plausible.
- Not all AEs were considered to contribute to a disutility for patients which is a departure from the method used by the ERG. Instead, judgement was used to reduce the list of AEs recorded in PSV-FAI-001 to a reasonable list of AEs.
    - As there is very limited information on the AEs likely for patients with a dexamethasone implant, nor was it possible to confirm if they were measured with the same definition as in the PSV-FAI-001 study, it was not possible to reduce the list further by the proportions experiencing these AEs as impacting their quality of life.
    - Therefore, the proportion of those experiencing the subset of AEs was not split into severe and non-severe, but instead, it was conservatively assumed that all patients who experienced these AEs in PSV-FAI-001 did so severely.
    - The disutilities sourced are assumed annual (where not reported) rather than cyclical

A.4 Assumptions

To inform the additional analyses, it was necessary to make assumptions in the course of modelling. These are in addition to any assumptions made in the course of original modelling and are listed below:

- Efficacy of dexamethasone is arbitrarily assumed equal to that of ILUVIEN.
- The profile of efficacy demonstrated by ILUVIEN over three years is the same as would be demonstrated by dexamethasone in a six-month period.
- Retreatment does not affect the efficacy profile.

- Patients may have the number of implants deemed in the analysis before moving to subsequent therapy. They are assumed to be treated as soon as possible (i.e. next cycle) to the total number selected.

- Time on treatment is limited to the time the implant is “Active” for the number of cycles selected.

- Retreatment is assumed to happen at the same cost and in the subsequent cycle.

- Patients can experience permanent blindness while “On Treatment” at half the rate that they would if they were in subsequent treatment when this option is selected.

    - This assumption is the same regardless of implant type (intervention or comparator).

- All AEs that contribute to the disutility a patient experiences are considered to be happening severely for all patients.

    - Where it is unknown, the rates at which a patient experiences an AE is the same for dexamethasone as ILUVIEN to follow the assumptions about the cost of AEs and the efficacy.

- In the absence of disutility data in uveitic patient population, disutility values were sourced from diabetic and mixed eye disease populations, which were considered generalisable to patients with uveitis.

- A small proportion of patients will experience anxiety related to retreatment due to the nature of the treatment and this is applied to all patients on treatment.

A.5 Limitations

As it was necessary to make assumptions to fulfil additional analyses, there are considerable limitations of the analysis.

The assumptions about the efficacy of dexamethasone are uninformed as evidence is not available to support them. This was described in the CS, the Company’s response to ERG and in the ERG report. It is conservatively assumed that there is equal efficacy although this is not known.

It is assumed that retreatments are allowed for each treatment line up to the number included in the scenario. However, this is unknown for ILUVIEN as it is not currently used in the UK in this way and the PSV-FAI-001 trial did not allow for retreatment. It is not known exactly how many times a patient may fail a dexamethasone implant as there are no clear guidelines for treatment in this indication.

The rate of blindness used for the transition from subsequent therapy to permanent blindness is assumed to be halved when “On Treatment”. This reduction is arbitrary and

there is no evidence to support this assumption. Additionally, it is conservatively assumed that there is no difference in this risk between treatments despite PSV-FAI-001 recording no patients with an ILUVIEN implant experiencing blindness. The likely rate of blindness for patients with a dexamethasone implant is not known.

The disutility values were sourced from a population with diabetes and a range of eye diseases. In the absence of any other disutility values, it is assumed that these decrements are generalisable to the population in PSV-FAI-001 although there is no evidence to directly support this assumption.

Given the necessary assumptions, it is strongly recommended that the analysis provided is viewed with these limitations in mind.

A.6 Analysis Conducted

Analysis requested by the committee was prioritised. Full cost-effectiveness results is provided for the following scenarios:

- ILUVIEN Implant vs Dexamthasone Implant (1, 2 and 3 of each)
- 1 ILUVIEN Implant vs 1, 2 and 3 Dexamethasone Implants
- 1 dexamethasone implant followed by 1 ILUVIEN Implant vs 2 and 3 Dexamethasone Implants

Due to the absence of data that can characterise the relationship of the efficacy data reported in PSV-FAI-001 to another eye a full cost-effectiveness analysis was not feasible. However, it is assumed that as the model reflects one eye, the results would be applicable to another diseased eye. Therefore, total costs for a bilateral treatment and the proportion estimated to be blind at 5 years will be reported for the scenarios listed above.

A.7 Results

A.7.1 *Cost Comparison: ILUVIEN vs Dexamethasone*

Error! Reference source not found. shows a direct cost comparison between ILUVIEN and dexamethasone. This does not take into consideration efficacy or time on treatment.

Table 2: Direct Cost Comparison between ILUVIEN and Dexamethasone

Dosing		**Cost**		
ILUVIEN	**Dexamethasone**	**ILUVIEN**	**Dexamethasone**	**Difference**

1	1	[redacted]	£870	[redacted]
2	2	[redacted]	£1,740	[redacted]
3	3	[redacted]	£2,610	[redacted]
1	2	[redacted]	£1,740	[redacted]
1	3	[redacted]	£2,610	[redacted]
1 Dexamethasone + 1 ILUVIEN	**Dexamethasone**			[redacted]
1,1	2	[redacted]	£1,740	[redacted]
1,1	3	[redacted]	£2,610	[redacted]

A.7.2 *Cost -Effectiveness Analysis*

No transition to blindness from "On Treatment"

Results are presented for the scenarios described in A.6 where no transition to blindness was considered from On Treatment. These results are shown in Table 3 to Table 9

Table 3. 1 ILUVIEN Implant vs 1 Dexamethasone Implant

Outcome	ILUVIEN	Dex	Δ	ICER	NMB
Life Years	[redacted]	[redacted]	[redacted]	-	-
Time On Treatment	[redacted]	[redacted]	[redacted]	-	-
QALYs	[redacted]	[redacted]	[redacted]	-	-
Costs	[redacted]	[redacted]	[redacted]	£13,027.18	[redacted]

Table 4. 2 ILUVIEN Implants vs 2 Dexamethasone Implants

Outcome	ILUVIEN	Dex	Δ	ICER	NMB
Life Years	[redacted]	[redacted]	[redacted]	-	-
Time On Treatment	[redacted]	[redacted]	[redacted]	-	-
QALYs	[redacted]	[redacted]	[redacted]	-	-
Costs	[redacted]	[redacted]	[redacted]	£2,909.93	[redacted]

Table 5. 3 ILUVIEN Implants vs 3 Dexamethasone Implants

Outcome	ILUVIEN	Dex	Δ	ICER	NMB
Life Years	[redacted]	[redacted]	[redacted]	-	-
Time On Treatment	[redacted]	[redacted]	[redacted]	-	-
QALYs	[redacted]	[redacted]	[redacted]	-	-
Costs	[redacted]	[redacted]	[redacted]	£3,953.37	[redacted]

Table 6. 1 ILUVIEN Implant vs 2 Dexamethasone Implants

Outcome	ILUVIEN	Dex	Δ	ICER	NMB
Life Years	[redacted]	[redacted]	[redacted]	-	-
Time On Treatment	[redacted]	[redacted]	[redacted]	-	-
QALYs	[redacted]	[redacted]	[redacted]	-	-
Costs	[redacted]	[redacted]	[redacted]	£7,638.90	[redacted]

Table 7. 1 dexamethasone implant followed by 1 ILUVIEN Implant vs 2 dexamethasone Implants

Outcome	Dexamethasone + ILUVIEN	Dexamethasone	Δ	ICER	NMB
Life Years	[redacted]	[redacted]	[redacted]	-	-
Time On Treatment	[redacted]	[redacted]	[redacted]	-	-
QALYs	[redacted]	[redacted]	[redacted]	-	-
Costs	[redacted]	[redacted]	[redacted]	£23,126.19	[redacted]

Table 8. 1 ILUVIEN Implant vs 3 Dexamethasone Implants

Outcome	ILUVIEN	Dex	Δ	ICER	NMB
Life Years	[redacted]	[redacted]	[redacted]	-	-

Time On Treatment	[redacted]	[redacted]	[redacted]	-	-
QALYs	[redacted]	[redacted]	[redacted]	-	-
Costs	[redacted]	[redacted]	[redacted]	£17.97	[redacted]

Table 9. 1 dexamethasone implant followed by 1 ILUVIEN implant s 3 Dexamethasone Implants

Outcome	Dexamethasone + ILUVIEN	Dexamethasone	Δ	ICER	NMB
Life Years	[redacted]	[redacted]	[redacted]	-	-
Time On Treatment	[redacted]	[redacted]	[redacted]	-	-
QALYs	[redacted]	[redacted]	[redacted]	-	-
Costs	[redacted]	[redacted]	[redacted]	£21,971.17	[redacted]

<u>Transition to blindness from "On Treatment" considered</u>

Results are presented for the scenarios described in A.6 where no transition to blindness was considered from On Treatment. These results are shown in **Error! Reference source not found.** to **Error! Reference source not found.**.

Table 10. 1 ILUVIEN implant vs. 1 Dexamethasone implant

Outcome	ILUVIEN	Dex	Δ	ICER	NMB
Life Years	[redacted]	[redacted]	[redacted]	-	-
Time On Treatment	[redacted]	[redacted]	[redacted]	-	-
QALYs	[redacted]	[redacted]	[redacted]	-	-
Costs	[redacted]	[redacted]	[redacted]	£16,836.47	[redacted]

Table 11. 2 ILUVIEN implants vs. 2 Dexamethasone implants

Outcome	ILUVIEN	Dex	Δ	ICER	NMB
Life Years	[redacted]	[redacted]	[redacted]	-	-

Time On Treatment	[redacted]	[redacted]	[redacted]	-	-
QALYs	[redacted]	[redacted]	[redacted]	-	-
Costs	[redacted]	[redacted]	[redacted]	£3,047.19	[redacted]

Table 12. 3 ILUVIEN implants vs. 3 Dexamethasone implants

Outcome	ILUVIEN	Dex	Δ	ICER	NMB
Life Years	[redacted]	[redacted]	[redacted]	-	-
Time On Treatment	[redacted]	[redacted]	[redacted]	-	-
QALYs	[redacted]	[redacted]	[redacted]	-	-
Costs	[redacted]	[redacted]	[redacted]	£2,581.09	[redacted]

Table 13. 1 ILUVIEN implant vs. 2 Dexamethasone implants

Outcome	ILUVIEN	Dex	Δ	ICER	NMB
Life Years	[redacted]	[redacted]	[redacted]	-	-
Time On Treatment	[redacted]	[redacted]	[redacted]	-	-
QALYs	[redacted]	[redacted]	[redacted]	-	-
Costs	[redacted]	[redacted]	[redacted]	£9,771.59	[redacted]

Table 14. 1 Dexamethasone implant followed by 1 ILUVIEN implant vs. 2 Dexamethasone implants

Outcome	Dexamethasone + ILUVIEN	Dexamethasone	Δ	ICER	NMB
Life Years	[redacted]	[redacted]	[redacted]	-	-
Time On Treatment	[redacted]	[redacted]	[redacted]	-	-
QALYs	[redacted]	[redacted]	[redacted]	-	-
Costs	[redacted]	[redacted]	[redacted]	£29,461.14	[redacted]

Table 15. 1 ILUVIEN implant vs. 3 dexamethasone implants

Outcome	ILUVIEN	Dex	Δ	ICER	NMB
Life Years	[redacted]	[redacted]	[redacted]	-	-
Time On Treatment	[redacted]	[redacted]	[redacted]	-	-
QALYs	[redacted]	[redacted]	[redacted]	-	-
Costs	[redacted]	[redacted]	[redacted]	-£226.22	[redacted]

Table 16. 1 Dexamethasone implant followed by 1 ILUVIEN implant vs. 3 dexamethasone implants

Outcome	Dexamethasone + ILUVIEN	Dexamethasone	Δ	ICER	NMB
Life Years	[redacted]	[redacted]	[redacted]	-	-
Time On Treatment	[redacted]	[redacted]	[redacted]	-	-
QALYs	[redacted]	[redacted]	[redacted]	-	-
Costs	[redacted]	[redacted]	[redacted]	£27,877.58	[redacted]

A.7.1 *Summary Bilateral Results*

Results are presented in Table 17 to describe the costs and likely outcomes for bilateral treatments. Values presented are double those reported in the model.

Table 17: Summary results for bilateral treatment

First Eye	Second Eye	Total Cost	Proportion Blind at 5 years
1 ILUVIEN Implant	1 ILUVIEN Implant	[redacted]	[redacted]
2 ILUVIEN Implants	2 ILUVIEN Implants	[redacted]	[redacted]
3 ILUVIEN Implants	3 ILUVIEN Implants	[redacted]	[redacted]
1 Dexamethasone Implant	1 Dexamethasone Implant	[redacted]	[redacted]

2 Dexamethasone implants	2 Dexamethasone implants	[redacted]	[redacted]
3 Dexamethasone implants	3 Dexamethasone implants	[redacted]	[redacted]
1 ILUVIEN Implant	2 Dexamethasone Implants	[redacted]	[redacted]
1 ILUVIEN Implant	3 Dexamethasone implants	[redacted]	[redacted]
1 Dexamethasone Implant, then 1 ILUVIEN Implant	2 Dexamethasone implants	[redacted]	[redacted]
1 Dexamethasone Implant, then 1 ILUVIEN Implant	3 Dexamethasone implants	[redacted]	[redacted]
Range		[redacted]	[redacted]

A.8 Interpretation of Results

The results shown in Section A.7.2 show that where ILUVIEN is compared to dexamethasone, ILUVIEN would be considered cost-effective at a willingness to pay threshold of £20,000. The only times this is not true is when the analysis shows ILUVIEN following one treatment of dexamethasone. However, these scenarios should be interpreted with caution for several reasons; Firstly, treatment for both arms in the first 6 months is the same and so the sample size for the comparison from six months onwards is reduced in an already uncertain analysis. Secondly, because one treatment is three years and the other is six months, it becomes difficult to compare treatments because these scenarios lead to examples where retreatment is allowed differently in each arm. This leads to an inherent overestimation of benefit for dexamethasone in scenarios of multiple administration. For these reasons, the results should be interpreted with caution.

Where a comparison is made between ILUVIEN and dexamethasone alone, regardless of whether a transition from On Treatment to Blindness is considered, ILUVIEN is always considered cost-effective. As dexamethasone was stipulated to be considered a comparator, it is considered appropriate to focus here. ILUVIEN is associated with slight increases in cost but also in time on treatment and QALYs gained by patients.

Analysis of the likely costs of treating two eyes show that there is a maximum of [redacted] across scenarios. In the least costly scenario where both eyes are treated with a single dexamethasone implant, [redacted] of patients could be expected to be blind at 5 years. However, where both eyes are treated with on ILUVIEN implant, [redacted] could be expected to be blind in at least one eye and this additional cost is [redacted] to prevent approximately [redacted] of blindness.

As dexamethasone is being considered a direct comparator, the most plausible scenarios are direct comparisons. Regardless of whether a transition is in place from “On Treatment” to “Permanent Blindness”, ILUVIEN is considered cost-effective where one implant is compared to two or three dexamethasone implants. All of these scenarios are considerably below the willingness to pay threshold and therefore are associated with a positive net-monetary benefit.

A.9 Conclusion

ILUVIEN represents a viable treatment option for patients who wish to prevent the recurrence of uveitis when compared to dexamethasone implants. ILUVIEN is associated with small additional costs but reduced blindness in patients, increased time on treatment and increased HRQoL. All direct comparisons are associated with a positive net monetary benefit and ICERs below the willingness to pay threshold.

A.10 References

1. Pochopien M, Beiderbeck A, McEwan P, et al. Cost-effectiveness of fluocinolone acetonide implant (ILUVIEN®) in UK patients with chronic diabetic macular oedema considered insufficiently responsive to available therapies. BMC Health Services Research. 2019;19(1):22.
2. Lee WJ, Song K-H, Noh JH, et al. Health-Related Quality of Life Using the EuroQol 5D Questionnaire in Korean Patients with Type 2 Diabetes. J Korean Med Sci. 2012;27(3):255-60.
3. Fenwick EK, Xie J, Ratcliffe J, et al. The Impact of Diabetic Retinopathy and Diabetic Macular Edema on Health-Related Quality of Life in Type 1 and Type 2 Diabetes. Investigative Ophthalmology & Visual Science. 2012;53(2):677-84.
4. Solli O, Stavem K, Kristiansen IS. Health-related quality of life in diabetes: The associations of complications with EQ-5D scores. Health Qual Life Outcomes. 2010;8:18.
5. Wang X, Lamoureux E, Zheng Y, et al. Health Burden Associated with Visual Impairment in Singapore: The Singapore Epidemiology of Eye Disease Study. Ophthalmology. 2014;121(9):1837-42.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Fluocinolone acetonide ocular implant for treating recurrent non-infectious uveitis [ID1039]

Company Response to ACD Modelling Requests: Updated Results

Contents

Tables and figures

ACD Model Adaptations Updated Results

A.1 Modelling Corrections

The following clarification points were requested by NICE on 2nd May 2019:

"For some of the analyses, the results show a difference in life years between the dexamethasone implant and fluocinolone acetonide implant groups. Please could you explain this given that the disease does not impact on mortality."

The corrections made to the model in response are described below and updated results are provided in Section A.2

Disparities in the Life Years were occurring where more than one ILUVIEN implant was being administered so only two of the scenarios presented would need to be altered.

This was due to the proportion being retreated not being adjusted for end of treatment. This lead to the subsequent treatment health state increasing slightly over 1. As the death state calculation is reliant on the other states being correct, this was also exceeding 1. These have now been altered.

While the absolute values have changed in two scenarios affected, the decision and conclusions have not. ILUVIEN would still be considered cost-effective in direct comparisons with Dexamethasone at a WTP threshold of £20,000.

A.2 Updated Model Results

A.2.1 *Cost -Effectiveness Analysis*

No transition to blindness from "On Treatment"

Results are presented for the scenarios described in the previous ACD Model Adaptations Document where no transition to blindness was considered from On Treatment. These results are shown in Table 1 to Table 7

in collaboration with:

ERASMUS UNIVERSITEIT ROTTERDAM
INSTITUTE OF HEALTH POLICY & MANAGEMENT

Maastricht University

Fluocinolone acetonide ocular implant for treating recurrent non-infectious uveitis
ERG critique: Company Response to ACD Modelling Requests

Produced by Kleijnen Systematic Reviews Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

This document contains the ERG critique of the additional analyses provided by the company in response to the NICE appraisal consultation document (ACD) concerning the cost effectiveness of fluocinolone intraocular implant (FAc) versus dexamethasone intraocular implant (DEX).[1, 2]

Methods

In these analyses, the company claimed to assume equal effectiveness between FAc and DEX during the period that each implant is active. However, this was only in terms of the percentage still remaining on the implant, but after different time periods. In particular, it was assumed that one DEX implant would be effective for only six months. The company therefore "scaled down" the efficacy of FAc from three years to six months. This means that the parametric time-to-event curve representing the proportion of patients on treatment with FAc was reduced to a six months' time frame (Figure 1). The proportion of patient still on treatment after 6 months with DEX was thus the same as the proportion of patient still on treatment after three years with FAc (i.e. [redacted]), assuming patients only received one DEX implant. The company assumed that patients are immediately retreated with a new implant (in the subsequent model cycle) upon treatment failure, which led to a regain in effectiveness and the costs associated with an implant.

Figure 1: Proportion of patients 'on treatment' with one FAc implant and one DEX implant.

Disutilities for the following relevant adverse events, identified in PSV-FAI-001, were included in the company's additional analyses:

- Anterior chamber flare
- Cataract (and cataract subscapular)
- Conjunctival haemorrhage
- Macular oedema (incl cystoid macular oedema)
- Iridocyclitis
- Macular fibrosis
- Posterior capsule opacification

- Uveitis
- Visual acuity reduced
- Visual impairment
- Vitreous Opacities
- IOP increased
- Viral upper respiratory infection
- Hypertension

For FAc, the AE rates were retrieved from the PSV-FAI-001 trials. For DEX, the incidence rates of cataract, conjunctival haemorrhage, and iridocyclitis were retrieved from the HURON trial (Lowder 2011[3]). The incidence rates for the remaining AEs were assumed to be the same as FAc. Disutilities for the following adverse events were identified through a literature search:

Table 1. Utility decrements associated with selected AEs applied in the model

Adverse Event	Disutility (Annual – assumed where not reported)	Indication	Source
Cataract	-0.016	Type 2 Diabetes	Lee (2012)[4]
Macular oedema	-0.04	Diabetic Retinopathy and Diabetic Macular Edema	Fenwick (2012)[5]
Visual Impairment	-0.063	Type 2 Diabetes	Solli (2010)[6]
Hypertension	-0.009	Mixed	Wang (2014)[7]

A disutility value of -0.032 (average of the values mentioned in Table 1) was assumed for the remaining adverse events (AEs). The total decrements per cycle on treatment were -0.0000243 and -0.00006922 for FAc and DEX, respectively. A disutility associated with the anxiety of repeated intraocular injections was included, based on Pochopien et al.[8]

ERG comments: The ERG is concerned by the following elements of the company's additional analyses: a) the "scaling down" of the effectiveness of FAc to obtain the effectiveness of DEX, b) the assumption that patients will receive a subsequent implant in the model cycle following failure, c) the assumption that the adverse events rates observed in HURON are transferable to the current patient population, d) the lack of transparency concerning the identification of disutility values.

a) The company claimed to assume equal effectiveness between FAc and DEX, however, by "scaling down" the effectiveness of FAc from three years to six months, the rate of relapse of DEX necessarily becomes much higher than that for FAc. Consequently, FAc and DEX do not have equal effectiveness in the analyses presented by the company. Equal effectiveness between FAc and DEX in the cost effectiveness model would only be fulfilled if the parametric time-to-event models for FAc and DEX are the same, as presented in the ERG report. Indeed, the assumption that the proportion still on treatment is the same for DEX after 6 months as that for FAc after 3 years implies a large decrease in the effectiveness of DEX compared to both as implemented by the ERG and in TA460. It is, of course, very likely that the DEX implant will fail for some patients within 6 months, but that is also the case for FAc. This does not imply that the rate of failure will be about six times greater with DEX than with FAc, as the assumption of equal proportion still on treatment at 6 months versus 3 years implies.
b) The company assumed that patients received a subsequent implant in the model cycle following treatment failure. This assumption seems implausible to the ERG because implanting a

subsequent implant while previous implants are still releasing their active substance will increase the dosage of the treatment which may affect the adverse event profile of the implants. In these analyses (allowing for multiple implants), the effectiveness and costs associated with multiple implants is likely overestimated. It seems more plausible to the ERG that patients will be considered for a subsequent implant after 6 months for DEX and 3 years for FAc, as presented in the ERG report.

c) Due to differences in patient population between the HURON trial and the population stated in the scope, the ERG wonders whether the adverse events' rates obtained from HURON may be directly applicable to the population included in the current assessment.
d) The document submitted by the company does not provide details on the methodology used to identify disutility values associated with the adverse events and the anxiety associated with repeated intraocular injections. The ERG was not able to assess whether the methodology used by the company adhered to the NICE reference case.

Additional analyses performed by the company

These additional analyses compare:

- FAc implant versus DEX implant (1, 2 and 3 of each)
- 1 FAc implant versus 1, 2 and 3 DEX implants
- 1 DEX implant followed by 1 FAc implant versus 2 or 3 DEX implants

All these analyses are presented with and without the transition from the 'on treatment' health state to the 'blindness' health state.

Finally, the company doubled the results of the model to obtain outcome for bilateral disease.

ERG comments: The ERG is concerned about a) the relevance of all of the company's additional analyses b) the lack of implementation of bilateral disease in the cost effectiveness model.

a) Comparing one, two, or three DEX implants versus the same amount of FAc implants (respectively 1, 2, and 3) results in different treatment durations, which, per definition will lead to larger health benefits obtained with FAc. The ERG think that comparing one FAc implant versus 6 DEX implants is a more informative comparison, as presented in the ERG report.
b) Outcomes for bilateral treatment with FAc and DEX were obtained by doubling the model outcomes (obtained for unilateral treatment). The ERG does not think this method is appropriate to obtain outcomes for the treatment of bilateral disease. Including the (health related quality of life and economic) impact of bilateral treatment, because of increasing/decreasing visual acuity of both eyes, would most likely yield more accurate results. This could have been achieved by assuming the same treatment regimens as in the PSV-FAI-001 trial and accounting for the effectiveness of FAc and (L)CP on visual acuity in the treated eye. In such model, local treatments would influence the visual acuity in the treated eye while systemic treatment would influence visual acuity (and thus outcomes) in both eyes. Doubling outcomes obtained from the model is not representative of the impact that local and systemic treatment can have on visual acuity when both eyes are affected by uveitis.

Results

Tables 4 to 16 of the company's additional submission present the results of the different analyses.

ERG comments: The ERG has doubts concerning the validity of the submitted results because the number of life years obtained with FAc differs from the number of life years obtained with DEX in several analyses while the disease does not affect mortality.

VISUAL ACUITY

The company presented visual acuity data in the ACD consultation comments.[1] Results show no effect at 12 months follow-up (Mean Difference = 2.5 (95% CI: -2.81 to 7.82)), [redacted] at 6 months (Mean Difference = [redacted] (95% CI: [redacted])) and 36 months (Mean Difference = [redacted] (95% CI: [redacted])).

ERG Comment: This may not be a reliable analysis. The company used a parametric method: one-way ANOVA. The main assumption for this method is that the outcome is normally distributed and that the standard deviation (SD) is similar in each group. Looking at the data, all the SDs are larger than the means which is an indication that the data are skewed, and therefore not normally distributed. However, the company does not report whether they tested the model assumptions; therefore, we do not know exactly how much the data deviate from normal distributions.

REFERENCES

[1] Alimera Sciences. *Fluocinolone acetonide ocular implant for treating recurrent non-infectious uveitis [ID1039]. Company ACD consultation comments*: Alimera Sciences, 2019 [accessed 25.4.19]. 1-6p.

[2] Alimera Sciences. *Fluocinolone acetonide ocular implant for treating recurrent non-infectious uveitis [ID1039]. Company response to ACD modelling requests*: Alimera Sciences, 2019 [accessed 25.4.19]. 1-17p.

[3] Lowder C, Belfort R, Jr., Lightman S, Foster CS, Robinson MR, Schiffman RM, et al. Dexamethasone intravitreal implant for noninfectious intermediate or posterior uveitis. *Arch Ophthalmol* 2011;129(5):545-53.

[4] Lee WJ, Song KH, Noh JH, Choi YJ, Jo MW. Health-related quality of life using the EuroQol 5D questionnaire in Korean patients with type 2 diabetes. *J Korean Med Sci* 2012;27(3):255-60.

[5] Fenwick EK, Xie J, Ratcliffe J, Pesudovs K, Finger RP, Wong TY, et al. The impact of diabetic retinopathy and diabetic macular edema on health-related quality of life in type 1 and type 2 diabetes. *Invest Ophthalmol Vis Sci* 2012;53(2):677-84.

[6] Solli O, Stavem K, Kristiansen IS. Health-related quality of life in diabetes: the associations of complications with EQ-5D scores. *Health Qual Life Outcomes* 2010;8:18.

[7] Wang X, Lamoureux E, Zheng Y, Ang M, Wong TY, Luo N. Health burden associated with visual impairment in Singapore: the Singapore Epidemiology of Eye Disease Study. *Ophthalmology* 2014;121(9):1837-42.

[8] Pochopien M, Beiderbeck A, McEwan P, Zur R, Toumi M, Aballea S. Cost-effectiveness of fluocinolone acetonide implant (ILUVIEN(R)) in UK patients with chronic diabetic macular oedema considered insufficiently responsive to available therapies. *BMC Health Serv Res* 2019;19(1):22.